Local Versus International Recommended TSH References in the Assessment of Thyroid Function During Pregnancy

Authors
A. Amouzegar[1], E. Ainy[2], M. Khazan[1], L. Mehran[1], M. Hedayati[3], F. Azizi[1]

Affiliations
[1] Endocrine Research Center, Research Institute for Endocrine Sciences, Shahid Beheshti University of Medical Sciences, Tehran, Iran
[2] Safety Promotion and Injury Prevention Research Center, Shahid Beheshti University of Medical Sciences, Tehran, Iran
[3] Molecular and Cellular Endocrine Research Center, Research Institute for Endocrine Sciences, Shahid Beheshti University of Medical Sciences, Tehran, Iran

Correspondence
F. Azizi, MD
Professor of Internal Medicine &
Endocrinology
Endocrine Research Centre
Research Institute for Endocrine
Sciences
Shahid Beheshti University of
Medical Sciences
P. O. Box 19395-4763
Tehran
I. R. Iran
Tel.: +98/21/22409 309
Fax: +98/21/22402 463
azizi@endocrine.ac.ir

Abstract
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The aim of this study was to compare the prevalence of subclinical and overt hypothyroidism based on local population-specific reference intervals versus arbitrary cutoffs that are not specific for the population studied or the assay used, during pregnancy in an area of iodine sufficiency. We tested a total of 203 pregnant women in the first trimester of pregnancy, and followed their status in the second and third trimesters. Serum samples from women were assayed for levels of total T4 and T3, FT4I, TSH, TPOAb, and TgAb. Of the 203 women based on our national trimester specific reference ranges of serum TSH and FT4I, 153, 157, and 157 were euthyroid in 3 consecutive trimesters of pregnancy. Accordingly, a total of 23, 12, and 13 had subclinical hypothyroidism in the first, second, and third trimester, respectively. Overt hypothyroidism was detected in 4, 5, and 1 women in the first, second, and third trimesters of pregnancy, respectively. The prevalence of subclinical hypothyroidism was 49, 31, and 34 in each of the trimesters respectively, when TSH > 2.5 mIU/l was considered for definition of hypothyroidism in the first trimester, and over 3 mIU/l in the second and third trimesters. Our results showed that using arbitrary cutoff values for TSH instead of population-specific reference intervals may inappropriately increase the rate of subclinical hypothyroidism.

Abbreviations
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hCG	Human chorionic gonadotropin
UIE	Urine iodine excretion
TSH	Thyroid stimulating hormone
T4	Thyroxine
T3	Triiodothyronine
FT4I	Free thyroxine index
TPOAb	Thyroid peroxidase antibody
TgAb	Thyroglobulin antibody
WHO	World Health Organization
SCH	Subclinical hypothyroidism
OH	Overt maternal hypothyroidism

Introduction
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Pregnancy has a profound impact on the thyroid gland function. The decrease in serum TSH during the first trimester is due to rising hCG concentrations, which are a weak stimulator of thyroid function by binding to the TSH receptor, increasing the thyroid hormone release that in turn decreases TSH secretion [1]. Approximately 10–20% of pregnant euthyroid women are positive for antibodies against thyroperoxidase (TPOAb) or thyroglobulin (TgAb). Sixteen percent of the women who are euthyroid and positive for TPOAb or TgAb in the first trimester will develop a TSH that exceeds 4.0 mIU/l by the third trimester, and 33–50% of women who are positive for TPO or Tg antibody in the first trimester will develop postpartum thyroiditis [2,3]. Indeed, thyroid disorders in pregnancy are common and untreated thyroid dysfunction (hyperthyroidism or hypothyroidism) is associated with adverse health outcomes for both the mother and child [4]. Hyperthyroidism during pregnancy is uncommon and has been reported in 0.05–3.0% of pregnancies [5]. Overt maternal hypothyroidism (OH) and subclinical hypothyroidism (SCH) with high TSH are relatively common abnormalities in pregnancy with a prevalence of 2.5 and 3%, respectively, using different TSH cutpoints to define hypothyroidism [3,6,7]. In the Casey et al. study, 2.3% of the cohorts were considered to have subclinical hypothyroidism, based on the 95th percentile value for serum TSH (3 mIU/l) [7]. Vaidya et al. used a TSH threshold of > 4.2 mIU/l

