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ORIGINAL ARTICLE

Reference Levels for TSH in Iodine-Sufficient Low-Risk Pregnant Women

Bharti Goel[1] · Poonam Goel[1] · Jasbinder Kaur[2]

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Abstract

Background Recent evidence suggests that thyrotropin (TSH) levels are population specific because of differences in ethnicity. As a result, the 2017 ATA guidelines state that treatment may be tailored as per the laboratory-specific reference ranges of TSH for the local population instead of using a fixed upper limit of 2.5 mIU/L during pregnancy.

Methodology This was a cross-sectional study in which we collected detailed clinical data of 604 pregnant women along with their TSH and spot urinary iodine excretion levels. Reflex testing for thyroid peroxidase antibodies (TPOAb) was done in women with TSH levels > 2.5 mIU/L in 1st trimester and 3.0 mIU/L in 2nd and 3rd trimester. After excluding 295 women who had high risk factors as per ATA 2017 guidelines and those who were TPOAb positive, we calculated the reference range for TSH in an iodine-sufficient low-risk cohort of 309 women.

Results With median urinary Iodine of 255 µg/l, our population had more than required iodine levels. The 5th and 95th percentiles of TSH in our study cohort of 604 women were 0.64 and 7.81 mIU/L, respectively, while the 5th and 95th percentiles of TSH for the low-risk cohort of 309 women were 0.59 and 4.48 mIU/L, respectively.

Conclusion An upper limit of 4.5 mIU/L for TSH level during pregnancy can be used to guide management decisions for low-risk North Indian women.

Keywords Hypothyroidism · Pregnancy · Reference range · TSH

Introduction

Thyroid health is very important for maternal health and fetal development. Changes in thyroid physiology during pregnancy and profound effect of thyroid hormones on feto-maternal well-being necessitate that pregnancy-specific reference range of TSH (thyrotropin) levels should be known. Previously, the American Thyroid Association (ATA, 2011) [1] and the Endocrine Society (2012) [2] had defined trimester-specific cutoffs for thyrotropin (TSH) levels with an upper limit of 2.5 mU/l in the 1st trimester and 3.0 mU/l in the 2nd and 3rd trimester to diagnose subclinical hypothyroidism (SCH), with levels > 10.0 mIU/L being cutoff for overt hypothyroidism in asymptomatic women. However, evidence suggests that TSH levels are population specific because of differences in ethnicity [3]. As a result, the 2017 ATA guidelines state that treatment with levothyroxine may be tailored as per the laboratory-specific reference ranges of TSH for the local population [4]. Adherence to a TSH level of 2.5 mIU/L as the upper limit of normal leads to over-diagnosis and overtreatment of a large group of asymptomatic women which is unwarranted. Studies all over the world have found very high prevalence rates of hypothyroidism when lower cutoff levels for TSH have been used during pregnancy [5]. Hence, it is imperative to have laboratory-specific reference ranges for TSH to guide management plans.

Dr Bharti Goel is a Professor, Department of Obstetrics & Gynaecology, GMCH, Chandigarh, India; Prof. Poonam Goel is a Professor, Department of Obstetrics & Gynaecology, GMCH, Chandigarh, India; Prof. Jasbinder Kaur is a Prof & Head Department of Biochemistry, Director Principal, Government Medical College & Hospital (GMCH), Chandigarh, India.

✉ Bharti Goel
bhartigoel14@gmail.com

[1] Department of Obstetrics and Gynaecology, Government Medical College and Hospital (GMCH), Sector - 32, Chandigarh, India

[2] Department of Biochemistry, Government Medical College and Hospital (GMCH), Sector - 32, Chandigarh, India

