Original Article

A Systematic Review on Normative Values of Trimester-specific Thyroid Function Tests in Indian Women

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Abstract

Background: Small cross-sectional studies are published on the trimester-specific normal ranges of thyrotropin and thyroxine levels in Indian women from various parts of the country. **Objective:** We sought to review the published literature on thyroid function tests in normal pregnant Indian women to see if the pooled data from various studies can define normative data and hypothyroidism in pregnancy. **Methods:** We retrieved 56 studies from online databases with detailed search using multiple search terms. Unanimously eight studies were finalized. **Results:** Data of 2703 pregnant women (age 16–45 years; 966 were in the first trimester, 1072 in their second trimester, and 1037 women in their third trimester) were analyzed. All eight studies included singleton pregnancies from the northern and eastern part of India with seven studies being cross-sectional in nature. The exclusion criteria in all studies included those with historical/clinical evidence of thyroid dysfunction, those with family history of thyroid dysfunction, infertility and those with history of recurrent miscarriages (usually >3). Ultrasound evidence of thyroid disease, urinary iodine assessment, and thyroid antibodies were included as additional exclusion criteria in two, three, and four studies, respectively. None of the studies included the outcome of pregnancy as part of follow-up. As part of the pooled data analysis, the 5th–95th centile values of normal TSH extended from 0.09 to 6.65 IU/mL in the first trimester, 0.39–6.61 IU/mL in the second trimester, and 0.70–5.18 IU/mL in the third trimester. The FT4 levels (5th–95th centile values) extended from 8.24 to 25.74 pmol/L in the first trimester, 6.82–26.0 pmol/L, and 5.18–25.61 pmol/L in the third trimester. **Conclusions:** With due limitations imposed by the quality of the available studies, the current review suggests that upper normal limit of TSH values can extend up to 5–6 IU/mL in pregnancy.

Keywords: Indian pregnant women, thyroid function test, thyroid-stimulating hormone, trimester-specific

Introduction

The major changes in thyroid function during pregnancy are an increase in serum thyroxine-binding globulin (TBG) concentrations and stimulation of the thyrotropin (TSH) receptor by human chorionic gonadotropin.[1] During pregnancy, serum TBG concentrations rise almost 2-fold (estrogen-related increased production and decreased clearance due to TBG sialylation).[2,3] With due acknowledgement of the methodological issues with free T4 assay during pregnancy, some studies reported a decrease in free T4 during pregnancy, others reported no change or even an increase.[1,4,5] Because of the changes in thyroid physiology during pregnancy, the guidelines of the American Thyroid Association (ATA) recommended using trimester-specific reference ranges for TSH and method and trimester-specific reference ranges for serum free T4.[6] Commercial laboratories are supposed to provide these reference ranges, but many do not do this. In one of the largest population-based studies (over 13,000 pregnant women), the reference range (2.5–97.5th percentile) for TSH in the first trimester was 0.08–2.99 mU/L.[7-10] This was the basis of the previous ATA recommendation of normal TSH values during pregnancy: first trimester 0.1–2.5, second trimester 0.2–3.0, and third trimester 0.3–3.0. However, more recent studies in pregnant women in Asia, India, and the Netherlands, have demonstrated only a modest reduction in the upper reference limit.[11-15] A study of 4800 pregnant women in China recently showed that the downward shift in the TSH reference range

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Access this article online

Quick Response Code:

Website: www.ijem.in

DOI: 10.4103/ijem.IJEM_211_17

How to cite this article: Kannan S, Mahadevan S, Sigamani A. A systematic review on normative values of trimester-specific thyroid function tests in indian women. Indian J Endocr Metab 2018;22:7-12.

occurred at weeks 7–12, but the upper reference limit was only reduced from 5.31 to 4.34 mU/L.[12] Separate data from a recent prospective intervention trial in the United States support this finding.[16] Analysis of the TSH and free T4 "set-point" in pregnant women showed that reductions in free T4 were observed only when the serum TSH was >4.8 mU/L. In some cases, this was not statistically different from the nonpregnant state.[13,15] There is limited availability of trimester-specific reference ranges calculated for most ethnic and racial populations with adequate iodine intake who are free of thyroid autoantibodies. The recent ATA guidelines[17] recommend using a TSH upper reference range of 4 mU/L when local assessments are not available. This reference limit should generally be applied beginning with the late first trimester, weeks 7–12, with a gradual return toward the nonpregnant range in the 2nd and 3rd trimesters. There are multiple small cross-sectional data from India on trimester-specific values of TSH from the northern and eastern part of India. We sought to pool this information to see if the pooled data from various studies can define normative data and thyroid dysfunction in pregnancy.

