

Reference intervals in evaluation of maternal thyroid function of Manipuri women

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ABSTRACT

Context: The population of Manipur is of different ethnic background from the rest of the country. Several authors have suggested population/ethnic and laboratory specific reference range of maternal thyroid profile of different trimesters. **Aims:** To find the reference range of thyroid stimulating hormone (TSH), total thyroxine (TT4) and total tri-iodothyronine (TT3) levels for normal pregnant women of native Manipur descendants. **Settings and Design:** The cross-sectional study was conducted at a teaching Institute after ethical clearance was obtained. **Subjects and Methods:** A reference populations of 375 normal pregnant women were established after screening about 600 pregnant women. The study excluded patients with hyperemesis gravid arum, past history or family history of thyroid disorders as well as the connective tissue disorders, WHO grade 1 or 2 goiter, or any medications that alter thyroid functions. The serum levels of TSH, TT4, and TT3 were measured using chemiluminescence assay. **Statistical Analysis Used:** Data for TT3 and TT4 were expressed as mean \pm standard deviation, median and 5–95th percentiles. **Results:** The mean TSH in the three trimesters was $1.06 + 0.45$, $1.23 + 0.30$, and $1.25 + 0.36$, respectively. The normal reference range thus was different from that of the kit reference range. On comparing to the Indian normative reference for the pregnant women, our results were not similar. However, the values were near similar to that of the American Thyroid Association guidelines. **Conclusions:** We conclude our study results with a new reference range for the pregnant population in Manipur and also emphasis the use of trimester-specific reference range of thyroid hormone.

Key words: Pregnancy, reference range, thyroid hormones

INTRODUCTION

During pregnancy, there is a profound physiological change in the mother, which will complicate the interpretation of maternal thyroid function tests.^[1-6] Human chorionic gonadotropin (hCG) have similar alpha-subunit to thyroid stimulating hormone (TSH) and a unique beta-subunit. As a result, hCG can stimulate the thyroid gland during the first trimester.^[7] During

pregnancy, the serum thyroxine-binding globulin concentrations rise almost two-fold and thyroid hormone production increase. Hence, total T4 and T3 concentrations rise during the first half of pregnancy followed by a plateauing at approximately 20 weeks of gestation. Fetal brain development in its early stage depends on the maternal thyroid hormones.^[6-12] Reference range were studied extensively across various countries and also American Thyroid Association (ATA) had published their guidelines.^[13-22] Although several studies are available from different regions of the world,

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it is essential to develop norms for different Indian population due to the ethnic variations.^[23-25]

SUBJECTS AND METHODS

The study primarily aimed at establishing the trimester-specific reference ranges for TSH and thyroid hormones (total tri-iodothyronine [TT3], total thyroxine [TT4]) from healthy pregnant women of the Manipuri descendants. We also compared the results with the Indian normative reference range and the ATA guidelines reference for thyroid disease in pregnancy. This was a cross-sectional study that was conducted after approval from the Institutional Ethics Committee. The women were recruited after a prior informed consent. The sample size was calculated with an absolute error of 0.5. The serum levels of TSH, TT4, and TT3 were measured using SIEMENS ADVIA third generation chemiluminescence assay which has an intra-assay variability of <10% for all the three parameters.

Healthy women with uncomplicated single intrauterine gestations consuming iodized salt in any trimester were consecutively recruited. A detailed obstetric history such as duration of gestation, parity and number of abortions and also history related to any thyroid-related illness were obtained. Physical examination included anthropometry, goiter grading^[25] and general and systemic examinations. Venous samples for the serum were drawn; serum separated and sent for analysis of thyroid hormones (TSH, TT3, and TT4). The following are the exclusion criteria to cone down the population for the reference range:

- History of hyperemesis gravidarum, thyroid illness or use of thyroid medications, connective tissue disorder and abortions
- Family history of thyroid illness
- Presence of goiter, WHO grade 1 or 2^[25]
- Overt hypothyroidism (OH) or hyperthyroidism.

