

Is TSH a Reliable Indicator of Thyroid Hormone Status in Pregnancy?

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ABSTRACT

Thyroid screening is recommended during pregnancy with serum thyrotropin (TSH) as the primary test. However, since human chorionic gonadotropin, the serum hallmark of pregnancy, has TSH-like effects, the adequacy of TSH as a screening tool in this constellation requires further study. This study aimed to evaluate the relationship between TSH and thyroid hormones during pregnancy in order to determine if TSH is an adequate screening tool. This was a retrospective study utilizing the Clalit Health Service, Jerusalem district database between 2006–2017 in which we analyzed TSH, FT4 and FT3 measurements from 32430 pregnancies resulting in live birth. We grouped FT4 and FT3 levels by trimester and by the following TSH levels: (1) below 0.1/0.2/0.3 mIU/l, (2) 0.1–2.5/0.2–3.0/0.3–3.0 mIU/l, (3) 2.6–4.0/3.1–4.0 mIU/l, (4) 4.1–10.0 mIU/l and (5) above 10.0 mIU/l. In the first trimester, the most important for fetal brain development, FT3 was below normal, defined as below the 2.5th percentile for the population, in only 15.3% of tests with TSH over 10 mIU/l. FT4 was below normal in only 12.8% of such tests. Similar findings were noted for the second and third trimesters. As expected, there were far less abnormal tests when lower TSH cutoff levels were tested. In conclusion, TSH levels beyond the range accepted as normal do not, in most cases, reflect abnormal thyroid hormone levels during pregnancy. TSH is not a good screen for overt hypothyroidism in pregnancy. This may be due, at least in the first trimester, to thyrotropic effects of HCG.

Introduction

Maternal thyroid dysfunction has been associated with a variety of adverse fetal and maternal effects, including increased risk of pre-term birth, placental abruption, fetal demise, future impaired neurological development, and maternal post-partum thyroid disease [1, 2]. Thyroid hormones regulate gene expression during fetal developmental stages and appropriate levels of these hormones appear to be critical for fetal brain development through control of gene transcription in neural cells [3]. Maternal laboratory measurement of thyroid function plays an important role in both low and high-risk pregnancy follow up [4] and is critical in order to achieve optimum fetal and neonatal outcomes. However, reference ranges for thyroid function in pregnant women differ significantly from those of non-pregnant women [4] due to the physiological changes mediated primarily by human chorionic gonadotropin (hCG) [5]. Therefore, utilization of non-pregnant reference intervals to interpret thyroid function in pregnant women may potentially cause suboptimal patient care [4, 6] through misclassification of normal results as abnormal and vice versa.

The interpretation of gestational thyroid function tests depends on the stage of pregnancy [7]. Reference intervals for thyroid hormones in pregnancy are mostly trimester-specific and predominantly refer to thyroid stimulating hormone (TSH) alone [6, 8]. The American Thyroid Association (ATA) and the United States National Academy of Clinical Biochemistry (NACB) both recommend using population-based, trimester-specific reference ranges for TSH and serum free Thyroxine (FT4) [6, 8]. TSH is generally considered the primary test for evaluating thyroid status during pregnancy. FT4, which also changes with gestational age advancement, particularly between the first and second trimester [9, 10] is considered a complementary test as well as free triiodothyronine (FT3), which is less commonly tested. In this respect it is noteworthy that triiodothyronine (T3) has been shown to regulate gene transcription in neural cells during fetal developmental stages and appropriate levels of this hormone appear to be critical for fetal brain development [3].

When population-based references are unavailable, the ATA recommends using a fixed upper threshold of 2.5 mIU/L for TSH during pregnancy for thyroid peroxidase antibodies (TPOAb) positive women. It is not clear what the recommendations are for the 2.5–4 mIU/L range of TSH levels. For the range of TSH between 4 and 10 mIU/L for TPOAb negative women no clear recommendation is given ("may be considered..."). The ATA recommends "consideration" (as opposed to "maybe considered") of levothyroxine therapy for thyroid peroxidase antibodies (TPOAb) negative women when their TSH level is greater than 10.0 mIU/L [8]. Clearly, this prestigious group cannot make clear recommendations because the evidence base is insufficient. Similarly, in the UpToDate physicians' reference, guidelines for screening and therapy of hypothyroidism in pregnancy are based on expert opinions with different recommendations by different experts in the same algorithm! [11].