to define hypothyroidism, and in this study 2.6% women had raised TSH levels [6]. Many studies show an increased risk of fetal death [8], reduced intelligence quotient (IQ) of offspring [9], higher incidence of placental abortion, and prenatal and neonatal morbidity and mortality in mothers with hypothyroidism, [10] although contradictory results have also been reported [11,12]. However, it is not clear if SCH during pregnancy affects the neuropsychological development of the offspring [6,13]. The bulk of evidence shows that mild maternal hypothyroidism is associated with delayed neuropsychological development in neonates and children [14]. It has been reported that the presence of antithyroid antibodies may increase the risk of miscarriage, gestational diabetes mellitus, post-partum thyroiditis, permanent hypothyroidism, and impaired child development, even in euthyroid women [15].

We conducted this study to compare the prevalence of subclinical and overt hypothyroidism with local population-specific reference intervals vs. arbitrary cutoffs that are not specific for the population studied or the assay used during pregnancy in an area of iodine sufficiency.

Subjects and Methods
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Data collection
This longitudinal study, performed in Tehran, an area of iodine sufficiency, included a total of 350 pregnant women in the first trimester of pregnancy referring to the mother and child health care clinics of 2 general hospitals of Tehran, who were consecutively recruited from November 2004 to November 2006. The last national study showed that Tehran meets the criteria of iodine sufficiency based on WHO criteria [15]. We collected demographic data (including age and parity); pregnancy history (preterm delivery and abortions) and medical history (including thyroid medications, history of thyroid disease, and/or autoimmune disorders). Trained midwives explained the rationale of the study to the pregnant women and obtained their written consent from all women. The study was approved by the appropriate human research committee of Shahid Beheshti University of Medical Sciences. We excluded 147 subjects for whom data on their clinical course of thyroid disease were not available in all trimesters or were lost to follow-up (referring elsewhere for nonviable, delivery pregnancy). Only women with singleton pregnancies were enrolled. Inclusion criteria required documented thyroid-related measurements for all 3 trimesters. A total of 203 participants recruited in the first and were followed up in other 2 consequent trimesters. Obstetric history was taken using a standard questionnaire and physical examination was performed. In the present study, gestational age was calculated from the first day of the last normal menstrual period; gestational ages ≤ 14.9, 28.9, and ≥ 29 weeks comprised the first, second, and third trimesters of pregnancy, respectively [16].

Laboratory measurements
Serum samples from women, in each trimester were stored at −40 °C and assayed for levels of total T4 and T3, TSH, thyroperoxidase antibody (TPOAb), and thyroglobulin antibody (TgAb) at the end of the study. Results were expressed as microgram of iodine per liter of urine (μg/l). Serum T3 and T4 were measured by the radioimmunoassay method and serum TSH measurements were done by immunoradiometric assay (Izotope, Budapest, Hungary) using the gamma counter Wallac Wizard, Turku, Finland. The inter- and intra-coefficients of variation were 6.2

and 3.3% for T4, 7.8 and 6.7% for T3, 5.8 and 3.8% for TSH, respectively. Measurement of TgAb and TPOAb were performed using enzymoimmunometric assay (EIMA) kits (Orgentec Diagnostica GmbH, Mainz, Germany). Laboratory results of positive serum thyroid peroxidase and thyroglobulin antibodies were TPOAb > 40 IU/ml or TgAb > 100 IU/ml.

Intra- and interassay coefficient of variation were 2.2 and 4.9% for TgAb and 3.0 and 5.1% for TPOAb, respectively. T3RU was measured by enzyme immunoassay (EIA) using Pishtazteb kit (Tehran, Iran) and intra- and interassay CVs were 2.5% and 3.3%, respectively. FT4I was calculated by multiplying TT4 in T3Ru and the result divided by mean T3Ru in each phase [FT4I = (TT4 × T3Ru)/Mean T3Ru]. All EIA and EIMA tests were measured by the Sunrise microplate reader (Tecan Co. Salzburg, Austria). For analysis population- and trimester-specific intervals were used as follows: TSH (0.2–3.9, 0.5–4.1, and 0.6–4.1 mIU/l) [17,18] for the first, second and third trimesters.

