Published in final edited form as:

Ther Drug Monit. 2007 October ; 29(5): 553–559. doi:10.1097/FTD.0b013e31815709ac.

Gestation-Specific Thyroxine and Thyroid Stimulating Hormone Levels in the United States and Worldwide

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Abstract

Background—Euthyroid women experience dramatic changes in the demand for thyroid hormone production as early as the first trimester of pregnancy. These changes are important for fetal neurodevelopment and organ development as well as maternal health and succesful full term pregnancy. Therefore, gestation-specific reference intervals assist in appropriate clinical management of thyroid disease in pregnancy to ensure maternal and fetal health.

Objective—To determine trimester-specific levels of serum thyroxine (T4) and thyroid stimulating hormone (TSH) in the U.S. population based on the National Health and Nutrition Survey III and compare these with published trimester-specific T4 and TSH means and medians obtained in other countries worldwide.

Methods—Trimester-specific means and medians for T4 and TSH were determined for the U.S. population based on the National Health and Nutrition Survey III database (1988–1994). These were compared with trimester-specific means and medians of other countries in the published literature.

Results—Mean serum T4 levels for the U.S. population were 141.35, 152.95, and 142.65 nmol/L in the three trimesters, respectively, whereas mean serum TSH levels were 0.91, 1.03, and 1.32 mIU/L.

Conclusions—Gestation-specific mean T4 and TSH levels for the representative U.S. population are well within the trimester-specific reference intervals. T4 and TSH measured during pregnancy in longitudinal and cross-sectional studies of populations worldwide demonstrate that, in some populations, T4 and TSH levels are outside the normal trimester-specific reference intervals.

Keywords

trimester-specific; pregnancy; thyroid stimulating hormone; triiodothyronine; free thyroxine; iodine

INTRODUCTION

During pregnancy, hormonal changes and increased metabolic demands lead to profound alterations in the biochemical parameters of thyroid function, resulting in an increase in

thyroid hormone synthesis. Thyroid hormone adequacy is crucial for normal fetal neurodevelopment and is essential for the developing fetal brain, heart, and lungs.¹ Thyroid disease is a common endocrine condition in women of reproductive age.² The most common thyroid disorder occurring around or during pregnancy is thyroid hormone deficiency, or hypothyroidism. If detected, an underactive thyroid gland can be easily treated with thyroid hormone replacement therapy. Because iodine is an essential element in thyroid hormone synthesis, median urinary iodine excretion levels serve as monitoring tools for the evaluation of the adequacy of iodine nutrition of a given population.^{3–5} However, the use of thyroid stimulating hormone (TSH) and serum thyroxine (T4) in pregnancy as screening tools for epidemiologic studies has not proven adequate, and no relationship has been shown between urinary iodine and TSH or T4 levels.⁶

Urinary iodine (UI) is not a valid tool for the estimation of thyroidal adequacy and iodine nutrition sufficiency on an individual basis, because it may only indicate the most recent dietary intake. Individual thyroidal adequacy can be measured by serum free thyroxine (FT4), total T4, total triiodothyronine (T3), TSH, and thyroglobulin. To detect abnormalities in thyroid hormone concentrations during the progression of pregnancy, it is necessary to determine their normal ranges throughout pregnancy. There is, of course, an advantage for using two or more thyroid function indicators, such as both T4 and TSH.

Clinically, enhanced glandular stimulation associated with iodine restriction can be assessed using biochemical parameters such as relative hypothyroxinemia (decreased serum FT4),⁷ changes in serum TSH (usually remaining within the normal range), frequent doubling of the initial TSH concentrations near term,⁸ and changes in thyroglobulin concentrations.⁹ Comparison of these parameters with the reference intervals during normal pregnancy is imperative.¹⁰ After delivery, there is a rapid reversal of these pregnancy-related changes, and serum T4 binding globulin as well as T4 and T3 concentrations return to pregestational levels within 4 to 6 weeks.