Furthermore, the different TSH cutoffs, used for deciding whether to repeat thyroid function measurements or to initiate thyroid hormone treatment, are based on the assumption that between the low and high TSH cutoffs the levels of FT4 and FT3 levels are "normal". However, there are insufficient data regarding the normal range of thyroid hormones during pregnancy and their relation to the TSH cut-off levels.

Our objective was to analyze FT4 and FT3 levels in relation to recommended pregnancy TSH cut-off levels in order to evaluate the relevance of TSH cut-off levels to thyroid function in pregnancy. We did not intend to evaluate whether subclinical hypothyroidism is detrimental, and this issue may require further study.

Subjects and Methods

We performed a retrospective study utilizing the Clalit health service, Jerusalem district, database between January 2006 and February 2017. Data were collected from electronic medical files of all pregnant women tested by request of physicians in community clinics for TSH (mIU/L) and in some patients, FT4 (pmol/L) and FT3 (pmol/L) as well. If multiple tests were done during pregnancy only the first test was used for calculating gestation-duration appropriate levels (see results in ► Table 1 and ► Fig. 1).

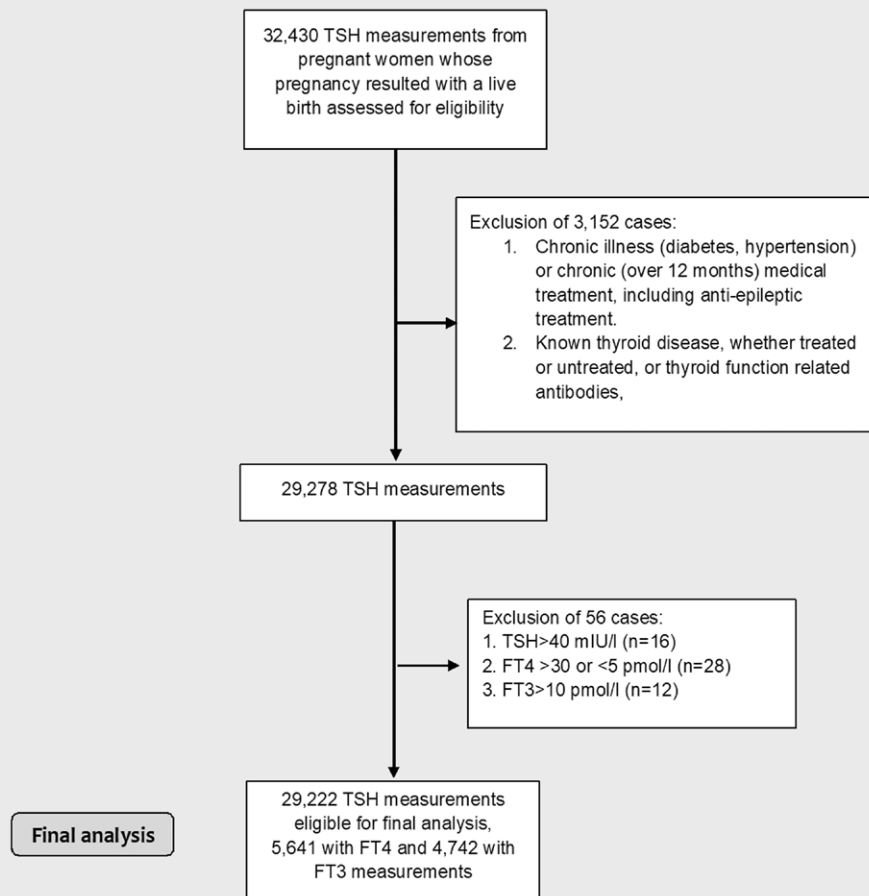
Inclusion criteria were women with a TSH measurement during pregnancy and a consequent live birth. Exclusion criteria were gestational trophoblastic disease, diabetes mellitus, chronic hypertension or any chronic medical therapy for at least 12 months prior to the current pregnancy. Women receiving anti-epileptic drugs or lithium prior to or during pregnancy were also excluded. Similarly, women with a known diagnosis of hyperthyroidism, hypothyroidism, positive titers of anti-thyroid peroxidase or anti-thyroglobulin and women who had been or were currently treated with methimazole, propylthiouracil, levothyroxine, recombinant thyrotropin, or glucocorticoids were excluded from the study.