The data were analyzed using the SPSS 17 (Chicago, SPSS Inc.). Data for TT3 and TT4 were expressed as mean \pm standard deviation (SD), median, and 5th to 95th percentiles. TSH was normalized using log transformation as it did not follow normal distribution. The 5th and 95th percentile values of serum TSH, TT3, and TT4 from this group were used to derive reference intervals for pregnant women.^[26]

RESULTS

A total of 600 normal pregnant women were examined, and 375 normal pregnant women were taken as the reference population after applying the exclusion criteria. Of the 375 women, 109, 148, and 118 were in the first, second,

and third trimester, respectively. Using the kit reference values, OH was found in 2 (0.5%) women (1 in the first trimester, 1 in the second trimester). The mean age groups of the women were 25.9 + 5.1, 27.3 + 5.6 and 27.1 + 5.1 in first, second, and third trimester, respectively. The basic characteristics of the women are shown in Table 1. The mean \pm SD, median and 5th and 95th percentiles for TT3, TT4, and TSH in each trimester of pregnancy are given in Table 2. The reference intervals for each trimester of our study population are shown in Table 3.

DISCUSSION

The International Federation of Clinical Chemistry recommends that the determination of the normal reference values have to be described in such a way that the reference population should be appropriately described, and criteria for the selection should be clearly made.^[26,27] The National Health and Nutrition Examination Survey of USA had used the exclusion criteria such as the personal or family history of thyroid illness, goiter but not ultrasound for an adult thyroid hormone reference population.^[15] Marwaha *et al.*, in their study had included the anti-thyroid antibodies and ultrasound in the Indian normative reference for the pregnant women.^[13] The reference population should be as exclusive as possible as the purpose of reference intervals is to decide on thyroid status of a pregnant woman, wherein the thyroid functions cannot be compromised. This is because the adverse outcomes in fetus arising from thyroid dysfunction during pregnancy are very well-established.^[5-8] In the Indian thyroid hormone reference study by Marwaha *et al.*, a total of 331 women were studied with 107 in the first trimester, 137 in the second trimester and 87 in the third trimester. From the 5th and 95th percentile, the trimester-specific TSH values were 0.6–5.0, 0.44–5.78, and 0.74–5.7 μ IU/ml, respectively.^[13] Unlike the ATA guidelines for the thyroid diseases in pregnant women the TSH in Marwaha *et al.* study were similar to that of the normal adult population reference range [Table 4]. However, the reference range of the ethnic Manipuri population was near similar to that of the ATA guidelines.^[14] Furthermore, in our study, we found a gradual increase in the median TSH levels as the trimester proceeds forwards. Another study from India

Table 1: The basic characteristics of the study population

	Patient recruited	First trimester	Second trimester	Third trimester
Number of patients (%)	375	109 (29)	148 (39.5)	118 (31.5)
Number of primigravida	215	64	83	68
Number of multigravida	160	45	65	50
Age (mean \pm SD)	375	25.9 \pm 5.1	27.3 \pm 5.6	27.1 \pm 5.1
Gestational age (mean \pm SD)	375	9.3 \pm 2.5	20.8 \pm 4.1	35 \pm 3.1

SD: Standard deviation

Table 2: Thyroid hormone levels of our study population

	Mean±SD	Median	5 th percentile	95 th percentile	Reference range
First trimester					
TSH (μIU/ml)	1.06±0.45	1.08	0.21	1.82	0.21-1.82
TT3 (ng/dl)	124.11±26.66	119.17	88.2805	176.80	88.28-176.80
TT4 (μg/dl)	9.98±2.18	6.49	6.49	13.75	6.49-13.75
Second trimester					
TSH (μIU/ml)	1.23±0.30	1.23	0.71	1.71	0.71-1.71
TT3 (ng/dl)	159.25±37.77	152.94	102.24	233.27	102.24-233.27
TT4 (μg/dl)	11.47±2.21	11.47	7.9	16.06	7.9-16.06
Third trimester					
TSH (μIU/ml)	1.25±0.36	1.23	0.7	1.93	0.70-1.93
TT3 (ng/dl)	153.20±34.19	154.42	88.46	205.50	88.46-205.50
TT4 (μg/dl)	11.48±2.35	11.80	7.77	15.30	7.77-15.30

TT4: Total thyroxine, TT3: Total tri-iodothyronine, TSH: Thyroid stimulating hormone, SD: Standard deviation