Definitions
We applied the local trimester specific reference range of TSH, TT4, TT3, and FT4I for this population [17,18]. Subclinical hypothyroidism was defined as TSH between > 3.9 and < 10 mIU/l in first and TSH between > 4.1 and < 10 mIU/l in both the second and third, with normal T4 in all trimesters of pregnancy. Overt hypothyroidism was defined as TSH > 10 mIU/l or TSH > 3.9 mIU/l and TT4 < 8.2 μg/dl in the first, TSH > 4.1 mIU/l and TT4 < 10.1 μg/dl in the second, and TSH > 4.1 mIU/l and TT4 < 10.1 μg/dl in the third trimesters of pregnancy. Reference intervals in the first, second, and third trimesters were as follows: TSH (0.2–3.9, 0.5–4.1, and 0.6–4.1 mIU/l); TT4 (8.2–18.5, 10.1–20.6, and 9–19.4 μg/dl); and FT4I (8.5–19, 9.7–21, and 8.7–20.4), respectively.

Statistical analysis
Normally distributed values are reported as mean ± SD, or if not so were reported as median and interquartile range IQR. Repeated measure test was used to compare TT4, TT3, and FT4I between 3 trimesters and Friedman test was used for TSH comparison. McNemar's test is applied for comparison of prevalence of hypothyroidism based on 2 different cut points of TSH; p-values < 0.05 denoted statistical significance. The statistical software SPSS version 20 was used for data analysis.

Results
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A total of 203 participants were recruited in the first trimester of pregnancy. The mean ± SD of age was 25.2 ± 5.0 years, and mean ± SD of gestational age was 12.2 ± 3.7 weeks.

Thyroid tests results
The median IQR of serum TSH concentration was 1.7 (0.9–2.7), 1.9 (1.2–2.7), and 1.8 (1.1–2.8) mIU/l in the first, second, and third trimester, respectively (p < 0.0004) (◉ **Table 1**). Considering local specific reference range for TSH, 27 (13.3%), 17 (8.4%), and 15 (7.4%) subjects had serum TSH values higher than the upper cutoff values in the 3 trimesters showing that hypothyroidism resolved with progression of pregnancy. Applying arbitrary recommended cutoff values for TSH in pregnancy (> 2.5 mIU/l in the first and 3 mIU/l in the both second and third trimesters, respectively), 54 (26.6%), 63 (31%), and 64 (31.5%) women had increased serum TSH levels.

There was significant difference in the number of women with TSH > 2.5 mIU/l in comparison to those with TSH > 3.9 mIU/l (p = 0.001). In TPOAb negative women median (IQR), TSH were 1.5 (0.8–2.6), 1.8 (1.1–2.7), and 1.8 (1.1–2.7) mIU/L in the first, second, and third trimesters, respectively. The values for TT4 ± SD were 13.5 ± 3.4, 14.1 ± 3.2, and 13.4 ± 3.3 µg/dl and for TT3 were 201 ± 50, 227 ± 60, and 226 ± 54 ng/dl, FT4I 13.05 ± 4.7, 14.1 ± 3.2, 13.5 ± 3.9 in the first, second, and third trimesters, respectively. The mean ± SD of TT4 was 12.9 ± 3.3 µg/dl in the first, 14.1 ± 3.1 µg/dl in the second, and 13.4 ± 3.2 µg/dl in the third trimester (p < 0.000). The mean ± SD of TT3 was 201 ± 51, 225 ± 58, and 227 ± 56 ng/dl in the first, second, and third trimesters, respectively, the differences being significant (p < 0.001). The mean ± SD of FT4I was 12.9 ± 4.5, 14.1 ± 3.4, and 13.5 ± 3.8 in the 3 consecutive trimesters (p < 0.001). A total of 16 (7.9%), 24 (11.8%), and 23 (11.3%) had TT4 out of range of our local reference interval in the first, second, and third trimester respectively, but it was 23 (11.3%), 25 (12.4%), and 23 (11.3%) based on FT4I reference intervals.

Thyroid autoantibodies

The median IQR of TPOAb was 9 (5–20), 10 (5–16), and 7 (5–14) IU/ml, in the first, second, and third trimester, respectively (◉ **Table 1**). TPOAb was positive in 29 (14.3%), 26 (12.8%), and 19 (9.4%) individuals in the first, second, and third trimesters, respectively. Out of 29 individuals who were TPOAb positive in the first trimester, 20 had positive titers in the second, and 15 in the third trimesters as well. A total of 6 developed TPOAb de novo in the second and 4 in the third trimesters of pregnancy. Of 174 women who were TPOAb negative during the first trimester, 6 and 4 individuals became TPOAb positive during the second and third trimesters, respectively. The median IQR of TgAb was 36 (16–84), 27 (11–56), and 26 (12–64) in the first, second and third trimesters, respectively. The kappa between TPOAb and TgAb positivity was 0.3 (p < 0.001), 0.2 (p < 0.001), and 0.1 (p = 0.002) in 3 consequent trimesters of pregnancy.