Gestational age was calculated using the date of last menstrual period in combination with ultrasound measurements of crown-

► **Table 1** Population based thyroid function tests in pregnant women by trimester of pregnancy.

	TSH (mIU/L)	FT4 (pmol/L)	FT3 (pmol/L)
1st Trimester			
n	19374	3076	2865
Mean ± SD (median)	1.93 ± 1.72 (1.61)	14.53 ± 2.39 (14.40)	4.92 ± 0.78 (4.80)
2.5 percentile	0.19	10.40	3.70
97.5 percentile	5.42	19.90	6.90
2nd trimester			
n	7281	1716	1257
Mean ± SD (median)	2.21 ± 1.77 (1.86)	12.99 ± 1.9 (12.89)	4.21 ± 0.61 (4.17)
2.5 percentile	0.39	9.63	3.21
97.5 percentile	5.95	16.91	5.78
3rd trimester			
n	2567	849	620
Mean ± SD (median)	2.38 ± 1.69 (2.09)	12.49 ± 2.05 (12.30)	3.98 ± 0.64 (3.90)
2.5 percentile	0.41	9.14	3.08
97.5 percentile	5.84	16.88	5.35

TSH: Thyrotropin; FT3: Free triiodothyronine; FT4: Free thyroxine.



► **Fig. 1** Flow chart for application of exclusion criteria.

rump length (CRL) in the first trimester, as CRL is considered to be the most reliable sonographic parameter for evaluation of gestational age (especially in the first trimester) [12]. For thyroid function tests in the second and third trimesters, gestational age was established based on last menstrual period and ultrasound dating performed in the first trimester if available or, otherwise, a later sonographic dating of gestational age.

TSH, FT3, and FT4 were measured using a commercial kit (Cobas kits used on modular analytics E-170 analyzer, Roche Diagnostics, Mannheim, Germany). TSH, FT4 and FT3 tests were ordered by either gynecologists or community physician's as they saw fit, and even when no thyroid abnormality was suspected.

We evaluated FT4 and FT3 mean, median, standard deviation (SD) and 2.5 and 97.5 percentiles in each trimester and compared those of our cohort with widely used gestational TSH cut-off levels [8, 13] as follows: (1) Below 0.1 mIU/l (first trimester), 0.2 (second trimester) and 0.3 (third trimester) mIU/l; (2) 0.1–2.5 mIU/l (first trimester), 0.2–3.0 mIU/l (second trimesters) and 0.3–3 mIU/l (third trimester); (3) 2.6–4.0 mIU/l (first trimester) and 3.1–4.0 mIU/l (second and third trimester); (4). 4.1–10.0 mIU/l; (5) TSH above 10.0 mIU/l.

We also calculated mean, median, standard deviation (SD) and 2.5 and 97.5 percentiles according to bi-weekly gestational age (5

weeks or less, 6–7, 8–9, 10–11, 12–13, 14–15, 16–17, 18–19, 20–21, 22–23, 24–25, 26–27, 28–29, 30–31, 32–33, 34–35, 36–37, 38–39) in our population. This enabled us to create population specific reference ranges and assess trends in these parameters throughout gestation. We defined trimesters of pregnancy as follows: First trimester, i.e., ≤ 13 weeks gestation; second trimester: 14–27 weeks and the third trimester: beyond 28 weeks of gestation.

Ethics

All data retrieval and analyses were computerized and anonymous. Clalit Health Service institutional review board approved the study (IRB ID number 015/2015, received in March 2015).

Statistical analysis

We calculated frequency of every TSH level category through the trimesters of pregnancy. We presented continuous data as mean \pm standard deviation (SD) and assessed significance of associations between TSH and FT4 and FT3 with the student's t-test and Pearson correlation coefficient ("R"). All statistical tests were two-tailed and a p-value of < 0.05 indicated a statistically significant difference. All analyses were conducted using statistical package for the social sciences (SPSS) (for Windows software, version 23; IBM Corp) and graphs were prepared with "excel" 2013 software.