Methods

A systematic review was performed to estimate (i) trimester-specific 5th–95th centile TSH values (ii) trimester-specific range of free T4 values in normal pregnant Indian women. This report follows a review protocol adhering to current standards for reporting of systematic reviews.[18]

Eligibility criteria

We chose to include studies involving thyroid function tests in normal Indian pregnant women. Normal singleton pregnancies were included in this study. The study had to have excluded those with any major comorbid illness including diabetes, hypertension, cardiac ailments, renal, or hepatic disorders and those on medications that can potentially affect thyroid function tests. Studies on women with recurrent miscarriages and infertility were excluded from the study. The chosen studies had to exclude women with history of thyroid disorder, medications for hypothyroid or hyperthyroidism, family history of thyroid dysfunction, and presence of goiter. Studies with prespecified cutoffs for diagnosis of hypothyroidism were excluded from the study.

Search strategy

The search strategy aimed to find both published and unpublished studies. A comprehensive search from each database's inception to March 2017 was conducted with no language restrictions. The databases included Ovid MEDLINE In-process and Other Nonindexed Citations, Ovid MEDLINE, CINNAHL, the Cochrane Controlled Trials Register, Ovid EMBASE, Web of Science, and Scopus. An initial limited search of these databases was undertaken followed by analysis of the text words contained in the title and abstract, and of the index terms used to describe article. A second search using all identified keywords and index terms was then undertaken across all included databases. Thirdly, the reference list of all identified reports and articles was searched for additional studies.

Keywords used for database search

The following key words were used primarily to search the database which include thyroid*, hyperthyr*, hypothyr*, tpo*, tsh, thyrotropin recep-tor antibod*, thyroid stimulating immunoglobulin*, thyrotropin-binding inhibit*, thyroxine, thyrotropin, thyroid microsomal antibodies, fertility, infertility, abortion*, miscarriag*, pregnan*, obstetric*, gestation * preterm deliver*, premature deliver*, intrauterine growth retardation*, fetal growth restriction*, intrauterine growth restriction* and child development*. MESH terms including thyroid gland, thyroid diseases immunoglobulins, thyroid-stimulating, thyrotropin, thyroxine, fertility, infertility, pregnancy pregnancy outcome, pregnancy complications, fetal growth retardation and child development were used for the search. The results were then filtered to only include those done in Indian women.

Study identification

Titles and subsequently abstracts of the articles were screened by two reviewers independently (SK and SM). Included articles for full-text screening were compared during a consensus meeting. In case of disagreement, a third reviewer (AS) was consulted for the decision on inclusion or exclusion for full-text evaluation. Articles that did not contribute to the answer of our research questions after full text evaluation were excluded. Only articles that described at least ten patients were eligible. Articles that did not report concentrations of TSH and/or free T4, and articles on thyroid antibodies in noneuthyroid

Table 1: Pooled data of selected studies

Author	Year	Sample size	TSH level checked (*n*)			State	Region
			T1	T2	T3		
Sekhri *et al*.	2016	86	86	86	86	Delhi	North India
Jebasingh *et al*.	2016	375	109	148	118	Manipur	East India
Rajput *et al*.	2016	983	301	308	374	Haryana	North India
Mankar *et al*.	2016	150	50	50	50	Nagpur	North India
Choudhary *et al*.	2015	276	88	92	96	West Bengal	East India
Maji *et al*.	2014	402	125	151	126	West Bengal	East India
Deshwal *et al*.	2013	100	1000	1000	100	Dehradun	North India
Marwaha *et al*.	2008	331	107	137	87	Delhi	North India

T1: First trimester, T2: Second trimester, T3: Third trimester, TSH: Thyrotropin

populations were excluded. After consensus, the remaining articles were included for critical appraisal and assessed by two reviewers independently (SK and SM). Articles were judged on scientific quality according to the CONSORT[11,19] and STROBE[12] statement.