Hypothyroidism

Of the 203 pregnant women, 153 (75.4.8%), 157 (77.3%), and 157 (77.3%) were euthyroid in all the 3 trimesters of pregnancy. Considering our local reference ranges, a total of 23 (11.3%), 12 (5.9%), 13 (6.4%) had subclinical hypothyroidism in the first second and third trimester respectively, but they were 49 (24.1%), 31 (15.3%), and 34 (16.7%) when TSH > 2.5 mIU/l was considered in the first and > 3 mIU/l in both the second and third trimesters for definition of hypothyroidism. Considering our local reference ranges, TPOAb negative women, 17 (9.8%), 9 (5.2%), and 7 (4%) had subclinical hypothyroidism in the first, second, and the third trimester, respectively, but they were 42 (24.1%), 27 (15.5%), and 23 (13.2%) when TSH > 2.5 mIU/l was considered in first and > 3 mIU/l in both the second and third trimesters for definition of hypothyroidism. In total cohorts there was significant difference in the prevalence of subclinical hypothyroidism based on 2 different cut points (p = 0.001). Overt hypothyroidism was detected in 4, 5, and 1 women in the first, second and third trimesters of pregnancy; 4, 7, and 5 individuals were found to be suffering from overt hypothyroidism in 3 consecutive pregnancy trimesters based on arbitrary recommended TSH levels (◉ **Table 2**). A total of 19 (12.4%) pregnant women were euthyroid but had positive TPOAb in the first trimester and remained euthyroid during follow-up in second and third trimesters.

Discussion
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Our results showed a high prevalence of thyroid autoimmunity and hypothyroidism during pregnancy. If the trimester population- and trimester-specific interval is used, 11.3% in the first, 5.9% in the second, and 6.4% pregnant women of our cohort in the third trimester will be considered as having subclinical hypothyroidism; these figures would be 24.1%, 15.3%, and 16.7% for the cut point that is recommended by ATA guidelines [2], comparing the prevalence of subclinical and overt hypothyroidism with local population-specific reference intervals vs.

Table 1 Biochemical parameters of thyroid function during gestation in healthy iodine sufficient women.

| | Trimester | | |
	First	Second	Third
Total population (n = 203)			
TSH (mIU/l)*	1.7 (0.9–2.7)	1.9 (1.2–2.7)	1.8 (1.1–2.8)
TT4 (µg/dl)†	12.9 ± 3.3	14.1 ± 3	13.4 ± 3.2
TT3 (ng/dl)‡	201 ± 51	225 ± 58	227 ± 56
FT4I	12.9 ± 4.5	14.1 ± 3.4	13.5 ± 3.8
TPOAb (IU/ml)*	9 (5–20)	10 (5–16)	7 (5–14)
TPOAb negative women (n = 174)			
TSH (mIU/l)*	1.5 (0.8–2.6)	1.8 (1.1–2.7)	1.8 (1.1–2.7)
TT4 (µg/dl)†	13.5 ± 3.4	14.1 ± 3.2	13.4 ± 3.3
TT3 (ng/dl)‡	201 ± 50	227 ± 60	226 ± 54
FT4I	13.05 ± 4.7	14.1 ± 3.2	13.5 ± 3.9

* Values are given as Median (IQR)
† Values are given as mean ± SD
‡ Values are given as mean ± SD
TSH: Thyotropin; TT4: Total thyroxin; TT3: Total triiodothyronin; FT4I: Free T4 index

Table 2 Prevalence of thyroid dysfunction during pregnancy using national and international recommended reference ranges.

Gestation		Euthyroid	Hypothyroidism	Subclinical hypothyroidism	TSH > 2.5 mIU/l
First Trimester		153 (75.4.8%)			
	National		4	23 (11.3%)‡	
	International		4	49 (24.1%)	54 (26.6%)
Second Trimester		157 (77.3%)			
	National		5	12 (5.9%)‡	
	International		7	31 (15.3%)	63 (31%)†
Third Trimester		157 (77.3%)			
	National		1	13 (6.4%)‡	
	International		5	34 (16.7%)	64 (31.5%)†

* Data in parentheses shows percent
† TSH > 3 mIU/l was applied
‡ p = 0.001

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arbitrary cutoffs that are not specific for the population studied or the assay used.