Results

Study population

Overall, 32 430 TSH measurements from pregnant women whose pregnancy resulted with a live birth were evaluated. We excluded women for evidence of being unhealthy and outliers with extreme thyroid hormone results (see details in ► Fig. 1). FT4 levels were available for 5641 of these women and FT3 measurements were available, as well as FT3, for 4742 women.

In the entire study population, median maternal age was 29.44 years (range 16–49). In the first trimester, 19 374 women were tested, with a mean maternal age for women tested during this trimester of 29.6 years and median gestational age of 8 weeks. In the second trimester, 7281 women were tested. The mean maternal age and median gestational age for these women were 29.62 years and 18 weeks respectively. For the third trimester, 2567 women were tested. Their mean maternal age and median gestational age were 30.04 years and 32 weeks, respectively. The mean, median standard deviation and 2.5th and 97.5th percentiles of TSH, FT4 and FT3 for each trimester and are shown in ► Table 1

TSH, FT4, and FT3 levels throughout pregnancy

The progress of TSH, FT4, and FT3 levels through pregnancy is presented in ► Fig. 2 (detailed data in ► Table 2). Note that the mean TSH level measured before or at 5 weeks was 2.66 mIU/L with a decline to a nadir of 1.59 mIU/L at 8–9 weeks and a subsequent rise until 20 weeks of gestation increasing to a maximum of 2.39 mIU/L. After this stage, TSH remained steady with minor fluctuations until term. FT4 values reached a maximum mean value of 14.95 pmol/L at 8–9

weeks and then decreased gradually to 12.66 pmol/L at term. FT3 values reached a maximum value of 5.10 pmol/L at weeks 8–9 and then remained overall steady with only a minor decrease until term.

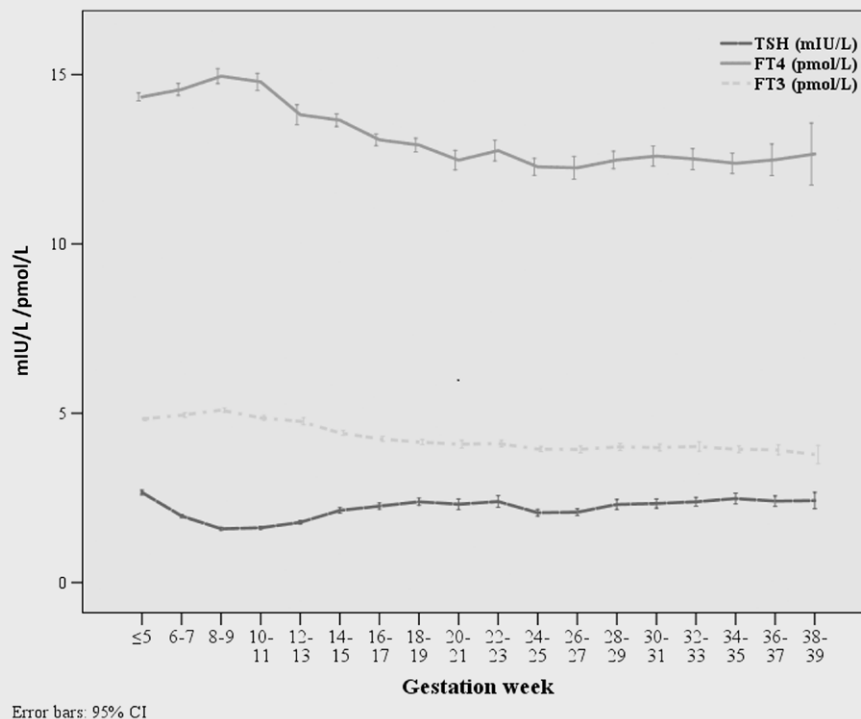
Thyroid hormones levels according to TSH cut-off levels

In ► Table 3, presenting data of patients with a TSH measurement plus a FT4 or FT3 test, the percentage of patients with FT4 and FT3 below the lower normal limits (–2 standard deviations for the study population, taken from the study data) are presented for different TSH recommended cut-off levels in the three gestational trimesters. As the TSH levels rise, the percentage of patients with FT4 below the lower normal limit increases. However, even for TSH levels above 10 mIU/L, FT4 levels are below the normal limit in only 12.8% in the first trimester. This trend was also shown for FT3, in which the percentage of measurements below the normal limit was higher for TSH levels above 10 mIU/L in both the first and second trimester (3.8% and 6.6%, respectively).