Methodology

We conducted a cross-sectional study in the outpatient clinic of Obstetrics and Gynecology Department in collaboration with the Department of Biochemistry, in a tertiary care center. The aim was to assess the thyroid function by measurement of TSH levels in a cohort of pregnant women. This study was funded by the Department of Science and Technology. After taking relevant approvals from the institutional research and ethics committee, we collected clinical data of 604 pregnant women presenting consecutively in Gynae OPD. Informed consent was taken prior to enrollment for study. Samples for thyrotropin (TSH) levels and spot urinary iodine excretion (UIE) levels were obtained at the first visit. Reflex testing for thyroid peroxidase antibodies (TPOAb) was undertaken for women with TSH levels > 2.5 mIU/L in 1st trimester and 3.0 mIU/L in 2nd and 3rd trimester (SCH). TSH and TPOAb levels were measured by chemiluminescence technique using commercially available kits by Advia Centaur XP analyzer system (Siemens Healthcare Diagnostics). Laboratory reference range for TSH was 0.35–5.5 mIU/L. Women with TPOAb value > 60 IU/ml were considered positive as per the manufacturer's recommendation. Urinary iodine was measured by an assay based on Sandell–Kolthoff reaction (wet digestion method).

The cohort was further divided into two groups based on clinical evaluation and TSH levels. Group A, the high-risk group, included women with past history of thyroid dysfunction in self or in family; any history of current signs/symptoms of thyroid dysfunction; history of type 1 diabetes or any other auto-immune disease; past history of miscarriage, pre-eclampsia, placental abruption or preterm delivery; or history of use of drugs/agents that can alter thyroid function such as amiodarone, lithium or iodinated radiologic contrast. Women with BMI > 35 kg/m^2, history of infertility, age > 30 years, history of two or more prior pregnancies and goiter on clinical examination were also included in group A. Further, women with SCH who were found to be positive for TPOAb were also included in Group A. All other low-risk women were included in group B.

Results

TSH levels ranged from 0.36 to 150.40 mIU/L for the study cohort of 604 women with 2.5th and 97.5th percentiles being 0.53 and 11.89 mIU/L, respectively, and 5th and 95th percentiles being 0.64 and 7.81 mIU/L, respectively. Trimester-wise distribution of enrolled women was 66.6% ($n = 402$), 28.3% ($n = 171$) and 5.1% ($n = 31$) women in 1st, 2nd and 3rd trimesters, respectively. 24.8% women ($n = 150$) in 1st trimester and 8.4% women ($n = 51$) in 2nd and 3rd trimester had TSH levels > 2.5 mIU/L and 3.0 mIU/L, respectively. TPOAb was tested in these 201 women, and 38.7% ($n = 77$) were found to be positive. Overt hypothyroidism was found in 3.8% ($n = 23$), and five women (0.8%) gave history of hyperthyroidism diagnosed prior to the index pregnancy and well controlled on medication. The lowest level of TSH in this study was 0.4 mIU/L. The median urinary iodine (MUI) level was 255 µg/l, which was more than adequate as per WHO standards [6]. After excluding high-risk women (Group A), we had a cohort of 309 low-risk women (Group B) who did not have iodine deficiency (MUI = 255 µg/l). Table 1 shows the trimester-wise distribution of TSH levels in these low-risk women.

Overall, the 2.5th and 97.5th percentile values for TSH for the low-risk cohort were 0.46 and 5.6 mIU/L, while the 5th and 95th percentiles were 0.59 and 4.48 mIU/L, respectively. On further analysis, we found that TPOAb positivity in pregnant women with TSH levels between 2.5 and 4.5 mIU/L was significantly lower than in women with TSH levels > 4.5 mIU/L, $p = 0.001$(Table 2). This prompts us to consider the 95th percentile value of 4.48 mIU/L as the upper limit of normal TSH level in our cohort.

Table 1 Trimester-wise range of TSH levels in 309 low-risk TPOAb-negative women

Percentiles	1st trimester ($n = 195$)	2nd trimester ($n = 95$)	3rd trimester ($n = 19$)
2.5	.4080	.4920	.4200
5	.5780	.6140	.4200
25	1.1500	1.6100	1.0300
50	1.6500	2.3000	2.1000
75	2.3000	2.7500	3.1400
95	4.6080	3.7260	4.7600
97.5	5.9290	4.4400	4.7600

Table 2 Correlation between TSH levels and thyroid peroxidase antibodies

	TPOAb negative (≤ 60 IU/ml)	TPOAb positive (> 60 IU/ml)
TSH ≤ 4.5 mIU/L	90 (70.3%)	38 (29.7%)
TSH > 4.5 mIU/L	34 (46.6%)	39 (53.4%)
p value	.001	
Linear-by-linear association	11.028	
Likelihood ratio	10.998	

