Published in final edited form as:
Endocr Pract. 2008 ; 14(1): 33–39.

ASSOCIATION OF FIRST-TRIMESTER THYROID FUNCTION TEST VALUES WITH THYROPEROXIDASE ANTIBODY STATUS, SMOKING, AND MULTIVITAMIN USE

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Abstract

Objective: To determine first-trimester thyroid function values and associations with thyroperoxidase antibody (TPO-Ab) status, smoking, emesis, and iodine-containing multivitamin use.

Methods: We collected information by interview, questionnaire, and blood draw at the initial obstetric visit in 668 pregnant women without known thyroid disease. We compared thyroid-stimulating hormone (TSH), total thyroxine (T_4), and free T_4 index (FT_4I) values by TPO-Ab status. Multiple regression was used to identify characteristics associated with thyroid function values.

Results: The following median (range containing 95% of the data points) thyroid function test values were obtained in 585 TPO-Ab–negative women: TSH, 1.1 mIU/L (0.04-3.6); FT_4I, 2.1 (1.5-2.9); and T_4, 9.9 μg/dL (7.0-14.0). The following median (range containing 95% of the data points) thyroid function test values were obtained in 83 TPO-Ab–positive women: TSH, 1.8 mIU/L (0.3-6.4) (P<.001); FT_4I, 2.0 (1.4-2.7) (P = .06); and T_4, 9.3 μg/dL (6.8-13.0) (P = .03) (P values denote statistically significant differences between TPO-Ab–positive and negative participants). Among TPO-Ab–negative participants, TSH level was not associated with use of iodine-containing multivitamins, smoking, or race. TSH increased 0.03 mIU/L for every year of maternal age (P = .03) and decreased by 0.3 mIU/L for every increase in parity (P<.001). T_4 decreased 0.04 μg/dL for every year of maternal age (P = .04). Mean FT_4I was 2.05 in smokers and 2.20 in nonsmokers (P<.01). There were no relationships between T_4 or FT_4I and parity, race, or iodine-containing multivitamin use.

Conclusion: TPO-Ab status of pregnant women should be considered when constructing trimester-specific reference ranges because elevated serum TPO-Ab levels are associated with higher TSH and lower T_4 values.

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DISCLOSURE
The authors have no conflicts of interest to disclose.

INTRODUCTION

Thyroid function test values change in gestation, especially within the first trimester, largely because of estrogen-induced increases in serum thyroxine-binding globulin (TBG) levels and human chorionic gonadotropin (hCG)–induced increases in thyroid hormone synthesis and release. The results of thyroid function tests during the first trimester of pregnancy often are outside nonpregnant reference ranges for commercial laboratories. Few US studies have provided first-trimester–specific thyroid function values (1-4). The American Thyroid Association has recently identified the determination of reference ranges for thyroxine (T_4) and thyroid-stimulating hormone (TSH) in pregnant women, especially in the first trimester, as a research priority (5). Because thyroid function test values may differ substantially in pregnant women with and without detectable thyroperoxidase antibody (TPO-Ab) levels (1, 6), measurement of TPO-Ab is advisable for the development of such reference ranges.

The fetus does not produce its own thyroid hormone until weeks 10 to 12 of gestation; before that, the fetus is dependent on maternal T_4 that crosses the placenta in very small quantities. Because thyroid hormone is required for normal neurodevelopment, maternal hypothyroxinemia or elevated maternal serum TSH values in pregnancy may result in cognitive delays in children (7-9). Determining reference ranges for first-trimester maternal thyroid function test values is needed to choose appropriate therapy.

In addition, more information is needed about modifiable and nonmodifiable determinants of early pregnancy thyroid function. Low iodine intake and cigarette smoking may influence maternal thyroid function and thus perhaps fetal brain development. Even mild iodine deficiency during pregnancy may cause meaningful decreases in maternal thyroid hormone levels (10). Recent survey findings suggest that the proportion of the US population with low iodine intake has increased since the 1970s, and low urinary iodine values are most prevalent among women of childbearing age (11,12). Thiocyanates from cigarette smoke decrease the uptake of iodine into the thyroid gland by competitively inhibiting the sodium/iodide symporter. It has been previously reported that women who smoke during pregnancy are more likely to give birth to neonates with decreased T_4 levels, increased TSH levels, and thyroid enlargement (13,14). However, the influence of smoking on first-trimester maternal thyroid function test values has not previously been reported.

Therefore, we performed this study using a US pregnancy cohort to determine first-trimester–specific thyroid function values and the extent to which maternal first-trimester TSH levels, total T_4 levels, and free T_4 index values are associated with maternal first-trimester smoking, intake of iodine-containing multivitamins, extent of pregnancy-associated emesis, and maternal TPO-Ab status.