As expected, a negative correlation (R = Pearson's correlation coefficient) between TSH and both FT4 and FT3 was shown in the first trimester (R = –0.31 and –0.25, p < 0.001 for both). However, this was true only for FT3 in both the second (R = –0.02, NS and –0.18, p < 0.001), and third trimester (R = –0.05, NS and 0.20, p < 0.001).

Discussion

The major finding in this study was that TSH does not appear to be a good index of thyroid function during pregnancy. In fact, for the



► Fig. 2 Thyroid stimulating hormone (TSH), free thyroxine (FT4), and triiodothyronine (FT3) levels throughout gestation.

► **Table 2** TSH and thyroid hormones levels throughout gestation.

	n	TSH (mIU/l)	n	FT4 (pmol/l)	n	FT3 (pmol/l)
Gestational week						
1st Trimester	19374	1.93 ± 1.72 (1.61)	3076	14.53 ± 2.39 (14.40)	2865	4.92 ± 0.78 (4.80)
≤ 5 weeks	3856	2.66 ± 2.09 (2.20)	1188	14.34 ± 2.11 (14.30)	803	4.83 ± 0.69 (4.80)
6–7 weeks	5310	1.97 ± 1.70 (1.66)	699	14.56 ± 2.40 (14.31)	571	4.94 ± 0.81 (4.90)
8–9 weeks	4901	1.59 ± 1.67 (1.28)	616	14.95 ± 2.80 (14.81)	772	5.10 ± 0.83 (5.00)
10–11 weeks	3313	1.62 ± 1.27 (1.38)	362	14.79 ± 2.44 (14.50)	487	4.86 ± 0.76 (4.77)
12–13 weeks	1994	1.78 ± 1.24 (1.55)	211	13.81 ± 2.18 (13.61)	232	4.76 ± 0.81 (4.60)
2nd trimester	7281	2.21 ± 1.77 (1.86)	1716	12.99 ± 1.90 (12.89)	1257	4.21 ± 0.61 (4.17)
14–15 weeks	1797	2.13 ± 1.77 (1.76)	457	13.65 ± 2.03 (13.58)	373	4.42 ± 0.67 (4.35)
16–17 weeks	1547	2.26 ± 1.80 (1.90)	418	13.07 ± 1.79 (12.95)	303	4.25 ± 0.65 (4.19)
18–19 weeks	995	2.39 ± 1.68 (2.02)	283	12.92 ± 1.73 (12.89)	197	4.15 ± 0.53 (4.10)
20–21 weeks	658	2.31 ± 2.05 (1.91)	158	12.47 ± 1.84 (12.27)	107	4.09 ± 0.59 (4.08)
22–23 weeks	537	2.39 ± 2.05 (1.99)	125	12.76 ± 1.75 (12.60)	85	4.11 ± 0.44 (4.20)
24–25 weeks	1106	2.06 ± 1.68 (1.76)	166	12.27 ± 1.64 (12.11)	125	3.94 ± 0.44 (3.91)
26–27 weeks	641	2.08 ± 1.27 (1.77)	109	12.25 ± 1.78 (12.10)	67	3.93 ± 0.40 (4.00)
3rd trimester	2567	2.38 ± 1.69 (2.09)	849	12.49 ± 2.05 (12.30)	620	3.98 ± 0.64 (3.90)
28–29 weeks	676	2.31 ± 1.94 (1.90)	243	12.48 ± 2.06 (12.30)	183	4.01 ± 0.69 (3.90)
30–31 weeks	607	2.34 ± 1.72 (2.07)	218	12.59 ± 2.24 (12.40)	163	3.99 ± 0.65 (3.90)
32–33 weeks	486	2.39 ± 1.44 (2.18)	139	12.50 ± 1.86 (12.30)	101	4.02 ± 0.71 (3.90)
34–35 weeks	435	2.48 ± 1.70 (2.15)	141	12.38 ± 1.80 (12.26)	95	3.94 ± 0.47 (3.85)
36–37 weeks	262	2.41 ± 1.26 (2.25)	81	12.49 ± 2.13 (12.36)	61	3.92 ± 0.57 (3.90)
38–39 weeks	91	2.42 ± 1.16 (2.18)	23	12.66 ± 2.22 (12.01)	16	3.78 ± 0.55 (3.67)
≥ 40 weeks	10	3.85 ± 4.11 (2.15)	4	10.62 ± 2.87 (10.81)	1	3.27 ± 0 (3.27)