Discussion

Thyroid gland and its functioning are affected by the physiological changes that occur during pregnancy. This influences the thyroid function tests in the pregnant women. Further, anomalies in thyroid function profoundly affect feto-maternal well-being. In a study conducted by Meena et al., apparently euthyroid women with significant levels of TPOAb levels were found to have adverse fetal outcomes [7]. Hence, precise measurement of thyroid function during pregnancy, especially in high-risk pregnancies, is of great importance. However, the reference ranges for the most widely applied tests, thyroid-stimulating hormone (TSH) and free thyroxine (FT4) may vary significantly in different populations because of ethnic and laboratory procedure-dependent variations. Also, studies have shown that thyroid function tests (TFTs) of healthy pregnant women differ from those of healthy non-pregnant women because of profound impact of pregnancy on thyroid gland [8]. This makes standardization of test results difficult. Current recommendations support screening of women at high risk of thyroid dysfunction in pre-pregnancy period or immediately after conception [4, 9]. However, there is high prevalence of subclinical thyroid dysfunction in India ranging from 10 to 15%. Hence, many clinicians prefer to universally screen all pregnant women to rule out thyroid dysfunction [10, 11].

Efforts have been made to define reference ranges of TSH during pregnancy to guide clinical practice. In 2008, Marwaha et al. established reference range for thyroid hormones in normal pregnant Indian women [12]. The authors used clinical evaluation and thyroid ultrasound to define their cohort of healthy pregnant women. Subsequently, population-specific range of thyroid function tests has been proposed by researchers from different regions of India [9, 13, 14]. Regional ethnic and procedural variations are evident from these studies. Hence, the recommendation of ATA in 2017 to use population-specific reference ranges holds ground [4].

With this context, reference range of TSH in iodine-sufficient, TPOAb-negative healthy pregnant women, without any high-risk features, has been computed in this study. The 5th and 95th percentile values have been used to define the reference range. While the normative range for TSH in the 1st trimester was found to be 0.58–4.61 mIU/L, the overall range for the healthy cohort irrespective of period of gestation was found to be 0.59 and 4.48 mIU/L. With an MUI level of 255 µg/l, this population had more than sufficient iodine levels. Also, these women were negative for TPOAb antibodies. Further, we found that women with TSH levels higher than 4.5 mIU/L had significantly higher positivity rates for TPOAb antibodies, $p = 0.001$. A Cochrane review has shown that mildly elevated TSH levels in TPOAb-negative women are not associated with adverse pregnancy outcomes [15]. These observations can significantly impact clinical practice by providing a reference point up to which levothyroxine replacement therapy need not be started in asymptomatic, low-risk TPOAb-negative pregnant women. Hence, overtreatment and undue anxiety can be prevented.

Further, we agree with Khadilkar that longitudinal studies and prospectively collected data regarding feto-maternal outcomes in these apparently normal pregnancies can further guide levothyroxine therapy. Until that time, the recommendation for screening women with TSH levels between 2.5 and 4.5 mIU/L for TPOAb can help us to identify women who might benefit from low-dose levothyroxine replacement therapy [16].

Implication for Policy and Practice

Population-specific reference range for TSH levels with an upper limit of 4.5 mIU/L will prevent unwarranted treatment of low-risk women with levothyroxine replacement therapy. Also obstetric management can be streamlined by preventing unnecessary interventions in low-risk pregnant women.

Limitation of the Study

We did not study free T4 levels in our study cohort. This could have strengthened our evidence if the levels of free T4 were found to be normal in our low-risk cohort with TSH levels ≤ 4.5 mIU/L. Also data regarding feto-maternal outcomes of the apparently healthy low-risk women were not collected.

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Author contributions BG contributed to the concept and design of study, acquisition of data, analysis and interpretation of data, and drafting the article. PG and JK performed refining the methodology and revising it critically for important intellectual content.

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Declarations

Conflict of interest None declared.

Ethical Approval The research project was approved by the Institutional research and ethics committee.