PATIENTS AND METHODS

Participants

Participants in this study were women enrolled in Project Viva, an ongoing cohort study of prenatal diet and other exposures and the health of mothers and children. We recruited women attending their initial prenatal visit at 8 urban and suburban obstetric offices of Harvard Vanguard Medical Associates, as previously described (15). Eligibility criteria included fluency in English, gestational age less than 14 weeks at the initial prenatal clinic appointment, and singleton pregnancy. Women were ineligible if they were health-plan employees, if they planned to relocate before delivery, or if their clinician refused referral. All participants provided informed consent. Project Viva was approved by institutional review boards at participating institutions.

Data Collection

At the first study visit, performed during the initial clinical obstetric appointment, we collected sociodemographic information, medical history, and information about pregnancy symptoms from participants using interviews and questionnaires. Reported use of iodine-containing multivitamins was recorded. We calculated gestational age from the last menstrual period or from second-trimester ultrasonography if the 2 estimates differed by more than 10 days.

Thyroid Assays

At the first study visit, maternal blood was collected in heparinized tubes, spun within 24 hours, and the plasma was stored at −70°C. TSH, total T_4 and triiodothyronine (T_3) resin uptake were assayed on the Bayer Advia Centaur (Bayer Diagnostics, Tarrytown, New York), and TPO-Ab was assayed on the Nichols Advantage (Nichols Institute Diagnostics, San Juan Capistrano, California). The serum nonpregnant reference ranges used were: TSH, 0.35-5.50 mIU/L; TPO-Ab, 0-2.0 IU/mL; and total T_4, 4.5-10.9 μg/dL. The free T_4 index was calculated from the total T_4 and T_3 uptake values (reference range, 1.0-4.0).

Analysis

Wilcoxon rank sum tests were used to compare thyroid function test results between TPO-Ab–positive and negative women and to compare characteristics of the women studied with those of the Project Viva cohort as a whole. The Kruskal-Wallis test was used to compare thyroid function test results between groups reporting different frequencies of vomiting during pregnancy. The chi-square test was used to compare the proportion of women with TSH values greater than 2.5 mIU/L between TPO-Ab–positive and negative women. Multiple linear regression was used to identify characteristics associated with thyroid hormone and TSH levels among women without TPO-Ab. Regression analyses could not be performed in TPO-Ab–positive women because of small sample numbers. Regression models included the independent variables maternal age, race/ethnicity, parity, smoking status, multivitamin iodine dose, and gestational age at delivery.

RESULTS

Of the 2128 Project Viva participants who delivered a single live infant, 724 had an initial study visit before 14 weeks of pregnancy and had stored plasma samples available for thyroid function testing. Of this group, 53 were excluded from the analysis because they were taking levothyroxine or antithyroid medications and/or reported a history of thyroid disease. Three subjects were excluded because of TSH values that were clearly outliers (2 TPO-Ab–negative women with TSH values of 11.2 and 94 mIU/L, and 1 TPO-Ab–negative woman with a TSH value of 19.3 mIU/L; we do not know whether their hypothyroidism was diagnosed and treated during pregnancy). No TPO-Ab–negative women included in the study had TSH values above the upper laboratory reference limit of 5.5 mIU/L. The final sample consisted of 668 women (Table 1). This subset was slightly older (mean age 32.5 years vs 31.2 years; $P<.001$) and less racially diverse (77.3% white vs 61% white; $P<.001$) than the Project Viva participants who were not included in the analysis; parity and smoking behavior did not differ from the larger cohort. Project Viva participants were older than most US mothers; the median maternal age at delivery in 2000 in the United States was 27.1 years (16). Participants were also relatively wealthy, with 64.2% (416 of 648 respondents) reporting household incomes of at least $70 000 per year, and well educated, with 94.3% having at least some college education.

The mean gestational age ± SD was 9.6 ± 1.4 weeks (median, 9.6 weeks; range, 5.6-13.9 weeks). The mean age ± SD of mothers was 32.5 ± 4.6 years. Approximately half of the women (338 of 668) were nulliparous. Seventyone women (10.6%) reported that they had smoked since becoming pregnant. Of 587 women who provided information about dietary supplement

use, 439 (74.8%) reported taking a prenatal multivitamin, 67 (11.4%) reported regularly taking a multivitamin, and 9 (1.5%) reported taking both a prenatal and a regular multivitamin. Among the 411 women for whom full information regarding prenatal vitamin iodine content was ascertained, only 7 (1.7%) used an iodine-containing prenatal multivitamin.