TRIMESTER-SPECIFIC CHANGES IN THYROID FUNCTION

Trimester-specific thyroid hormone reference intervals are especially important because thyroid insufficiency may be associated with fetal neurodevelopment deficits and adverse obstetric outcome. It is important to recognize that normal reference intervals are method specific and depend on the method of analysis. Furthermore, ethnicity and age may lead to different ranges considered normal for that specific population in health, although Price et al¹¹ found no differences in trimester-specific thyroid hormones between the Asian and white populations in the United Kingdom. While Rasmussen et al¹² found no changes in TSH levels during pregnancy and 1 year post partum, and Romano et al¹³ found TSH remains within a normal range, this is not true in areas of some iodine deficiency⁹ where TSH increased and FT4 decreased throughout gestation.

Despite the importance of TSH measurements in the assessment of thyroid status before or during pregnancy, FT4 measurements are also useful in determining thyroidal status, although it represents only a minute fraction (0.02%) of the total T4. However, because of the very low concentrations and protein binding, FT4 is more difficult to measure.¹⁴ A direct equilibrium dialysis method is considered analytically accurate and is the current gold standard.^{15,16} Compared with equilibrium dialysis, other FT4 immunoassays show significant biases related to protein-bound T4 or to the serum T4-binding capacity,¹⁷ resulting in a high, method-dependent number of decreased results.^{18–20} The presence of circulating iodothyronine-binding autoantibodies that interfere with total T4 and T3 immunoassays is a known phenomenon.^{21–24} These autoantibodies may give falsely high or falsely low values of thyroid hormone measurements, depending on the assay separation

method used, and are often in discordance with the clinical features.^{25–28} As discussed above, direct serum FT4 and FT3 (free triiodothyronine) measurements are technically difficult to determine because they are measured in the picomole range and must be free from interference by the much higher total hormone concentrations to be valid.

TRIMESTER-SPECIFIC CHANGES IN MATERNAL TSH IN THE UNITED STATES

The National Health and Nutrition Survey (NHANES) is a cross-sectional ongoing study of the U.S. population designed to give the national normative estimates of the health and nutrition status of the U.S. civilian, noninstitutionalized population.²⁹ National surveys of urinary iodine excretion to determine iodine sufficiency of the population can be misleadingly reassuring because the median is usually skewed toward the higher end of the distribution curve of urinary iodine excretion. For example, in the United States, a country considered to be iodine-sufficient (median urinary iodine was 168 $\mu\text{g/L}$ in NHANES 2001–2002), as many as 15% of the women of childbearing age and almost 7% of pregnant women had iodine excretion levels below 50 $\mu\text{g/L}$, which can indicate moderate iodine deficiency.³⁰

The NHANES 1988–1994 (NHANES III) database was used to determine trimester-specific means and medians for T4 and for TSH in the U.S. population. An iodine-sufficient population, as defined by the World Health Organization has a median UI $\geq 100 \mu\text{g/L}$ and with a UI of less than 50 $\mu\text{g/L}$ in no more than 20% of the population. Analysis of the NHANES III data indicates that, as a population, the U.S. population is iodine-sufficient according to World Health Organization criteria.³¹ The median urinary iodine concentration for the U.S. population (NHANES III) was $145 \pm 3 \mu\text{g/L}$; for pregnant women it was $141 \pm 14 \mu\text{g/L}$, whereas for nonpregnant women of reproductive age (15–44 yr) it was $127 \pm 4 \mu\text{g/L}$. Nevertheless, some subpopulations are mildly to moderately iodine-deficient. A closer look at NHANES III data indicates that over 25% of pregnant women and women of childbearing age had urinary iodine levels indicating an iodine intake lower than the recommended daily intake.³² In the same NHANES III survey, it was determined that 4.6% of the U.S. population (age 12 and up) were hypothyroid (overt and subclinical).³³

METHODS

The NHANES is an ongoing, stratified, multistage probability study designed to give national normative estimates of the health and nutritional status of the U.S. civilian, noninstitutionalized population. The survey, conducted through the Centers for Disease Control and Prevention, entails a comprehensive questionnaire, an expanded physical examination, and an extensive array of laboratory biomarkers. NHANES III, conducted between 1988 and 1994, represents (but does not include) all 50 states and the District of Columbia. Biological samples (urine and serum/plasma samples) were collected from participants for a large number of biochemical indicators of health status.