Data extraction

Reviewers worked independently and in duplicate using a standardized web-based form collected the following information from each eligible study: (i) Year and Place where the study was conducted (ii) number of pregnant women studied in each trimester and their mean (standard deviation [SD]) age (iii) type of study (cross-sectional or longitudinal) and its exclusion criteria described in the study (iv) methodology of thyroid function tests done (v) mean, SD, median, range, 5th–95th centile of TSH and T4 and/or free T4 in each study (vi) adequacy of Iodine intake assessed by urinary iodine studies (vii) outcome of pregnancy if mentioned.

Data analysis

All results were subject to double data entry. The mean, SD, median and range were calculated for continuous variables. Where statistical pooling was not possible the findings are presented in narrative form including tables and figures to aid in data presentation.

Results

Search results

Out of 56 search results, nine studies were selected based on our objectives. Among the 9 studies, 8 studies were considered for review and data extraction. One was excluded in view of poor quality. Sevens studies are published manuscripts[13-16,20-22] while one study was poster at an endocrine conference (Choudhary *et al*.) [Table 1]. The detail of the study selection was described in Figure 1.

Study types

Among the eight selected studies seven were cross-sectional and one was longitudinal study.

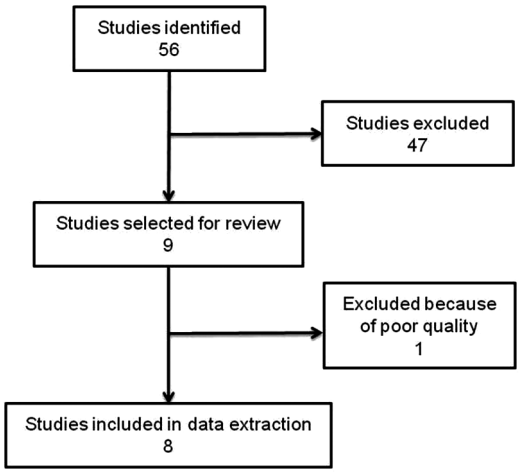

Figure 1: Selection of studies

Laboratory methods

TSH was measured by different assay methods which include electrochemiluminescence,[13,15,20] enzyme-linked immunosorbent assay,[14] enzyme immunoassay,[21] and chemiluminescence immunoassays.[16,22]

Results

We reviewed eight studies for trimester-specific TSH levels in normal Indian pregnant women. A total of 2703 pregnant woman were studied in the selected 8 studies out of which 966, 1072, and 1037 women were tested for TSH levels during first, second, and third, trimesters, respectively. Most of these studies were performed in the Northern and Eastern part of India. None of these studies followed up till the outcome of pregnancy. The exclusion criteria in all studies included those with historical/clinical evidence of thyroid dysfunction, those with family history of thyroid dysfunction, infertility and those with history of recurrent miscarriages (usually >3). Ultrasound evidence of thyroid disease, urinary iodine assessment, and thyroid antibodies were included as additional exclusion criteria in two, three, and four studies, respectively [Supplementary file 1]. While six studies mentioned the mean (SD) TSH and fT4 levels [Table 2], only four studies reported median TSH values with interquartile range [Table 3]. Out of the seven studies which reported fT4/T4 levels, six studies checked the free thyroxine (FT4) values while one reported total T4 levels. All the FT4 values are converted into pmol/L and presented in Table 4. As part of the pooled data analysis, the 5th–95th centile values of normal TSH levels were 0.09–6.65 IU/mL during the first trimester [Figure 2], 0.39–6.61 IU/mL during the second trimester [Figure 3], and 0.70–5.18 IU/mL during the third trimester [Figure 4]. The FT4 levels (5th–95th centile values) were 8.24–25.74 pmol/L in first trimester, 6.82–26.0 pmol/L and 5.18–25.61 pmol/L in the third trimester.

Discussion

Although there is considerable heterogeneity in the exclusion criteria in the included studies, only the study from Marwaha *et al*. had a comprehensive exclusion criteria including clinical, sonographical and serological thyroid peroxidase antibodies