Data presented as mean ± SD (median).

majority of women who would have been considered hypothyroid by TSH values, the diagnosis would have been subclinical hypothyroidism (because they had normal levels of free thyroid hormone levels, from same-population based data), which is a debatable issue with differing views regarding its significance [14, 15] and this study can determine the final verdict. The correlations between TSH and FT4/FT3 are rather low at first trimester: $R = -0.25$ to -0.31 , which means a R^2 between 6 and 9%. During the second/third trimester there are no correlations at all. These R 's show a very low effect size, meaning they are clinically not relevant. It is unlikely that this was due solely to an effect of HCG [5] because the correlations between TSH and FT4/FT3 seem to disappear with increasing term when the hCG concentrations largely decrease.

In this study, our large cohort enabled us to establish population specific reference ranges for TSH, FT4 and FT3 and study the relationship between TSH and the thyroid hormones FT3 and FT4. We included a population of several thousand healthy women whose pregnancy ended in delivery of a live child, who did not have preexisting treated thyroid disease and who were not taking chronic medication. Our healthy population-based data are in agreement with previous studies [4, 16–18] showing similar patterns of changes in TSH, FT4 and FT3 levels through gestation. TSH decreased

dramatically until 8–9 weeks and later (12 weeks) began increasing gradually and stabilized, the FT4 pattern reflected a quite similar though less drastic "mirror image" pattern. FT3 levels remained rather steady with a gradual minor decrease throughout gestation.

Thyroid physiology changes significantly during gestation and particularly in the first trimester, so the interpretation of thyroid function tests are challenging [8, 13, 19]. Since the first trimester is a critical period for fetal neurological development [3, 7], maternal thyroid function and its pathologies need to be evaluated and addressed early and accurately. For this purpose, understanding the relationship of TSH to the FT4 and FT3 levels is important. As expected, our findings indicate lower mean levels of FT4 and FT3 with higher levels of TSH.

When we applied recommended TSH cut-off levels – i. e., 2.5 mIU/l or 4.0 mIU/l [8], we surprisingly found that with TSH above each of these cut-off levels, less than 10% of samples were associated with low FT3 or low FT4. In fact, even at TSH above 10 mIU/l only 15.3% of samples were associated with low FT3 and 12.8% were associated with low FT4 in the first trimester. The strengths of this study are the source, i. e., the fact that women are sampled for TSH, FT4 and FT3 without prior selection, thus allowing for a large number of healthy women for whom all three param-

► **Table 3** Free thyroxine (FT4) and free triiodothyronine (FT3) levels across the different thyrotropin (TSH) cutoffs according to trimesters of pregnancy.