Of the 668 women in the sample, 83 (12.4%) had elevated TPO-Ab. Thyroid function test results for all the women are reported in Table 2. Serum TSH levels were higher ($P<.001$) and serum T_4 levels and free T_4 index values were marginally lower in TPO-Ab–positive women ($P = .03$ and $P = .06$, respectively) compared with TPO-Ab–negative women. Among the TPO-Ab–negative women, the 2.5th to 97.5th percentile ranges were: TSH, 0.04-3.6 mIU/L; free T_4 index, 1.5-2.9; and total T_4, 7.0-14.0 μg/dL. Among TPO-Ab–positive women, the 2.5th to 97.5th percentile ranges were: TSH, 0.3-6.4 mIU/L; free T_4 index, 1.4-2.7; and total T_4, 6.8-13.0 μg/dL. TSH values greater than 2.5 mIU/L were more frequent among TPO-Ab–positive women (26 of 83, or 31.3%) than among TPO-Ab–negative women (50 of 580, or 8.7%) ($P<.001$).

The number of women with positive TPO-Ab was insufficient to allow multivariate analyses in this group. On multivariate analysis among TPO-Ab–negative participants, first-trimester TSH values were not associated with gestational age at blood collection, use of iodine-containing multivitamins, smoking status, or race. In multivariate models, TSH increased by 0.03 mIU/L for every additional year of maternal age ($P = .03$) and decreased by 0.3 mIU/L for every increase in parity ($P<.001$); maternal age did not modify the effect of parity on TSH level. The adjusted total T_4 level was lower by 0.04 μg/dL for every additional year of maternal age ($P = .02$). The adjusted mean total T_4 level was lower in women who reported smoking during pregnancy (9.81 μg/dL in smokers vs 10.32 μg/dL in nonsmokers), although this was of only borderline significance ($P = .05$). The adjusted mean free T_4 index was lower in women who smoked during pregnancy (2.04 in smokers vs 2.18 in nonsmokers; $P = .01$). There were no relationships between T_4 or free T_4 index values and reported use of iodine-containing multivitamins, parity, or race.

Women who reported the most frequent vomiting during their pregnancies (Table 3) had lower median TSH values ($P<.001$) and higher median T_4 ($P<.001$) and free T_4 index ($P = .01$) values.

DISCUSSION

Among 585 TPO-Ab–negative women without known thyroid disease in the first trimester of singleton pregnancies, the central 95% range of values for TSH were lower and values for T_4 and the free T_4 index were higher than for nonpregnant adults. These observations are consistent with the known physiologic changes in thyroid function that occur during pregnancy. The presence of TPO-Ab was associated with higher TSH values and slightly lower T_4 and free T_4 index values in the first trimester of pregnancy.

Serum thyroid hormone levels change throughout pregnancy and can be particularly difficult to interpret in the first trimester. Few US studies have provided trimester-specific thyroid function test results (1-4). Perhaps for this reason, it has recently been reported that the interpretation of screening thyroid function tests from obstetric patients is quite variable from practice to practice (17).

The clinical diagnosis of hyperthyroidism is difficult to make in early pregnancy because symptoms of fatigue, heat intolerance, and tachycardia are common to both conditions. In addition, uncertainty about normative thyroid function test results in the first trimester makes it more difficult to distinguish between conditions such as Graves disease, which may require treatment, and physiologic pregnancy-related thyroid function alterations. TSH is the most sensitive indicator of maternal thyroid status in pregnancy. hCG is a weak thyroid stimulator,

binding to the TSH receptor. Thus, during the first trimester, when hCG levels are highest, serum TSH concentrations are often slightly below or at the low end of the usual nonpregnant laboratory reference range. In the present study, we found that the 2.5th percentile for TSH values in thyroid disease–free, TPO-Ab–negative women in the first trimester of pregnancy was 0.04 mIU/L. This is similar to 2.5th percentile values of 0.03 mIU/L recently noted in a sample of 100 TPO-Ab–negative US pregnant women (1) and 0.02 mIU/L noted at the 10th week of gestation in a sample of 13 599 women with unknown TPO-Ab status (2). Lower first-trimester TSH values have recently been reported in TPO-Ab–negative African American women compared with TPO-Ab–negative white women (3), a finding that was replicated in the present study (median TSH level for TPO-Ab–negative white women 1.12 mIU/L vs 1.02 mIU/L for TPO-Ab–negative African American women; $P = .03$). On the basis of this and previous reports, it is likely that serum TSH values as low as 0.03 mIU/L in the first trimester of pregnancy are physiologic and should prompt observation or additional thyroid function tests rather than an automatic diagnosis of hyperthyroidism.

