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Thyroid function and thyroid autoimmunity in apparently healthy pregnant and non-pregnant Mexican women

Abstract

Background: Thyroid disorders are common in women of reproductive age, and thyroid dysfunction during pregnancy has been associated with adverse outcomes for mother and child. Thyroid function and thyroid function tests (TFTs) can be influenced by a variety of factors, such as ethnicity, the presence of autoimmune thyroid disease (AITD), dietary iodine intake, pregnancy, and methodological differences. However, no large-scale studies have been published which examine TFTs and prevalence of AITD in Mexican pregnant women and women of reproductive age.

Methods: TFTs and thyroid autoantibody testing were performed on 660 pregnant and 104 non-pregnant women from Mérida, Yucatán, Mexico. After removal of thyroid autoantibody positive individuals and women with thyroid stimulating hormone (TSH) >4.94 mIU/L, reference intervals were calculated for TFT for non-pregnant women and pregnant women by trimester.

Results: Anti-thyroidperoxidase antibodies (TPO-Ab) and/or anti-thyroglobulin antibodies (Tg-Ab) were positive in 14.4% and 13.5% of non-pregnant and pregnant women, respectively. TSH values were significantly higher in women who were positive for TPO-Ab and co-positive for TPO-Ab and Tg-Ab. TSH values were also significantly higher in Tg-Ab positive pregnant women. Other TFTs were not significantly different based on antibody status. Using antibody negative women, reference intervals were determined for TFTs in pregnant (gestational age-specific) and non-pregnant women.

Conclusions: Laboratory evidence of AITD is common in this population of Mexican pregnant and non-pregnant women. TFT results and reference intervals are influenced by pregnancy and thyroid autoimmunity. For optimal interpretation of TFT results, gestational age-specific reference intervals established using a local patient population should be used.

Keywords: autoimmune thyroid disease; Mexico; pregnancy; thyroid function.

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Introduction

Thyroid disorders are common in pregnant women, however, they often go unrecognized and undertreated [1–3]. During pregnancy, at least 2%–3% of women are affected by thyroid dysfunction, and approximately 10% have laboratory evidence of thyroid autoimmunity (TAI), despite being clinically and biochemically euthyroid [4]. Proper thyroid function during pregnancy is critical because maternal thyroid dysfunction, including the presence of thyroid autoantibodies, has been associated with numerous adverse outcomes (e.g., increased risk of miscarriage, preterm birth, impaired neurological development of the child, maternal postpartum thyroid disease, etc.) for both the mother and developing child [1, 2]. Thyroid hormones play an important role in fetal development, particularly during the first trimester, when the fetus is entirely dependent on the mother for thyroid hormones [1]. Pregnancy places increased demands on the maternal thyroid, and if the mother has occult or undertreated thyroid disease, TAI, or sub-optimal iodine nutrition, maternal thyroid function during pregnancy can be compromised [1, 2]. For these reasons, it is important to understand maternal thyroid status either pre-conception, or early during the pregnancy, especially in women

already being treated for thyroid disease or those with known risk factors, such as a personal or family history of thyroid disease, presence of thyroid autoantibodies or other autoimmune disease, a history of head or neck irradiation, and age >30 years old [2, 4]. Clinical diagnosis of thyroid disease during pregnancy presents special challenges, as many of the signs and symptoms of thyroid dysfunction are non-specific, may not be present at all until disease is well advanced, or may be attributed to the pregnancy itself [5]. In this context, laboratory testing assumes even greater importance in assessing maternal thyroid function [5, 6]. However, physiological changes associated with pregnancy can complicate the interpretation of maternal thyroid function tests (TFT) [1, 6].