1st trimester					
FT4	TSH <= 0.1	0.1 < TSH <= 2.5	2.5 < TSH <= 4	4 < TSH <= 10	10 < TSH
n	121	1371	426	992	101
Mean ¹ ± SD	17.38 ± 3.06	14.74 ± 2.01	14.25 ± 1.9	13.99 ± 2.06	12.37 ± 2.5
Median	17.21	14.50	14.18	13.99	12.30
2.5–97.5%	12.44–25.44	11.3–19.52	10.44–18.05	9.99–18.00	7.62–18.17
% below LNL *	0	0.07	1.43	2.0	12.8
FT3	TSH <= 0.1	0.1 < TSH <= 2.5	2.5 < TSH <= 4	4 < TSH <= 10	10 < TSH
n	210	1768	322	315	47
Mean ² ± SD	5.46 ± 0.79	4.86 ± 0.58	4.67 ± 0.57	4.51 ± 0.65	4.23 ± 0.94
Median	5.40	4.80	4.70	4.50	4.10
2.5–97.5%	4.06–7.00	3.9–6.12	3.61–5.89	3.39–5.94	2.83–7.48
% below LNL *	0	0.16	0.6	1.6	15.3
2nd trimester					
FT4	TSH <= 0.2	0.1 < TSH <= 3.0	3.0 < TSH <= 4	4 < TSH <= 10	TSH > 10
n	60	852	188	511	46
Mean ³ ± SD	13.25 ± 2.07	12.83 ± 1.68	13.15 ± 1.87	12.99 ± 1.86	12.91 ± 2.30
Median	12.95	12.72	12.99	12.90	13.21
2.5–97.5%	9.46–18.23	9.69–16.38	9.51–17.53	9.51–16.81	7.18–16.97
% below LNL *	1.5	0.7	1.4	0.8	3.8
FT3	TSH <= 0.2	0.1 < TSH <= 3.0	3.0 < TSH <= 4	4 < TSH <= 10	TSH > 10
n	78	718	157	198	30
Mean ⁴ ± SD	4.44 ± 0.58	4.17 ± 0.47	4.11 ± 0.54	4.04 ± 0.54	3.75 ± 0.91
Median	4.40	4.12	4.05	4.00	3.58
2.5–97.5%	3.19–5.95	3.3–5.2	3.23–5.81	3.1–5.29	2.31–6.80 ⁺
% below LNL *	1.2	0.7	1.6	0.4	14.7
3rd trimester					
FT4	TSH <= 0.3	0.3 < TSH <= 3.0	3.0 < TSH <= 4	4 < TSH <= 10	TSH > 10
n	31	462	108	212	15
Mean ⁵ ± SD	13.28 ± 2.13	12.41 ± 1.74	12.72 ± 2.07	12.13 ± 1.87	11.79 ± 2.65
Median	12.79	12.29	12.49	11.92	11.34
2.5–97.5%	10.18–17.40 ⁺	9.24–16.02	9.4–17.95	8.74–15.89	6.95–18.05 ⁺
% below LNL *	0	0	1.6	1.2	6.6
FT3	TSH <= 0.3	0.3 < TSH <= 3.0	3.0 < TSH <= 4	4 < TSH <= 10	TSH > 10
n	38	379	86	83	10
Mean ⁶ ± SD	4.33 ± 0.39	3.92 ± 0.47	3.83 ± 0.38	3.86 ± 0.45	3.51 ± 0.66
Median	4.28	3.90	3.74	3.80	3.40
2.5–97.5%	3.58–5.20 ⁺	3.01–4.99	3.21–4.79	3.12–4.97	2.8–4.8 ⁺
% below LNL *	0	0.21	0	0	0

¹ p < 0.05 in comparison between each consecutive TSH group except between 2.5 < TSH <= 4 and 4 < TSH <= 10, which was non-significant. ² p < 0.05 in comparison between each consecutive TSH group all the TSH groups except between the fourth and fifth group. ³ T here is no difference between the groups. ⁴ p < 0.05 in comparison between each consecutive TSH group except the comparison between the third and the adjacent groups.

⁵ p < 0.05 in comparison only between the first and fourth group. ⁶ p < 0.05 in comparison to the first group (the last group is too small for comparison) ⁺ Highest number (due to low sample number). * LNL: Lower normal limit, this figure was derived after including hypothyroid women (before treatment) who were previously excluded from the cohort in order to derive normal values.

eters were available. Secondly, by producing our own population-based normal thyroid hormone data we were able to calculate the relationship between TSH and normal thyroid hormone levels in the same population.

Apart from its retrospective nature, this study has several limitations: presence of FT4 and FT3 levels in some but not all of the women, lack of concomitant hCG levels and exclusion of women whose pregnancy ended in spontaneous miscarriage.

Conclusion

Though our results do not eliminate TSH from acting as part of the thyroid function tests during pregnancy, based on our findings, it is imperative to test FT4 and FT3 levels and not to make decisions based on TSH levels alone when diagnosing hypothyroidism during pregnancy.

Data Availability

Data may be provided upon request to the corresponding author.

Author Contributions

GK, LDS and DS designed the study, collected the data, analyzed the data, and drafted the manuscript. CM analyzed the data, drafted the manuscript and reviewed it. DG contributed to the study design, data analysis and drafting the manuscript. All authors approved the final version of the manuscript.

Conflict of Interest

The authors declare that they have no conflict of interest.

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