Using NHANES III database, we determined the means and medians for TSH and T4 for each month of gestation and for the three trimesters of pregnancy. The NHANES-III files (EXAM, LAB, and LAB2) were downloaded from the Centers for Disease Control and Prevention web site.²⁹ Information on sex, age at examination, pregnancy status, urinary iodine, creatinine, T4, TSH, anti-thyroid-peroxidase antibody (TPOAb), and anti-thyroglobulin antibody (TgAb) were extracted from these files and merged into a single analytical file on the basis of subject ID number.

T4 was measured using an immunoassay for T4 (Roche Molecular Biochemicals, Indianapolis, IN), which had a reference interval of 57.9 to 169.9 nmol/L (4.5–13.2 µg/dL). TSH was measured with a chemiluminescence immunometric assay (Nichols Institute Diagnostics, San Juan Capistrano, CA).¹⁴ The working range for this method is 0.01 to 50 mIU/L. At the time, the reference interval for the test was 0.39 to 4.6 mIU/L.

TgAb and TPOAb were measured by a highly sensitive, direct RIA (Radioimmunoassay) system (Kronus, San Clemente, CA).^{15,16} The reference interval for TPOAb was less than 0.5 IU/mL and for TgAb less than 1.0 IU/mL. NHANES III participants who reported having thyroid disease, goiter, or use of thyroid medications were excluded, as were subjects who were positive for anti-TgAb or TPOAb (or both). This excluded 29 pregnant women from the analysis.

RESULTS

Trimester-Specific Concentrations of Maternal TSH

Tables 1 and 2 summarize gestation-specific concentrations of T4 and TSH obtained from the NHANES database for the U.S. population. The geometric mean for TSH in the first trimester was 0.91 mIU/L, which increased as expected to 1.03 mIU/L during the second trimester and to 1.32 mIU/L in the third trimester. Similarly, the medians were 0.95, 1.10, and 1.20 mIU/L, respectively. These serum TSH levels are well within the reference intervals for pregnancy.²⁸ The decrease in TSH levels during the first trimester is well illustrated in the monthly means, in which TSH levels decreased in the second month of gestation to 0.83 mIU/L, increased in the second trimester to 1.25 mIU/L, and stabilized through the remainder of pregnancy (Table 1).

A comparison of these NHANES results with the serum TSH levels obtained in a longitudinal study of a well-followed healthy population shows a very similar trend.²⁶ The means are slightly lower than the medians. In comparison with non-pregnant women, TSH concentrations are lower in the first trimester, increase during the second trimester, and remain constant until delivery.²⁶

Trimester-Specific Concentrations of Maternal T4

The mean for T4 in the first trimester was 141.35 nmol/L, increased slightly to 152.95 nmol/L during the second trimester, and to 142.65 nmol/L in the third trimester (Table 2). The medians were very similar at 142.90, 155.7, and 146.05 nmol/L in the three trimesters, respectively. These serum T4 levels are well within the normal reference intervals for pregnancy when compared with other trimester-specific intervals established in a longitudinal study of iodine-sufficient thyroid-disease-free population^{26–28} (means 139.2, 142.4, 144.5 nmol/L, respectively, when using immunoassays). In the same study, the mean TSH levels were 0.89, 1.17, and 1.16 mIU/L in the three trimesters, respectively, and 1.06 1 year post partum. One must take into consideration that NHANES is a cross-sectional study and that some of the women included in the study may have been mildly or moderately iodine deficient, which would explain the increase in TSH levels in the third trimester (well within the normal range). Mean T4 concentrations increase during the first trimester from 130.42 to 154.77 nmol/L in midgestation. These levels are very similar to those obtained in the longitudinal study.²⁶ Similarly, the medians follow the same pattern and are within the reference interval.²⁶

In comparison with mean T4 levels in nonpregnant women (94.7 nmol/L), T4 concentrations measured in NHANES III, even during the first month of pregnancy, were much higher (130.43 nmol/L), increased steadily during the second trimester, and remained constant for the remainder of pregnancy.