It is well established in the literature that gestational age-specific reference intervals are needed to allow proper interpretation of TFT results during pregnancy [6–10]. It is also known that thyroid function and TAI can be influenced by genetic and dietary factors and that TFT results can be method-specific [6–10]. Due to these variables, population and method-specific TFT reference intervals can aide interpretation of TFT results [6–10]. Optimally, reference intervals for laboratory tests are best established using patient specimens representative of the population served by the laboratory [11]. However, it is often not practical for clinical laboratories to establish local reference intervals for all tests they perform, and many clinical laboratories use reference intervals reported in the literature or provided by the assay manufacturer, which may or may not be appropriate for the local patient population. There are very little published data on thyroid function, prevalence of autoimmune thyroid disease (AITD), and population-specific reference intervals in Mexican women. The objectives of our study were to determine the prevalence of laboratory evidence for AITD in pregnant and non-pregnant Mexican women, determine TFT reference intervals in thyroid autoantibody negative non-pregnant women, determine gestational age-specific reference intervals for TFT in thyroid autoantibody negative women, and compare the prevalence of TAI and TFT reference intervals in pregnant and non-pregnant women.

Materials and methods

The study was performed on 660 de-identified surplus fresh serum samples from ambulatory pregnant women at local outpatient clinics (Mérida, Yucatán) who had laboratory testing performed as part of their routine antenatal care, and 104 samples from ambulatory non-pregnant women of approximately the same age at outpatient clinics who were having laboratory testing as part of routine care. Sample collection and testing for the study took place from August 2010 to July 2011. All women had no personal or family history of thyroid disease, no other endocrine disorders, no history of goiter or neck irradiation, and were not using any medications except nutritional supplements. For pregnant women, patients with known fetal genetic abnormality or multiple gestations were excluded, and gestational age was calculated using the last menstrual period (LMP). Smoking status was not assessed. Each sample was tested once for thyroid stimulating hormone (TSH), free thyroxine (FT4), total thyroxine (TT4), free tri-iodothyronine (FT3), total tri-iodothyronine (TT3), anti-thyroidperoxidase antibodies (TPO-Ab), and anti-thyroglobulin antibodies (Tg-Ab). Assay testing was performed by chemiluminescent immunoassay on the Abbott ARCHITECT analyzer (Abbott Laboratories, Abbott Park, IL, USA) according to manufacturer's instructions. The principles of this instrument system and performance characteristics for these assays have been previously described [12–15]. Manufacturer's cut-off values for Anti-TPO (<5.6 IU/mL) and Anti-Tg (<4.11 IU/mL) were used. Reference intervals for both pregnant and non-pregnant populations were calculated after exclusion of women who were antibody positive and women who had TSH values >4.94 mIU/L (the manufacturer's upper limit of normal). Stata (version 12.0, StataCorp. 2011. Stata Statistical Software: Release 12. College Station, TX, USA: StataCorp LP.) was used for all data processing and analysis. Medians, means and standard errors (using bootstrapping) were calculated for serum TSH, TT4, TT3, FT4, and FT3 for pregnant women by trimester and for non-pregnant women. Student's t, Kruskal-Wallis, and Mann-Whitney tests were used to determine significant differences examining all group comparisons. Tukey's correction for multiple comparisons was performed. Chi-square testing was used to examine associations between categorical variables and Pearson's correlation was used for continuous measures. The 2.5th and 97.5th percentiles (95% interval) were calculated as the reference interval for each hormone for non-pregnant women and by trimester for pregnant women. A two-tailed p-value of $p<0.05$ was considered statistically significant. The study design and protocol were approved by the Institutional Ethics Committee, and informed consent was obtained from each subject.

Results

In this cross-sectional study conducted in Merida, Mexico, TFTs and thyroid autoantibody status were evaluated in 660 ambulatory pregnant and 104 ambulatory non-pregnant women. Characteristics of the study population and thyroid auto-antibody prevalence are shown in Table 1. The non-pregnant population was significantly older than the pregnant population (mean age 28.6 vs. 25.8, respectively, $p<0.001$). Antibody negative non-pregnant women (n=89) were significantly older than antibody negative pregnant women (n=571), with a mean age of 28.4 vs. 25.7 years, respectively ($p<0.001$). However, there were no significant differences between pregnant and non-pregnant women for laboratory evidence of TAI (positive for TPO-Ab and/or Tg-Ab; 13.48% and 14.42%, respectively). TSH level was not associated with age in any patient grouping

Table 1 Characteristics of the study population.

