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Original Article

Biochemistry Section

Region Specific Reference Intervals for TSH in the First Trimester of Pregnancy: A Three Year Retrospective Study

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ABSTRACT

Introduction: Alterations in thyroid hormones levels affect maternal health and fetal neurocognitive development. Variation in geophysical and socio-economic factors, and placental Human Chorionic gonadotropin (hCG) influence thyroid hormone secretion, and decreases Thyroid Stimulating Hormone (TSH) levels. Therefore, American Thyroid Association (ATA) recommends establishment of trimester and region-specific ranges for better detection and management of thyroid hormone dysfunction.

Aim: To determine the region-specific TSH values in the first trimester of pregnancy.

Materials and Methods: In the three-year retrospective study, serum TSH levels of 1221 healthy pregnant women attending the antenatal OPD at GITAM Institute of Medical Sciences and Research, Visakhapatnam, Andhra Pradesh, India, were measured by the Electrochemiluminescence Immunoassay "ECLIA". Reference interval of TSH was calculated using the Statistical Package for the Social Sciences (SPSS) software by applying the non-parametric statistical method. The central 95% intervals (normal range), the 90% confidence intervals and the confidence ratios were calculated.

Results: For TSH levels in the first trimester, the central 95% intervals were 0.43-4.5 mU/L, 90% confidence intervals were 0.27-0.45 (Upper Limit), 3.9-4.84 (Lower Limit) and the confidence ratio was 0.24. These values were found to be slightly higher than the ATA 2017 guidelines.

Conclusion: Our region-specific reference interval for TSH was found to be 0.43-4.5 mU/L. The established region-specific reference intervals will help assessment of TSH levels in the first trimester of pregnancy and thereby prevent misdiagnosis and inadequate treatment.

Keywords: American thyroid association, Human chorionic gonadotropin, Iodine, Reference values, Thyroxine

INTRODUCTION

Thyroid dysfunction during pregnancy has been an important health concern due to its critical impacts on maternal and fetal outcomes that often results in miscarriage, premature delivery, pre-eclampsia, low fetal weight, reduced cognitive function in offspring and fetal death [1]. Literature suggests that pregnancy affects thyroid function by increasing renal iodine excretion, degradation of thyroxine by placental deiodinases and by stimulation of Human Chorionic Gonadotropin (HCG) [2]. The placental hCG known to stimulate thyroid hormone secretion, in turn, decreases TSH levels in early pregnancy. Therefore, routinely thyroid screening is recommended during pregnancy to monitor the hormone levels while the upper reference limit for TSH remains inconclusive. TSH is considered as the most sensitive marker of thyroid function and its levels are influenced by several factors, such as age, sex, dietary iodine intake and thyroid auto-antibodies [3]. Guan H et al., from China reported that the reference interval of serum TSH levels in a mildly iodine-deficient area was found to be 0.33-3.42 mIU/L, and in an iodine-excess area was found to be 0.59-5.98 mIU/L indicating the importance of the role of iodine in the maintenance of serum TSH levels [4].

Recent guidelines by ATA 2017 increased the upper limit of 2011 TSH range from 2.5 to 4.0 uIU/mL. In addition to it, ATA recommends the established use of trimester and region-specific reference ranges for maternal serum TSH levels [5,6]. The guidelines also stated that "Although the downward shift in TSH reference ranges is seen in essentially all populations, the extent of this reduction varies significantly between different racial and ethnic groups". Hence, the use of fixed cut-off points for TSH may lead to unnecessary medication or overtreatment. Based on these findings, the need for establishment of region-specific TSH reference intervals in healthy pregnant women is evident. Since there were no region-specific data available for TSH levels in north coastal district of Andhra Pradesh, the current study was carried out to determine the region-specific TSH values in the first trimester of pregnancy among healthy pregnant women.

MATERIALS AND METHODS

The present retrospective study was conducted on 1221 pregnant women attending the antenatal OPD, at GITAM Institute of Medical Sciences and Research, Visakhapatnam, Andhra Pradesh, India, in the North Coastal district of Andhra Pradesh viz., Visakhapatnam, Vijayanagaram and Srikakulam. Ethical clearance was obtained from the Institutional Ethics Committee (GIMSR/Admin/Ethics/Approval/30/2018). By using a pilot study, the sample size was calculated and a three year (January 2016 to December 2018) retrospective analysis of TSH values of healthy pregnant women attending the OPD in the first trimester (defined as 4 to 12 weeks) was done. Patients with a history of thyroid disease, chronic illness, twin pregnancy or altered renal function were excluded.

About 80% of pregnant women attend the OPD in the first trimester and continue until the delivery and postpartum period. A social obstetric initiative "Savitri Prasootha Pathakam" motivates them to attend our OPD as it provides free services to them.

Measurement of TSH: Serum TSH was measured on the Roche company's Cobas e411 immunoassay analyser using the electrochemiluminescence immunoassay "ECLIA" sandwich principle.