The importance of diagnosis and treatment of thyroid dysfunction during pregnancy has been widely recognized. Pregnancy affects thyroid function tests in various ways. FT4 increases and serum TSH decreases during the first trimester, followed by FT4 decrease in later gestation as hCG values decline. However, FT4 tends to decrease in late gestation [1]. Because trimester specific reference ranges of TSH and T4 vary in different populations (due to differences in amount of iodine intake, ethnicity, sample size, study selection criteria and laboratory methods for assessment of thyroid function) and also due to changes of thyroid function during pregnancy, there is consensus that for each population, thyroid function must be defined based on normal reference limits. Because a different reagent is used to recognize distinct circulating TSH isoforms the results fluctuate even for the same sample [19].

We used our trimester specific TSH and TT4 reference ranges derived from the present population under study and also ATA guidelines to define thyroid disease and to compare the prevalence of hypothyroidism based on 2 different cutpoints [2, 17, 18] and significant differences between the prevalence of subclinical hypothyroidism. Application of an arbitrary pregnancy TSH reference interval that does not fit well with the specific population involved large increase of the number of women diagnosed with hypothyroidism, imposing a heavy financial burden on our medical care system.

There is no doubt that untreated overt hypothyroidism results in not only adverse pregnancy outcomes but also leads to permanent cognitive, neurological, and developmental abnormalities of offspring if untreated [20]. The bulk of evidence shows that subclinical hypothyroidism during pregnancy has adverse outcome; there are, however, conflicting results regarding the adverse effects of subclinical hypothyroidism on fetal neurodevelopment [21].

The prevalence of subclinical hypothyroidism in our study was higher than that reported in previous studies [22, 23]. Klein et al. found this to be 2.5% using a TSH cutoff of 6.0 mIU/l, which is higher than the upper limit of our local reference intervals [23]. This may also be due to a higher prevalence of TPOAb positivity in the first trimester in the pregnant, women of our study; however as thyroid autoimmune activity decreases in pregnancy, the prevalence of hypothyroidism also decreased in the second and third trimesters of their pregnancy. The prevalence of overt hypothyroidism was comparable to those of other studies. Sahuet et al. reported the prevalence of subclinical hypothyroidism and overt hypothyroidism in women to be 6.47 and 4.58%, respectively, using TSH >5.5 mIU/l as abnormal value [24]. Recently Blatt et al. reported the prevalence of hypothyroidism to be 15.5% during pregnancy [25]. Our study shows that, without universal screening, probably a significant number of such pregnant women with thyroid dysfunction might not be identified, but each woman had 3 sera all measured at the end. The measurement of thyroid autoantibodies in pregnant women is mainly useful in predicting the risk for development or deterioration of maternal thyroid dysfunction [26].

Additionally the presence of TPOAb positivity predisposes the pregnant women to postpartum thyroid dysfunction or postpartum lymphocytic thyroiditis. We found TPOAb in 13.9% of pregnant women in the first trimester, which decreased to 9.3% in the third trimester. Presence of TPOAb, which was reported to be detected in 10% of women in early pregnancy, is also associated with decreased thyroid functional reserve and may put the pregnant women at risk of developing hypothyroidism as gestational age increases [27].

Our study has some limitations. One of our limitations was the thyroid function tests were performed just once in this study. Second, our cohort may not represent other populations with different socioeconomic statuses in Tehran, because their socioeconomic statuses range between low to medium. Third, we relied on patient recall in ascertaining personal and family history of their thyroid and other autoimmune disorders and these were not verified by reviewing case records. Fourth, we excluded 147 pregnant women at the beginning of study due to missing thyroid function tests, so results could have been skewed. One of the strengths is that we used the trimester specific reference ranges of thyroid function tests of this population to define overt and subclinical hypothyroidism. Moreover, we have the data regarding thyroid function tests in 3 trimesters without loss to follow-up to evaluate the changes of thyroid parameters.

In conclusion, this study showed a high rate of thyroid hypofunction and TPOAb positivity in the pregnant women examined. The evaluation of thyroid hormone needs gestational age-specific values. Hypothyroidism during pregnancy may be more common than is generally believed.

Conflict of Interest
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The authors declare that they have no conflicts of interest in the authorship or publication of this contribution.

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