	Pregnant women	Non-pregnant women
n	660	104
Age, years		
Mean	25.8	28.6[a]
Range	12–45	16–42
Median	25	27[b]
Thyroid antibody status, %		
TPO-Ab positive	7.42	6.73
Tg-Ab positive	11.06	13.46
TPO-Ab and/or Tg-Ab positive	13.48	14.42
TPO-Ab and Tg-Ab positive	5.00	5.77

[a]p<0.001; [b]p=0.05.

(entire population, pregnant, non-pregnant, antibody negative non-pregnant, and antibody negative pregnant). For both pregnant and non-pregnant women, there were no significant differences in age between antibody negative and antibody positive women. There was no association between pregnancy status and antibody status, and no association between pregnancy trimester and antibody status. In non-pregnant women (n=104), TPO-Ab positive women had higher mean TSH values when compared to TPO-Ab negative women (3.33 vs. 1.82 mIU/L, respectively, p=0.0011). Mean TSH values were also higher in women who were co-positive for TPO-Ab and Tg-Ab, when compared to antibody negative women (3.61 vs. 1.82, respectively, p<0.001). Mean values for other TFTs were not significantly different based on TPO-Ab or Tg-Ab status. In pregnant women (n=660), mean TSH values were higher in TPO-Ab positive women when compared to TPO-Ab negative women (2.46 vs. 1.99 mIU/L, respectively, p=0.0097), and also higher in Tg-Ab positive women when compared to Tg-Ab negative women (2.43 vs. 1.97 mIU/L, respectively, p=0.0029). Additionally, when compared to antibody negative women, women who were co-positive for TPO-Ab and Tg-Ab had higher mean TSH values (3.61 vs. 1.82 mIU/L, respectively, p<0.001), and women who were positive for either TPO-Ab or Tg-Ab also had higher mean TSH values (2.30 vs. 1.98, p=0.0216). The distribution of TSH values in antibody positive and antibody negative women by pregnancy status is shown in Figure 1. Mean values for other TFTs were not significantly different based on TPO-Ab or Tg-Ab status.

Using antibody negative women and excluding women who had a TSH value >4.94 mIU/L (the manufacturer's upper limit of normal), TFT reference intervals were calculated for pregnant and non-pregnant women (Table 2). Statistically significant differences in TFT values between the two populations, and across trimesters, are summarized in Table 2. For TSH, third trimester mean and median TSH was significantly different (higher) from first and second trimester, and non-pregnant values. For FT4, third trimester mean values were significantly different

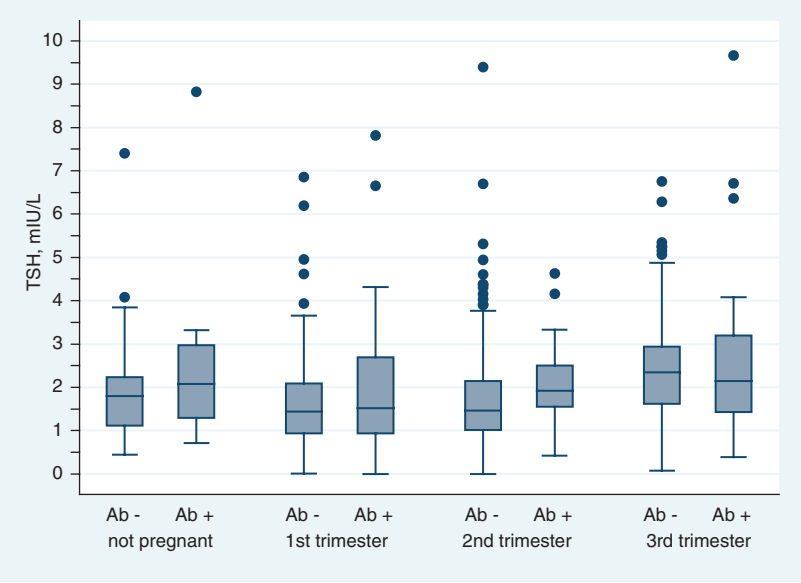

Figure 1 Box plot of TSH values by pregnancy status in pregnant and non-pregnant women.
The upper and lower edges of the box represent the 75th and 25th percentiles of the population, respectively. The median value is indicated by a solid line within the box. The whiskers define upper and lower values that are 1.5x the interquartile range above and below the 75th and 25th percentiles, respectively. Solid dots represent values outside of this range.