Table 3: Comparison of the manufacturer's reference range and the trimester specific range of our study population

	Nonpregnant range (manufacturer's range)	First trimester range (median)	Second trimester range (median)	Third trimester range (median)
TSH (μIU/ml)	0.35-5.5	0.21-1.82 (1.07)	0.72-1.71 (1.23)	0.69-1.93 (1.25)
T4 (μg/dl)	4.50-12.60	6.49-13.75 (9.53)	7.9-16.06 (11.46)	7.77-15.3 (11.21)
T3 (ng/dl)	60-181	88.28-176.8 (124.11)	102.24-233.27 (159.25)	88.46-205.49 (153.2)

TT4: Thyroxine, TT3: Tri-iodothyronine, TSH: Thyroid stimulating hormone

Table 4: Comparison of our TSH reference range with the proposed Indian normative range and the ATA guidelines reference range

	Our reference range (μIU/ml)	Indian normative range (μIU/ml) ^[13]	ATA guidelines (μIU/ml) ^[14]
First trimester	0.21-1.82 (1.07)	0.6-5.0 (2.42)	0.1-2.5
Second trimester	0.72-1.71 (1.23)	0.44-5.78 (2.49)	0.2-3
Third trimester	0.69-1.93 (1.25)	0.74-5.7 (2.6)	0.3-3

TSH: Thyroid stimulating hormone, ATA: American Thyroid Association

evaluated 124 pregnant women using radioimmunoassay also showed an increase in TSH progressively with each trimester. When mean serum TT3 and TT4 were analyzed, both values increased from first to the second trimester but declined from second to the third trimester.^[16] Similarly, in our study, the TT3 and TT4 increased from first to the second trimester, followed by a decline during the third trimester. A longitudinal study by Price *et al.*, also arrived at the trimester-specific reference range. They found the serum TSH levels increase from first to the second trimester, while FT4 decreased with progress in the pregnancy. However, the serum FT3 did not change between the first and second trimesters. Furthermore, the study did not find any difference in the thyroid hormone changes between pregnant Asian and pregnant Caucasian women.^[17] In a longitudinal study by Panesar *et al.*, on pregnant Chinese women, the authors found a decrease in FT4 and FT3 by about 25% with gestational age from peak to nadir. Whereas, TSH, which was suppressed in the first trimester and increased subsequently with the advancing pregnancy.^[18] A longitudinal study by Soldin *et al.*, through the trimesters from a group of pregnant women used

immunoassay and mass spectrometry to analyze the thyroid functions. The mean TSH increased with advancing gestational age from first to the second trimester, while it remained stable from second to the third trimester.^[19] In an another cross-sectional study of 522 pregnant women from Japan, the authors showed a significant decrease in both free T3 (FT3) and free T4 (FT4) and increase in the TSH with advancing pregnancy.^[20] Our study showed a TSH reference range, which is different from that of the proposed Indian normative range for pregnant women [Table 4]. In the study by Marwaha *et al.*, the author suggests that the Asian pregnant women are more prone for gestational thyrotoxicosis.^[13] However, in our study, we did not find women with overt hyperthyroidism. A study on thyroid function that was carried out only in the second trimester by La'lulu and Roberts showed a higher prevalence of raised TSH in whites compared with Asians and Blacks.^[21] Hence, the ethnic variations still remain a concern, and the studies that address this aspect are very scant. Hence, we can overview that there is a definite difference in the thyroid reference range across various countries and also within the Indian population due to its ethnic origin. The limitations in our study are that we did not measure the anti-thyroid antibodies as well as the free thyroid hormone levels.

This study concludes the following reference intervals for TT3, TT4, and TSH for the each trimester of pregnancy (TT3 [88.28–176.8, 102.24–233.27 and 88.46–205.49 ng/dl], TT4 [6.49–13.75, 7.9–16.06 and 7.77–15.3 μg/dl] and TSH [0.21–1.82, 0.72–1.71 and 0.69–1.93 IU/ml]) for

the pregnant Indian women of Manipur state. We also emphasize, there is a definite difference in the trimester-specific reference range of thyroid hormones within country like India due to its ethnic variation.

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Conflicts of interest

There are no conflicts of interest.

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