References

1. Stagnaro-Green A, Abalovich M, Alexander E, et al. Guidelines of the American Thyroid Association for the diagnosis and management of thyroid disease during pregnancy and postpartum. Thyroid. 2011;21(10):1081–125.
2. Garber JR, Cobin RH, Gharib H, et al. Clinical practice guidelines for hypothyroidism in adults: cosponsored by the American Association of Clinical Endocrinologists and the American Thyroid Association. Endocr Pract. 2012;18(6):988–1028.
3. Haddow JE, Knight GJ, Palomaki GE, et al. The reference range and within-person variability of thyroid stimulating hormone during the first and second trimesters of pregnancy. J Med Screen. 2004;11:170–4.
4. Alexander EK, Pearce EN, Brent GA, et al. Guidelines of the American Thyroid Association for the Diagnosis and Management of Thyroid Disease during pregnancy and the postpartum. Thyroid. 2017;27(3):315–89.
5. Lara MC, Sánchez ÁV, Solano CC, et al. Hypothyroidism screening during first trimester of pregnancy. BMC Pregnancy Childbirth. 2017;17(1):438.
6. WHO. Urinary iodine concentrations for determining iodine status deficiency in populations. Vitamin and Mineral Nutrition Information System. Geneva: World Health Organization; 2013. WHO/NMH/NHD/EPG/13.1. http://www.who.int/nutrition/vmnis/indicators/urinaryiodine. Accessed 20 Jan 2020.
7. Meena A, Nagar P. Pregnancy outcome in euthyroid women with anti-thyroid peroxidase antibodies. J Obstet Gynecol India. 2016;66(3):160–5.
8. Kalra S, Agarwal S, Aggarwal R, et al. Trimester-specifc thyroid-stimulating hormone: an Indian perspective. Indian J Endocr Metab. 2018;22(1):1–4.
9. National Guidelines for Screening of Hypothyroidism during Pregnancy. Maternal Health Division Ministry of Health & Family Welfare Government of India December 2014. http://www.nrhmorissa.gov.in/writereaddata/Upload/Documents/National_Guidelines_for_Screening_of_Hypothyroidism_during_Pregnancy.pdf. Accessed on 9 Jan 2021.
10. Ajmani SN, Aggarwal D, Bhatia P, et al. Prevalence of overt and subclinical thyroid dysfunction among pregnant women and its effect on maternal and fetal outcome. J Obstet Gynecol India. 2014;64(2):105–10.
11. Goel B, Singh A, Goel P, et al. Evaluation of high risk screening protocol for detection of overt hypothyroidism in pregnancy. Int J Reprod Contracept Obstet Gynecol. 2018;7(11):4581–6.
12. Marwaha RK, Chopra S, Gopalakrishnan S, et al. Establishment of reference range for thyroid hormones in normal pregnant Indian women. BJOG. 2008;115(5):602–6.
13. Maji R, Nath S, Lahiri S, et al. Establishment of trimester-specific reference intervals of serum TSH & fT4 in a pregnant Indian population at North Kolkata. Indian J Clin Biochem. 2014;29:167–73.
14. Jebasingh FK, Salam R, Meetei TL, et al. Reference intervals in evaluation of maternal thyroid function of Manipuri women. Indian J Endocrinol Metab. 2016;20:167–70.
15. Spencer L, Bubner T, Bain E, et al. Screening and subsequent management for thyroid dysfunction pre-pregnancy and during pregnancy for improving maternal and infant health. Cochrane Database Syst Rev. 2015;9:CD011263.
16. Khadilkar S. Thyroid-stimulating hormone values in pregnancy: cutoff controversy continues? J Obstet Gynecol India. 2019;69:389–94.

About the Author

Dr. Bharti Goel has been working as a Consultant in Obstetrics & Gynecology at Government Medical College & Hospital, Chandigarh for the last sixteen years. She has a keen interest in the preventive aspects of diseases. She has been actively involved in the management of women with STIs and HIV/AIDS after her training as Resource Faculty for the State AIDS Control Organization. After her training in surgical oncology at Tata Memorial Hospital, Mumbai, she has been engaged in managing patients with gynecologic cancers.