Table 2 Reference intervals for thyroid function tests in antibody negative women.

Assay	Pregnancy status	Unit	n	Mean	Median	Reference range (percentile)	
						2.5th	97.5th
TSH	Non-pregnant	mIU/L	88	1.79	1.79	0.52	3.77
	First trimester	mIU/L	165	1.56	1.40	0.04	3.46
	Second trimester	mIU/L	181	1.65	1.45	0.06	4.22
	Third trimester	mIU/L	211	2.32[a,b,c]	2.31[a,b,c]	0.51	4.53
FT4	Non-pregnant	ng/dL	88	1.09	1.10	0.83	1.37
		pmol/L		14.03	14.16	10.68	17.63
	First trimester	ng/dL	165	1.08	1.09	0.75	1.39
		pmol/L		13.90	14.03	9.65	17.89
	Second trimester	ng/dL	181	1.04	1.02	0.74	1.30
		pmol/L		13.38	13.13	9.52	16.73
	Third trimester	ng/dL	211	0.90[a,b,c]	0.89	0.65	1.12
		pmol/L		11.58	11.45	8.37	14.41
Total T4	Non-pregnant	µg/dL	88	7.18	7.11	4.45	10.86
		nmol/L		92.41	91.51	57.27	139.77
	First trimester	µg/dL	165	9.44[c]	9.24	5.86	13.37
		nmol/L		121.49	118.92	75.42	172.07
	Second trimester	µg/dL	181	10.93[a,c]	10.91	7.08	14.18
		nmol/L		140.67	140.41	91.12	182.50
	Third trimester	µg/dL	211	9.56[b,c]	9.59	6.55	13.35
		nmol/L		123.04	123.42	84.30	171.81
FT3	Non-pregnant	pg/mL	88	2.41	2.44	1.70	3.26
		pmol/L		3.70	3.75	2.61	5.01
	First trimester	pg/mL	165	3.13[c]	3.17	2.21	4.03
		pmol/L		4.81	4.87	3.39	6.19
	Second trimester	pg/mL	181	3.36[c]	3.23	2.44	4.15
		pmol/L		5.16	4.96	3.75	6.37
	Third trimester	pg/mL	211	2.79[b,c]	2.73	2.14	3.61
		pmol/L		4.29	4.19	3.29	5.54
TT3	Non-pregnant	ng/mL	88	0.99	0.97	0.63	1.68
		nmol/L		1.52	1.49	0.97	2.58
	First trimester	ng/mL	165	1.40	1.40	0.82	2.05
		nmol/L		2.15	2.15	1.26	3.15
	Second trimester	ng/mL	181	1.68	1.63	1.15	2.20
		nmol/L		2.58	2.50	1.77	3.38
	Third trimester	ng/mL	211	2.07	1.48	1.09	1.94
		nmol/L		3.18	2.27	1.67	2.98

[a]$p<0.05$ two-tailed significantly different from 1st trimester; [b]$p<0.05$ two-tailed significantly different from 2nd trimester; [c]$p<0.05$ two-tailed significantly different from non-pregnant. Manufacturer's non-pregnant adult reference intervals: TSH=0.35–4.94 mIU/L; FT4=9.01–19.05 pmol/L (0.7–1.48 ng/dL); TT4=62.7–150.8 nmol/L (4.87–11.72 µg/dL); FT3=2.63–5.70 pmol/L (1.71–3.71 pg/mL); TT3=0.89–2.44 nmol/L (0.58–1.59 ng/mL).

(lower) from non-pregnant women, first and second trimester, and mean FT4 value was lowest during the third trimester. For TT4, first, second, and third trimester mean values were statistically different (higher) from non-pregnant women, and mean TT4 was highest during the second trimester. For FT3, first, second, and third trimester mean values were statistically different (higher) from non-pregnant women, and mean FT3 was highest during the second trimester. Finally, for TT3, mean values were not significantly different for pregnant and non-pregnant women, or across trimesters.