hCG-related first-trimester gestational thyrotoxicosis may occur in women with morning sickness, particularly in those with hyperemesis gravidarum (18). The severity of nausea and vomiting in pregnant women has previously been shown to correlate with the degree of first-trimester TSH suppression (19). Women in the present study who reported the most frequent vomiting during their pregnancies had the highest median T_4 and free T_4 index values and the lowest median TSH concentrations. It is likely that first-trimester TSH values were not significantly associated with gestational age at blood collection in regression analyses in our study because the relationship between TSH and gestational age in the first trimester is U-shaped rather than linear.

High estrogen levels in pregnant women induce an increase in the sialylation of TBG, leading to reduced hepatic TBG clearance and increased circulating concentrations (20). Therefore, total T_3 and T_4 levels are increased throughout pregnancy. Serum T_4 levels in pregnant women are generally 1.5 times those found in nonpregnant individuals (21). Free T_4 and free T_3 levels remain in the nonpregnant reference range except late during the first trimester when they may be high-normal or elevated (22). The slight increase in adjusted T_4 values with gestational age seen in the present study likely reflects increasing TBG levels, while the slight decrease in the free T_4 index with gestational age is likely due to decreasing thyroidal stimulation by hCG after the 10th week of pregnancy. Total T_4 values in this study were higher than the laboratory reference range for nonpregnant adults and were similar to the 2.5th percentile and 97.5th percentile first-trimester values of 6.3 and 14.6 μg/dL, respectively, recently reported in a group of 50 TPO-Ab–negative, first-trimester pregnant women (23). No first-trimester–specific reference ranges for free T_4 analog assays currently exist, and available commercial analog free T_4 assays are unreliable in pregnant women (depending on the assay and the trimester of pregnancy, either underestimating or overestimating the free T_4 level) (1,24). For this reason, we used a free T_4 index instead of a commercial free T_4 analog assay.

Because of uncertainty about the upper limit of the TSH reference range, diagnosing mild hypothyroidism in pregnant women can be difficult. In the present study, the 97.5th percentile for TSH values in thyroid disease–free, TPO-Ab–negative women in the first trimester of pregnancy was 3.6 mIU/L. Different groups have previously reported the 97.5th percentile for TSH in the first trimester of pregnancy as 2.4 mIU/L (1), 3.12 mIU/L (in the 10th week of gestation) (2), and 5.20 mIU/L (the 98th percentile) (4). It has been suggested that a conservative upper limit for TSH in the first trimester of pregnancy is 2.5 mIU/L (21), which corresponds to the lowest 97.5th percentile reported to date in a US series. This conservative approach seems reasonable in the absence of definitive data because of the potentially deleterious effects of even very mild hypothyroidism in the first trimester.

Detectable serum TPO-Ab has been reported in up to 17% of adult US women (25). Most women with detectable TPO-Ab do not have clinical hypothyroidism, although, as demonstrated in the present study and others, they do tend to have higher TSH and lower free T_4 index values in the first trimester than women without thyroid antibodies (1,6). The presence of detectable maternal thyroid antibodies may be a risk factor for postpartum thyroiditis, miscarriage, and premature birth (26-28). In fact, findings from a recent study suggest that treatment of TPO-Ab–positive euthyroid women with levothyroxine results in improved obstetric outcomes (29). Thus, information about TPO-Ab positivity is important for the development of trimester-specific reference ranges for thyroid function test values.

We found that women who reported smoking during pregnancy had lower T_4 and free T_4 index values than non-smokers, which is in contrast to a recent report that smoking is associated with elevated free T_4 levels in nonpregnant individuals (30). In light of the cognitive impairment in offspring associated with even mild maternal hypothyroxinemia, this is potentially concerning and provides another reason to counsel women against smoking during pregnancy.

At the time of the first National Health and Nutrition Examination Survey (NHANES I), performed in 1971-1974, 1% of pregnant US women had urinary iodine values less than 50 μg/L, but by the time of NHANES III (1988-1994), that proportion had increased to 6.9% (8). The most recent NHANES survey (2000-2001) demonstrated that urinary iodine values in pregnant women have stabilized (12). A limitation of the present study is that urine samples were not available for iodine measurements. However, we recently reported that low urinary iodine values (less than 50 μg/L) were present in 9 out of 100 pregnant Boston-area women sampled (31). Relatively few of the women in this study were taking multivitamins that contained iodine. The lack of correlation between thyroid function test values and the use of iodine-containing multivitamins could be because iodine-containing supplements contain relatively little iodine compared with intake of iodine from foods and iodized salt, or because the number of women taking iodine-containing supplements in the present study was small. In the absence of definitive data regarding the dietary iodine sufficiency of US women, it has recently been recommended that all pregnant US women take a daily prenatal multivitamin that contains 150 mcg iodine (32), a suggestion with which we concur.