DISCUSSION AND CONCLUSIONS

Reported here is an analysis of thyroid function (TSH and T4) in 216 pregnant women from the NHANES III database to determine trimester-specific mean and median TSH and T4 levels. TSH levels (both mean and median) are suppressed in the first trimester and recover to nonpregnant levels in the third trimester, whereas T4 levels (both mean and median) increased in the first trimester and remained high throughout pregnancy. During normal pregnancy, the increase in plasma volume and plasma concentration of T4 binding globulin result in a several-fold increase in the total T4 pool. In addition, the stimulatory effect of human chorionic gonadotropin on the thyroid induces a partial TSH suppression below the normal range at the end of the first trimester, returning to the levels seen before pregnancy in the second and third trimesters. These physiologic changes result in a 40% to 100% increase in thyroid hormone synthesis to meet maternal and fetal needs. The fetus is totally dependent on maternal T4 supply during the first trimester of gestation for normal neurologic development and nervous system maturation. It is therefore imperative that thyroid hormone synthesis is adequate. Accordingly, trimester-specific reference intervals for thyroid hormones provide an appropriate basis for clinical treatment of thyroid disease in pregnancy.

The data provided in Table 1 and Table 2 present gestation-specific means and medians for the U.S. population for T4 and TSH for each month during gestation and for the trimesters. NHANES III survey participants were iodine-sufficient as a population. However, more than 25% of pregnant women and women of childbearing age had urinary iodine levels representing an iodine intake lower than the recommended iodine intake. Nevertheless, trimester-specific T4 and TSH means and medians for the NHANES III subjects representing the U.S. population were well within the normal trimester-specific intervals.²⁸

Tables 3 and 4 summarize some trimester-specific thyroid function test data found in the literature. Both tables provide trimester-specific thyroid hormone and TSH concentrations for comparison, with the difference existing between some of the information given as the mean $\pm$ SD and the other as median (interquartile ranges). The tables combine either longitudinal or cross-sectional studies and reported means and reference intervals (Table 3) for TSH, T4, T3, FT4, and urinary iodide from the Europe, India, Africa, Middle East, and Japan.^{9,11,34–40} Medians and interquartile ranges from Singapore, Hong-Kong, China, Sudan, and Sweden are combined in Table 4.^{41–45} Comparison of these data suffers from several drawbacks because some of the studies rely on very few subjects, whereas others rely on hundreds and even thousands of participants. In addition, race or ethnicities are rarely noted. Inclusion and exclusion criteria are not consistent, nor are statistical methods of analysis, and in many of the studies, dietary intake and supplementation are not accounted for.

In addition, the tables contain valuable information, which can be difficult to compare because of the variation of units used, and therefore conversion factors are listed at the end of Table 3. What should be discerned from the given information are the hormone levels and trends of TSH/T4/T3 to determine whether a clinical problem exists.

As seen in Tables 3 and 4, there is an increase in TSH levels from the first trimester onward in areas of some iodine deficiency, whereas FT4 levels decrease. This is true for some countries in Europe and for Japan^{9,11,35,42} and is not as pronounced as the increase from 1.2 to 3.3 mIU/L during the third trimester in India.⁴¹ In women who gave birth to “small for date” babies, babies born with body weight less than 2.5 kg at term, the increase is visibly significant.³⁴ As can be seen in Table 3, these babies were born to mothers who showed an increase in their TSH levels from 2.9 mIU/L in the first trimester, 7.9 mIU/L in the second trimester, to 8.2 mIU/L in the third trimester.