Discussion

In our study of 660 pregnant and 104 non-pregnant ambulatory Mexican women in Mérida, Yucatán, we have determined the prevalence of TPO-Ab and Tg-Ab positivity, calculated TFT reference intervals in antibody negative non-pregnant women, and trimester-specific TFT in antibody negative pregnant women. To the best of our knowledge, this is the largest study to date to examine these parameters in apparently healthy pregnant and non-pregnant Mexican women of reproductive age.

In both pregnant and non-pregnant women, laboratory evidence of AITD was common, with 13.48% and 14.42% being positive for TPO-Ab and/or Tg-Ab, respectively. There was no significant difference in thyroid antibody status between pregnant and non-pregnant women. Comparison of these data to other published studies must be done with caution. Although most automated assays for TPO-Ab and Tg-Ab are standardized to the same international reference material, there is still a lack of concordance between different manufacturer's assays [14]. When thyroid autoantibody prevalence data from the current study are compared to several studies in pregnant women using similar assay methodology, they roughly agree with those of Gilbert (15.7% in pregnant women in Australia) and Bocos-Terraz (14.8% in pregnant women in Spain), but are lower than those of Stricker (19.7% in pregnant woman in Switzerland) [7, 16, 17]. Our thyroid antibody prevalence is higher than that reported by Mendez-Villa et al. in their study of non-pregnant women of child-bearing age in Querétero, Mexico (TPO-Ab 6.7% vs. 5.9%, Tg-Ab 13.5% vs. 5.0%, respectively), however, their study population was significantly younger than ours (mean age of 21.7 vs. 28.6 years in the present study) and used a different assay methodology [18]. Pregnant and non-pregnant women who were positive for thyroid autoantibodies had significantly higher mean TSH values when compared to antibody negative women. This result agrees with other studies of pregnant women using the same methodology [7, 17]. Other TFTs in non-pregnant and pregnant women were not significantly different based on TPO-Ab or Tg-Ab status. Using the same assay methodology, Stricker et al. found that FT4 and TT4 were not influenced by antibody status, but FT3 was significantly higher in antibody positive pregnant Swiss women [7].

TAI, particularly the presence of TPO-Ab, has important implications for women of reproductive age because the presence of TPO-Ab has been associated with increased risk of infertility, miscarriage, pre-term birth, postpartum thyroid disease, the development of maternal thyroid disease later in life, and increased maternal risk for other autoimmune disorders [1, 19, 20]. Maternal TPO-Ab positivity during pregnancy has also been linked to abnormal thyroid function parameters in the offspring, even in adolescence [21]. As the presence of TAI also suggests the potential for decreased thyroid functional reserve during pregnancy, ensuring proper maternal iodine nutrition in these women is especially important. It is recommended that pregnant women have a minimum of 250 μg daily intake of iodine, and a median urinary iodine excretion of between 150 and 249 μg/L to assure adequate iodine intake [22]. Mexico has a universal salt iodinization program, and a reported population-based median urinary iodine excretion of 235 μg/L [22]. In their study of pregnant women in Querétero, Mexico, Garcia-Solis et al. found a median urinary iodine excretion of 260 μg/L [23]. In a subsequent study of women of childbearing age in Querétero, Mexico, Méndez-Villa et al. found a median urinary iodine excretion of 141 μg/L, which is slightly deficient [18]. These investigators also reported that <50% of women in their study knew pregnant women need more iodine than non-pregnant women, or that iodine deficiency can cause mental retardation in children [18]. Given these data and the prevalence of AITD in our study population, understanding maternal thyroid status pre-conception or in early pregnancy may be of benefit for both the mother and child. This is especially true for women being treated with thyroxine for hypothyroidism pre-conception, as they are likely to require an increased dose to maintain optimal thyroid health, and require careful monitoring throughout the pregnancy [1, 2]. These data are also relevant when assessing the thyroid health of women who smoke, as it has been reported that smoking can decrease uptake of iodine into the thyroid gland [24].