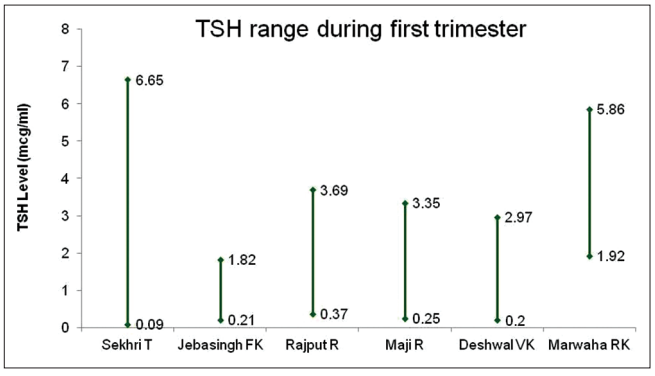

Figure 2: Extent of TSH (5th–95th centiles) during the first trimester across various studies

Table 2: Trimester-specific mean thyroid-stimulating hormone values from selected studies

Author	*n*	Age (years)	TSH values (mIU/mL)			
			Trimester	Mean±SD	Median	Range
Sekhri *et al*.	86	18-45	T1	2.07±1.46	NA	NA
			T2	2.63±1.60		
			T3	2.50±1.08		
Jebasingh *et al*.	375	25.9±5.1	T1	1.06±0.45	1.08	NA
		27.3±5.6	T2	1.23±0.30	1.23	
		27.1±5.1	T3	1.25±0.36	1.23	
Rajput *et al*.	983	23.89±3.24	T1	1.63±1.02	1.4	NA
			T2	1.79±0.73	1.74	
			T3	2.28±0.98	2.22	
Mankar *et al*.	150	25.38±5.36	T1	1.65±0.85	NA	NA
			T2	2.59±1.09		
			T3	2.77±1.19		
Maji *et al*.	402	16-37	T1	1.81±0.79	1.8	NA
			T2	2.22±1.70	1.84	
			T3	2.20±0.88	2.07	
Deshwal *et al*.	100	20-35	T1	1.41±0.93	NA	NA
			T2	1.56±0.86		
			T3	2.73±0.63		
Marwaha *et al*.	331	NA	T1	2.42±1.65	2.1	0.04-10.8
			T2	2.49±1.90	2.4	0.026-10.85
			T3	2.60±1.90	2.1	0.2-9.55
Choudhary *et al*.	276	NA	T1		NA	0.42-4.48
			T2			0.57-3.94
			T3			0.38-5.37

T1: First trimester, T2: Second trimester, T3: Third trimester, NA: Not available, SD: Standard deviation, TSH: Thyrotropin

Table 3: Trimester-specific median thyroid-stimulating hormone values from selected studies

Author	*n*	Age (years)	TSH values (mIU/mL)		
			Trimester	Median	5th and 95th centile value
Jebasingh *et al*.	375	25.9±5.1	T1	1.08	0.21-1.82
		27.3±5.6	T2	1.23	0.71-1.71
		27.1±5.1	T3	1.23	0.70-1.93
Rajput *et al*.	983	23.89±3.24	T1	1.40	0.37-3.69*
			T2	1.74	0.54-4.47*
			T3	2.22	0.70-4.64*
Maji *et al*.	402	16-37	T1	1.80	0.25-3.35*
			T2	1.84	0.78-4.96*
			T3	2.07	0.90-4.60*
Marwaha *et al*.	331	NA	T1	2.1	0.60-5.00
			T2	2.4	0.44-5.78
			T3	2.1	0.74-5.70

*2.5th and 97.5th centile. T1: First trimester, T2: Second trimester, T3: Third trimester, NA: Not available, TSH: Thyrotropin

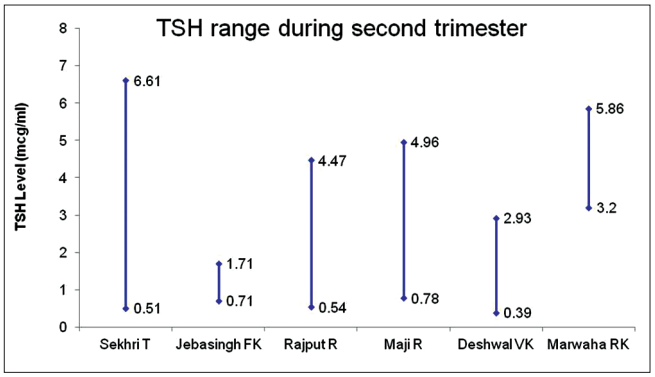

Figure 3: Extent of TSH (5th–95th centile) during the second trimester across various studies