CONCLUSION

Data from the present study are meant to contribute to the development of trimester-specific thyroid function reference ranges for pregnant women. It will be important to take into account the TPO-Ab status of pregnant women in constructing trimester-specific reference ranges because elevated serum TPO-Ab levels are associated with higher TSH and lower T_4 values. Smoking during pregnancy may decrease first-trimester free T_4 values, which could, in turn, have adverse consequences for fetal neurodevelopment.

ACKNOWLEDGMENT

The authors are indebted to Erika Line-Nitu for her help with sample preparation. This work was supported by grants from the Harvard Pilgrim Health Care Foundation and the National Institutes of Health, 5K23DK4611 (ENP), R01 HD34568 (MWG), and HD44807 (EO).

Abbreviations

hCG, human chorionic gonadotropin; SD, standard deviation; T_4, thyroxine; TBG, thyroxine-binding globulin; TPO-Ab, thyroperoxidase antibody; T_3, triiodothyronine; TSH, thyroid-stimulating hormone.

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Table 1

Characteristics of 668 Pregnant Women Without Known Thyroid Disease[a]

Characteristics	No. (%) Participants (n = 668)
Age, y	
14 to <20	13 (1.9)
20 to <25	27 (4)
25 to <30	138 (20.7)
30 to <35	284 (42.5)
35 to <40	178 (26.6)
≥40	28 (4.2)
Race	
White	517 (77.3)
Black	67 (10)
Hispanic	32 (4.8)
Asian	28 (4.2)
Other	24 (3.6)
Parity	
0	338 (50.6)
1	231 (34.6)
2	77 (11.5)
3	17 (2.5)
≥4	5 (0.7)
Gestational age, wk	
5	5 (0.7)
6	16 (2.4)
7	45 (6.7)
8	155 (23.2)
9	199 (29.8)
10	127 (19)
11	79 (11.8)
12	22 (3.3)
13	20 (3)
Smoked during pregnancy	71 (10.6)

[a] Because of rounding, percentages may not total 100.

Table 2

First-Trimester Thyroid Function Test Results in Pregnant Women With Present or Absent Thyroperoxidase Antibodies

	Thyroperoxidase Antibody Absent[a] (n = 585)			Thyroperoxidase Antibody Present[b] (n = 83)			
	Median	Range	2.5-97.5 Percentile Range	Median	Range	2.5-97.5 Percentile Range	*P* Value[c]
TSH, mIU/L	1.1	<0.01-4.9	0.04-3.6	1.8	0.25-8.61	0.3-6.4	<.001
Free T_4 Index	2.1	1.3-6.0	1.5-2.9	2.0	1.4-3.4	1.4-2.7	.06
T_4, μg/dL	9.9	3.9-24.4	7.0-14.0	9.3	6.0-14.7	6.8-13.0	.03

Abbreviations: TSH, thyroid-stimulating hormone; T_4, thyroxine.

[a] TSH level was greater than 2.5 mIU/L in 50 (8.6%) of 580 women without detectable thyroperoxidase antibodies.

[b] TSH level was greater than 2.5 mIU/L in 26 (31.3%) of 83 women with detectable thyroperoxidase antibodies.

[c] *P* values are for difference between medians determined by the Wilcoxon rank sum test.

Table 3

Median Thyroid Function Test Values and Self-Reported Frequency of Emesis in 667 Pregnant Women Without Known Thyroid Disease[a]

	Emesis Frequency, No. of Instances					
	Never (n = 424)	**1-2 (n = 98)**	**3-10 (n = 92)**	**11-20 (n = 26)**	**>20 (n = 27)**	***P* Value[b]**
TSH, mIU/L	1.2	1.0	1.2	1.0	0.5	<.001
Free T_4 Index	2.1	2.0	2.1	2.3	2.3	.005
T_4, μg/dL	9.7	9.8	10.1	10.8	11.4	<.001

Abbreviations: TSH, thyroid-stimulating hormone; T_4, thyroxine.

[a] Self-reported frequency of vomiting was unavailable for 1 participant; thus data was ascertained for 667 of the 668 study participants.

[b] *P* values are for the Kruskal Wallace test.