After exclusion of antibody positive women and women with TSH values >4.94 mIU/L (the manufacturer's upper limit of normal), TFT reference intervals were calculated for non-pregnant and pregnant women (Table 2). For non-pregnant woman, TFT reference intervals were, in general, narrower than those reported by the manufacturer. This could reflect differences in the sample population, as well as the fact that thyroid autoantibody positive women and women with TSH >4.94 mIU/L were excluded from the current analysis, but not in the determination of the manufacturer's reference intervals. For pregnant women, the gestational age-specific reference intervals established in this study were significantly different from those provided by the manufacturer for non-pregnant woman. Many of the trimester-specific reference intervals were also significantly different when compared to local non-pregnant women of reproductive age (see Table 1), as well as across trimesters. These findings are in agreement with previously published studies, and highlight the importance of using pregnancy-specific reference intervals established in the local population [7–10]. Direct comparison of the reference intervals determined in this study with those of other published reports is problematic. Method-specific differences in TFTs are well known, and even comparison to studies using the same methodology is difficult due to different sample inclusion and exclusion criteria. In the absence of method-specific reference intervals, and because of the central importance measurement of TSH plays in assessing maternal thyroid

function, the American Thyroid Association (ATA) recommends the following trimester-specific reference intervals for TSH: first trimester, 0.1–2.5 mIU/L; second trimester, 0.2–3.0 mIU/L, and; third trimester, 0.3–3.0 mIU/L [6]. However, in the present study, the upper limit of normal for TSH in each trimester is higher than the ATA recommendations (3.46 vs. 2.5 mIU/L, 4.22 mIU/L vs. 3.0 mIU/L, and 4.53 vs. 3.0 mIU/L, respectively). The ATA recommendations are expert opinion based on consideration of published data, however, methodological differences across studies can be significant. Reference intervals may also be impacted by subjects with possible occult thyroid disease. In our study, even after exclusion of subjects based on patient history and antibody status, a small number of women still had elevated TSH values (Figure 1). There are published studies with rigorous exclusion criteria where the upper limit of normal for TSH is significantly higher than the ATA recommendations [25–27]. These differences serve to reinforce the importance of establishing method-specific reference intervals following local practice using a sample population representative of the patients served by the laboratory, ideally in an iodine-sufficient population after exclusion of individuals with positive thyroid antibodies and any history of thyroid disease.

Our study has some potential limitations, the most significant of which is that iodine nutrition status was not assessed in our study population. Based on published data, the general Mexican population is iodine sufficient [22]. However, data published for pregnant women and women of childbearing age report median urinary iodine excretion ranging from sufficient to slightly deficient [18, 23]. In most individuals, if dietary iodine intake is not sufficient, the pituitary responds by secreting more TSH [28]. In the present study, if women with insufficient dietary iodine were included in our reference range analysis, there is a potential for the reference ranges to possibly be skewed up (TSH) or down (FT4, TT4, FT3, TT3). However, the potential impact of this limitation is mitigated by two factors; women with any history of goiter were excluded from the study, and women with TSH values >4.94 mIU/L were excluded from the reference range analysis (along with women who were positive for TPO-Ab and/or Tg-Ab). Another potential limitation of our study is that thyroid ultrasound was not used to identify possible occult thyroid disorders. The possible impact of this limitation is mitigated by patient exclusion criteria, particularly no personal or family history of thyroid disease. Finally, gestational age was based on LMP and not thyroid ultrasound. However, local medical practice is to determine gestational age based on LMP, and the reference values reported here are aligned with this practice.

In conclusion, we have determined the prevalence of laboratory evidence of AITD in apparently healthy Mexican pregnant and non-pregnant women of reproductive age. Laboratory evidence of AITD is common in this population. Mean TSH values are significantly higher in both non-pregnant and pregnant women who are positive for thyroid autoantibodies. Method- and gestational age-specific references intervals were established for TSH, FT4, TT4, FT3 and TT3, and these reference intervals should prove useful in the interpretation of TFT results in this population. Further work is needed to better understand the iodine nutrition status of pregnant women and women of childbearing age in Mexico.

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Conflict of interest statement

Authors' conflict of interest disclosure: The authors stated that there are no conflicts of interest regarding the publication of this article. Research funding played no role in the study design; in the collection, analysis, and interpretation of data; in the writing of the report; or in the decision to submit the report for publication.
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