In areas of iodine-sufficiency, TSH levels tend to remain constant, and T4 levels reach a stable level within the first few weeks of pregnancy (approximately 40–50% higher than post partum). In general, the trend for lower TSH in the first trimester persists throughout. Also, the increase in T4 relative to nonpregnancy and from first to second trimesters is seen in most studies. FT4 slightly decreases in most studies, although FT4 methods of analysis are notorious for their variability in results, even within the same study population.^{18,19,35}

Mild to moderate iodine deficiency is still present in certain countries or geographic areas despite national efforts to implement the mandatory use of iodized salt to affect T4 and TSH levels.^{36,37} Furthermore, iodine intake may vary unexpectedly because of significant variations in the natural iodine content of the local food and water and because of the variability in response to supplementation.^{38,39} Therefore, in comparing gestation-specific data, it is important to note the methods of analysis, take into account iodine status, group sample size, subject inclusion, and exclusion criteria, determine statistical methods used for data analysis and study design (cross-sectional or longitudinal), as well as note ethnicity, age, and singleton pregnancy status.

Acknowledgments

The authors would like to thank Dr. John C. Pezzullo for his assistance with the statistical analysis.

Dr. O. P. Soldin is supported in part by grant 5U10HD047890-03, Obstetric Pharmacology Research Unit, National Institutes for Child Health and Development and the Office of Research on Women's Health, The National Institutes of Health.

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TABLE 1

National Health and Nutrition Survey (NHANES) III Mean Thyroid Stimulating Hormone (TSH) Concentrations in Pregnant Women, N = 216^{*,†}

Month	1	2	3	4	5	6	7	8	9
n	12	29	30	29	31	23	21	25	16
Mean TSH (mIU/L)	1.38	0.84	0.83	0.88	1.26	0.96	1.11	1.23	1.86
SEM	1.10	0.20	0.23	0.31	0.43	0.26	0.31	0.33	0.91
Median (mIU/L)	1.38	0.83	.91	1.00	1.25	1.08	1.08	1.10	1.75
	Trimester 1		Trimester 2		Trimester 3				
n	71		83		62				
Mean TSH (mIU/L)	0.91		1.03		1.32				
SEM	0.17		0.20		0.27				
Median (mIU/L)	0.95		1.10		1.20				

* Geometric means; newly calculated from NHANES III (1988–1994) database.

[†] NHANES III median UI for pregnant women $141 \pm 14 \mu\text{g/L}$ and for nonpregnant women of reproductive age (15–44 yr) $127 \pm 4 \mu\text{g/L}$.³¹ More than 25% of pregnant women and women of childbearing age had UI levels representing an iodine intake lower than recommended iodine intake.³²

TABLE 2

NHANES III Mean T4 Concentration in Pregnant Women, N = 216^{*,†}

Month	1	2	3	4	5	6	7	8	9
n	12	29	30	29	31	23	21	25	16
Mean T4 (nmol/L)	130.42	137.13	149.80	150.59	154.77	153.49	152.30	133.95	143.58
SEM	6.78	4.86	4.49	4.23	3.31	3.73	6.49	5.41	7.49
Median (nmol/L)	139.00	139.00	153.80	153.20	160.90	155.70	153.20	136.40	149.30
Trimester	Trimester 1			Trimester 2			Trimester 3		
n	71			83			62		
Mean T4 (nmol/L)	141.35			152.95			142.65		
SEM	3.07			2.17			3.73		
Median (nmol/L)	142.90			155.70			146.05		

* Newly calculated from NHANES III (1988–1994) database.