STATISTICAL ANALYSIS

Reference intervals of TSH were calculated using the Statistical Package for the Social Sciences (SPSS) software, which applies the non-parametric statistical method [7]. The central 95% intervals (normal range), the 90% confidence intervals and the confidence

ratios were calculated. The p-values <0.05 were considered statistically significant.

RESULTS

Percentage of cases under different ranges of TSH values in the first trimester of pregnancy are shown in [Table/Fig-1]. The results for TSH levels, central intervals, confidence intervals and confidence ratio are shown in [Table/Fig-2].

S. No.	TSH (mU/L)	Number of cases	%
1	3.0-5.0	318	26
2	2.5-3.0	154	13
3	2.0-2.5	202	17
4	0.2-2.0	547	45

[Table/Fig-1]: Percentage of cases under different ranges of TSH values in the first trimester of pregnancy.
TSH: Thyroid stimulating hormone

TSH (mU/L)	First trimester
Reference interval (Central 95% intervals)	0.43-4.5
90% CI for lower limit	0.27-0.45
90% CI for upper limit	3.9-4.84
Confidence ratio	0.24

[Table/Fig-2]: Central 95% reference intervals, 90% confidence intervals and the confidence ratio for TSH in first trimester.
CI: Confidence interval; TSH: Thyroid stimulating hormone. For calculating the 95% CI, non-parametric statistical method was used [7]

DISCUSSION

Pregnancy is commonly associated with thyroid hormone alterations. Changes in the levels of thyroid hormones are routinely monitored during pregnancy to assess the functions of thyroid. Previous studies from American Thyroid Association (ATA) (2011), the Endocrine Society (2012) and the European Thyroid Association (2014) documents 2.5 mU/L as the upper cut-off for TSH in the first trimester of pregnancy [8,9]. Various population-based studies report geographic and ethnic diversity significantly affect the TSH level during pregnancy [11-18]. Based on the region-specific studies from the Asian subcontinent, China, Korea, and the Netherlands, the ATA has revised the guidelines and has specified the upper limit for TSH as 4.0 mU/L [10].

The results of the present study showed that the reference intervals of TSH in the first trimester of pregnancy were 0.43-4.5 mU/L. These values were in accordance with other studies conducted in India (0.6-5.0 mU/L), Spain (0.12-5.76 mU/L), and Korea (0.12-5.76 mU/L), where the TSH upper limit during the first trimester of pregnancy was higher than the ATA 2017 guidelines [12-14]. In the Indian study, upper limit value of TSH was 5.0 mU/L which was similar to the present study. The upper limits from Spain and Korea were as high as 5.76 mU/L that indicated the importance of ethnicity.

Apart from ethnicity, while monitoring the levels of TSH during pregnancy, the effect of iodine status must be considered. Since the present study comprised of pregnant women from the coastal area where the majority of the population is pescetarian, it was presumed that the patients coming to the present hospital are iodine sufficient. The present result of 4.5 mU/L was very similar to the result of 4.04 mU/L and 4.34 mU/L reported by Li C et al., from China and Medici M et al., from Netherlands, respectively where iodine was sufficient [10,19]. Studies carried out in mild to moderate iodine deficient regions showed a wide range of upper limits varying from 2.15 to 3.67 [20]. In contrast, a study conducted in Switzerland on pregnant women presumed to be iodine sufficient reported a TSH value of 2.82 mU/L [21]. In another study from UAE, TSH upper limit in the first trimester was observed to be 3.33 mU/L where iodine was presumed to be sufficient as per the declaration by the UAE Ministry of Health [22]. Therefore, the differences in the upper limit of reference interval for TSH among different studies can be attributed to not only the differences in the iodine status of the population but also the ethnicity.

In the current study, the upper limit for TSH in the first trimester was 4.5 mU/L which was slightly higher than the ATA 2017 value of 4.0 mU/L but was found to be lesser than the other population based studies where the average value was 5.7 mU/L. These variations in the present study can be attributed to the dietary habits (most of them are seafood eaters) as the population under consideration was from the coastal area.

A recent study by Dong AC et al., had clearly stated that "Population-based, trimester-specific TSH cut-offs for diagnosis of hypothyroid disease in pregnancy result in more accurate diagnosis and better estimates for the prevalence of disease" [23]. Using the region-specific TSH values, the healthcare centre can avoid overdiagnosis, unnecessary treatment, and overtreatment in pregnant women.

LIMITATION

Since it was a retrospective study, the present authors could not include fT4 which was only estimated in individuals with abnormal thyroid function. In addition, the factors affecting the thyroid function such as iodine status and Body mass index (BMI) could not be studied.

CONCLUSION

Region-specific and trimester-specific reference intervals for TSH during pregnancy need to be established in different demographic and ethnic groups with respect to the iodine levels. The region-specific reference interval for TSH was found to be 0.43-4.5 mU/L were majority of the population was pescetarian, and was presumed to have iodine-sufficiency.

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