and anti-Tg (TPO and anti-Tg).[13] However, it does come as a surprise when the range of TSH reaches up to 10 in some individuals in their study. One of the biggest limitation of the studies conducted have been lack of follow-up of the studied cohort to get details on their pregnancy outcomes. In one of the few outcome studies related to thyroid function, Nambiar *et al*. studied a cohort of 483 consecutive pregnant women in the first trimester and followed them till delivery.[23] Subjects were prespecified classified as TSH <2 μIU/mL and TPOAb negative (Group 1) TPOAb positive (Group 2), patients with TSH 2–4 μIU/mL and TPOAb negative (Group 3) TPOAb positive (Group 4) and TSH >4 μIU/mL (Group 5). Those with TPOAb positivity and TSH >4 μIU/mL were treated with thyroxine. A TSH >4 μIU/mL and TPOAb positivity were associated with increased rates of miscarriages. In another study of outcomes in patients with preeclampsia, mean (SD) TSH levels significantly different among those with normal blood pressure: TSH 2 (1.18), those with mild preeclampsia: 3.42 (1.61) mIU/L, and in those with severe preeclampsia

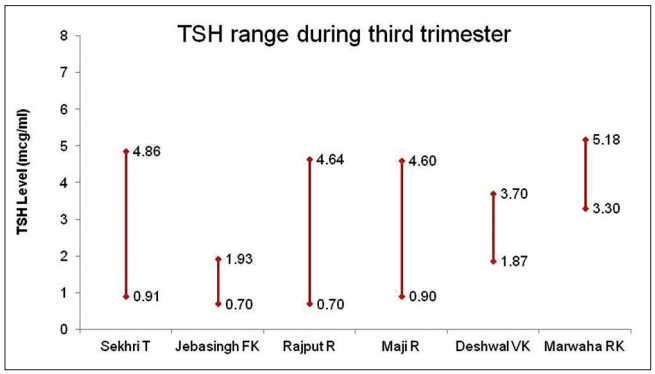

Figure 4: Extent of TSH (5th–95th centiles) during the third trimester across various studies

Table 4: Trimester-specific free thyroxine values

Author	*n*	Age (years)	FT4 values (pmol/L)	
			Trimester	5th and 95th centile value
Sekhri *et al*.	86	18-45	T1	9.81-18.53
			T2	8.52-19.43
			T3	7.39-18.28
Rajput *et al*.	983	23.89±3.24	T1	11.33-22.93*,[a]
			T2	11.73-22.91*,[a]
			T3	10.68-22.27*,[a]
Maji *et al*.	402	16-37	T1	8.24-25.74*,[a]
			T2	6.82-26.00*,[a]
			T3	8.24-25.61*,[a]
Deshwal *et al*.	100	20-35	T1	11.43-16.96
			T2	9.22-15.50
			T3	5.18-10.52
Marwaha *et al*.	331	NA	T1	12.00-19.45
			T2	9.48-19.58
			T3	11.32-17.7

*2.5th and 97.5th centile values, [a]Converted to pmol/L from ng/dL.
FT4: Free thyroxine, NA: Not available, T1: First trimester, T2: Second trimester, T3: Third trimester

5.63 (2.37). Those with preeclampsia and higher TSH levels had higher risk of low birth weight.[24]

From the above discussion, it seems safe to diagnose thyroid dysfunction once TSH starts crossing 4.5–5 mIU/L which is the typical cutoff in nonpregnant state. It is important to understand that this is valid in those with proper exclusion criteria particularly those with negative antibodies. Hence, if a clinician decides not to treat a TSH levels between 3 and 5, it is important to make sure the anti-thyroid antibody (TPOAb and/or anti-Tg) is negative. More outcome-based studies are required to know the normative data on antibody positive and antibody negative patients. Studies from outhern and western part of India are also needed to see if there are any regional variations in thyroid functions.

Conclusions

With due limitations imposed by the quality of the available studies, the current review suggests that upper normal limit of TSH values can extend up to 5–6 IU/mL in pregnancy and one can possibly use nonpregnant cutoffs for TSH to diagnose thyroid dysfunction in pregnancy provided appropriate exclusion criteria are met. These results also are closely in line with the recommendations from the recent ATA guidelines for diagnosis of hypothyroidism in pregnancy.

Acknowledgment

The authors would like to acknowledge Mr. Annapandian VM, Consultant (Academic) Narayana Hrudayalaya Foundations, Narayana Health, Bengaluru, Karnataka, India.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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