[†] NHANES III median UI for pregnant women $141 \pm 14 \mu\text{g/L}$ and for nonpregnant women of reproductive age (15–44 years) $127 \pm 4 \mu\text{g/L}$.³¹ More than 25% of pregnant women and women of childbearing age had UI levels representing an iodine intake lower than the recommended iodine intake.³²

TABLE 3
Worldwide Trimester Specific Thyroid Function Tests Means and Reference Intervals

Country	Analyte	Means (Reference Intervals)			
		Trimester 1	Trimester 2	Trimester 3	Post Partum
U.K. Asians (2001) [11]	TSH (mIU/L)	0.9 (0.6–1.3)	1.3 (1.0–1.8)		1.3 (1.1–1.6)
	FT4 (pmol/mL)	12.6 (11.8–13.4)	11.5 (10.9–12.1)		13.1 (12.6–13.6)
	Urinary iodine µg/L	125	170		
U.K. whites (2001) [11]	TSH (mIU/L)	0.9 (0.7–1.1)	1.3 (1.2–1.5)		1.7 (1.5–1.9)
	FT4 (pmol/mL)	12.4 (12.0–12.8)	11.5 (11.2–11.8)		13.2 (12.7–13.6)
	Urinary iodine µg/L	125	170	147	
Belgium (1990) [9]	TSH (mIU/L)	0.75 ± 0.04	1.05 ± 0.04	1.29 ± 0.04	(0.2–4.0 mIU/L)
	T4 (nmol/L)	138 ± 3	148 ± 3	148 ± 3	(50–150 nmol/L)
	FT4 (nmol/mL)	17.9 ± 0.3	14.5 ± 0.1	13.4 ± 0.1	(10–26 nmol/mL)
	UI (µg/L)	58 ± 3	58 ± 3	53 ± 3	(150 µg/L)
Italy (2002) [36]	TSH (µU/mL)	1.1 ± 0.08			
	Tg (ng/mL)	25 ± 5.6			
	FT4 (pg/mL)	10.4 ± 0.3			
India (2003) [37]	UI (µg/g cr)	116 ± 14			
	TSH (mIU/L)	1.20	2.12	3.3	
	T4 (nmol/L)	164.50	165.80	159.90	
	T3 (nmol/L)	1.85	2.47	1.82	
Hungary (2004) [35]	TSH (mIU/L)		1.6 ± 0.8	1.7 ± 0.7	1.3 ± 0.5 (23–4.0)
	T4 (nmol/L)		133 ± 24		97 ± 9 (5–151)
	T3 (nmol/L)		2.8 ± 0.5		2.0 ± 0.3 (1.2–3.0)
	FT4 ELISA (pmol/L)		10.4 ± 1.1	6.5 ± 1.1	15.6 ± 2.8 (11.8–24.6)
Nigeria (2005) [34]	FT4 MEIA (pmol/L)		14.3 ± 1.3	11.4 ± 1.5	16.3 ± 2.4 (9.1–23.8)
	FT4 RIA (pmol/L)		12.7 ± 1.8	8.5 ± 2.0	16.1 ± 2.1 (10–26)
	TSH (mIU/L)	2.7 ± 0.9	2.12 ± 1.6	2.29 ± 2.1	3.1 ± 1.9
	T4 (nmol/L)	129.1 ± 34.1	157.2 ± 38.2	173.1 ± 42.3	139.6 ± 35
	T3 (nmol/L)	2.6 ± 0.48	2.7 ± 0.62	2.91 ± 0.51	2.7 ± 0.52
	TSH (mIU/L) w/SFD babies	2.9 ± 0.89	7.9 ± 2.1	8.2 ± 2.9	7.4 ± 2.0
	T4 (nmol/L) w/SFD babies	84.2 ± 15.2	107.6 ± 18.1	121.4 ± 23.3	88.2 ± 16.3

Country	Analyte	Means (Reference Intervals)			
		Trimester 1	Trimester 2	Trimester 3	Post Partum
Japan (2005) [38]	T3 (nmol/L) w/SFD babies	1.9 ± 0.36	1.96 ± 0.42	2.4 ± 0.68	2.1 ± 0.41
	Urinary iodine (µg/L) w/SFD babies				79 ± 24
	TSH (mIU/L)	1.05 ± 0.97	1.51 ± 0.94	1.23 ± 0.75	2.96 ± 0.51 (0.27–4.2)
	FT3 (pg/mL)	3.60 ± 0.50	3.39 ± 0.44	3.17 ± 0.43	3.57 ± 55 (2.6–5.1)
United Arabs (2006) [39]	FT4 (ng/dL)	1.43 ± 0.21	1.11 ± 0.13	1.02 ± 0.15	1.08 ± 0.14 (1.0–1.8)
	TSH (mIU/L)	0.71 (0.06–8.3)	1.04 (0.17–5.9)	1.20 (0.21–6.9)	1.32 (0.3–4.32)
	FT4 (pmol/L)	14.6 (8.9–24.6)	12.7 (8.4–19.3)	12.0 (8.0–18.0)	13.7 (9.8–18.6)
	TSH (mIU/L)	0.63 (0.04–9.3)	1.1 (0.23–5.7)	1.30 (0.31–5.3)	
Other Arabs (2006) [39]	FT4 (pmol/L)	14.9 (10.5–22.3)	13.3 (9.5–18.7)	12.4 (8.8–17.4)	
	TSH (mIU/L)	0.95 (0.12–7.4)	1.30 (0.3–5.5)	1.1 (0.30–4.85)	
	FT4 (pmol/L)	15.7 (11.3–2.19)	13.4 (9.7–18.5)	12.1 (8.9–16.6)	
	TSH (mIU/L)	0.89 ± 0.08	1.17 ± 0.08	1.16 ± 0.08	1.06 ± 0.07
Sweden (2004) [29]	T4 MS/MS (nmol/L)	127.7 ± 3.6	127.7 ± 3.6	129.3 ± 3.6	89.2 ± 2.90
	T3 MS/MS (nmol/L)	2.7 ± 0.09	2.8 ± 0.1	3.2 ± 0.1	1.9 ± 0.06
	FT4 (pmol/L)	12.3 ± 0.4	10.5 ± 0.3	10.5 ± 0.2	13.7 ± 0.5
	Tg (ng/mL)	15.48 ± 1.96	14.92 ± 2.05	18.55 ± 2.84	13.95 ± 1.6
	Urinary iodine (µg/L)	180 µg/day	170 µg/day	145 µg/day	

To convert to SI units, use www.unc.edu/~rowlett/units/scales/clinical_data.html To convert to SI units: T4 µg/dl × 12.87 to nmol/L; T3 ng/dL × 0.0154 to nmol/L; FT4 ng/dL × 12.87 to pmol/L.

TSH, thyroid stimulating hormone; FT4, serum free thyroxine; T4, serum thyroxine; Tg, thyroglobulin; T3, triiodothyronine; ELISA, enzyme-linked immunosorbent assay; MEIA, microparticle enzyme immunoassay; RIA, radioimmunoassay; SFD, small for date; FT3, serum free triiodothyronine; MS/MS, tandem mass spectrometry.

TABLE 4
Worldwide Trimester Specific Thyroid Function Tests Medians and Interquartile Ranges

Country	Analyte	Median (IQR)					Post Partum
		Trimester 1	Trimester 2	Trimester 3			
Singapore (2001) [41]	TSH (mIU/L)	0.65	1.2				
	Urinary iodine (µg/L)	107 µg/L	116 µg/L	124 µg/L			105 µg/L
Sweden (2000) [42]	TSH (mIU/L)	1.0 (0.6–1.5)	1.2 (0.8–1.7)	1.7 (1.2–2.5)			
	T3 (nmol/L)	2.8 (2.5–3.2)	2.6 (2.1–3.0)	2.6 (2.2–3.0)			
	FT4 (pmol/mL)	11.7 (10.8–12.6)	8.8 (7.8–9.8)	8.7 (7.7–9.7)			
	Urinary iodine (µmol/L)	0.7 (0.5–0.9)	0.7 (0.4–0.8)	0.6 (0.4–0.8)			
Sudan (2000) [42]	TSH (mIU/L)	1.1 (0.5–1.5)	1.2 (0.7–1.8)	1.0 (0.6–1.6)			
	T3 (nmol/L)	2.6 (2.1–3.2)	2.7 (2.2–3.5)	2.6 (2.2–2.9)			
	FT4 (pmol/mL)	11.4 (9.6–13.4)	9.6 (8.6–10.8)	10.2 (9.4–12.6)			
	Urinary iodine (µmol/L)	0.3 (0.2–0.4)	0.2 (0.2–0.3)	0.3 (0.2–0.4)			
Hong Kong (2000) [43]	TSH (mIU/L) (Ref range: 0.23–3.4)	0.49 (0.12–1.00)	0.96 (0.62–1.28)	0.95 (0.60–1.36)			1.15 (0.74–1.58)* 1.14 (0.81–1.61) ‡
	FT4 (pmol/L) (Ref range: 12–23)	13.4 (12.2–15.0)	11.9 (10.7–13.1)	11.7 (10.1–13.0)			14.5 (13.1–16.0)* 14.4 (13.0–15.8) ‡
	T4 (nmol/L) (64–152)	154 (132–176)	126 (110–143)	125 (106–142)			89 (81–98)* 92 (82–101) ‡
	Urinary iodine (µmol/L)	0.84 (0.60–1.09)	0.91 (0.65–1.14)	0.98 (0.72–1.24)			0.83 (0.56–1.08)* 0.79 (0.51–1.14) ‡
Sudan (2000) [44]	TSH (mIU/L)		2.2 (1.7–2.7)	1.0 (0.8–1.9)			2.2 (1.7–2.7) ‡
	Tg (µg/L)		29 (13.5–44.5)	27 (13.5–40)			29 (13.5–44.5) ‡
	T3 (nmol/L)		2.2 (1.9–2.5)	2.6 (2.2–2.9)			2.2 (1.9–2.5) ‡
	FT4 (pmol/L)		9.7 (8.5–10.4)	8.7 (7.3–9.4)			9.7 (8.5–10.4) ‡
	Urinary iodine (µmol/L)		0.4 (0.2–0.5)	0.3 (0.1–0.4)			0.4 (0.2–0.5) ‡
China (2001) [45]		Week 7 week 11	Week 15 week 19 week 23	Week 27 week 31 week 35 week 39			
	TSH (mIU/L)	1.22 (0.05–2.3)	0.87 (0.03–2.8)	1.09 (0.08–3.5)			1.17 (0.39–3.51)
		0.8 (0.03–2.3)	1.1 (0.03–3.1)	1.28 (0.46–3.8)			
			1.33 (0.03–3.7)	1.28 (0.13–3.4)			
				1.56 (0.03–3.56)			
	FT3 (pmol/L)	3.9 (3–5.7)	3.7 (2.8–4.9)	3.2 (2.5–4.1)			3.9 (3.3–6.2)
		4.0 (3–5.7)	3.6 (2.5–4.9)	3.1 (2.3–3.9)			

Country	Analyte	Median (IQR)			
		Trimester 1	Trimester 2	Trimester 3	Post Partum
	FT4 (pmol/L)		3.5 (2.8–4.2)	3.4 (2.4–4.1)	
		14.8 (11.8–20.8)	13.4 (10.1–17)	4.2 (2.4–4.2)	
		16.2 (11.1–22.9)	11.8 (9.5–15.4)	11 (8.7–15.1)	14.2 (10.7–18)
			11.5 (8.1–16.7)	11.45 (7.8–13.7)	
				11.6 (8.5–14.4)	
				11.1 (9.1–15.6)	

IQR, interquartile range; TSH, thyroid stimulating hormone; T3, triiodothyronine; FT4, serum free thyroxine; T4, serum free thyroxine; Tg, thyroglobulin; FT3, serum free triiodothyronin.

*Six weeks post partum.

†Three months post partum.