Original Article

Thyroid status of the pregnant women of Manipur: A comparison of American Thyroid Association guidelines and normal laboratory reference range

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ABSTRACT

Gestation is the period when the thyroid function parameters undergo several changes. As the range of thyroid hormone levels differ in the gestational period due to the various physiological changes, the hormonal range, which is used for the normal population cannot be used for pregnant women. Our study was done to find the thyroid status of pregnant women by comparing the trimester specific range as published by American Thyroid Association (ATA) guidelines with the normal population/ laboratory reference range. A total of 377 patients with a distribution of 110,149 and 118 among the trimesters were studied. One patient each in first and second trimester had overt hypothyroidism when trimester specific reference range as published by ATA was followed. The prevalence of subclinical hypothyroidism as per ATA guidelines were 34.4, 31.5 and 30.5%, in the respective trimesters. The prevalence of subclinical hypothyroidism on taking into account the normal laboratory reference range of 3.6, 2.6 and 6.8% in the respective trimesters. Overt hypothyroidism was seen, one each in the first and second trimester and 29.3% were misdiagnosed as normal patients in this study. It is inferred that large number of patients will be misdiagnosed as having normal thyroid function during pregnancy if the trimester specific reference range is not followed. Thus we conclude that the pregnancy reference range should be used to interpret the thyroid hormones in pregnancy to avoid the misdiagnosis, as thyroid hormones are necessary for the normal fetal brain development.

Key words: Hypothyroidism, pregnancy, subclinical hypothyroidism, thyroid hormones

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INTRODUCTION

Thyroid hormones are critical for the development of the fetal brain. Since the fetus does not completely establish its own thyroid functions until 20 weeks of pregnancy, fetal thyroid hormones are derived mainly from the mother in early pregnancy.[1-3] Haddow *et al*.[2] and Pop *et al*.[3] reported that maternal hypothyroidism and hypothyroxinemia occurring in the first half of pregnancy might be harmful to embryo-fetal brain development and lead to intellectual retardation in the offspring. The availability of thyroxine to the developing fetal neurones is vital for their maturation and proper function.[4]

Human chorionic gonadotropin (hCG) is raised during pregnancy, which as a result of structural similarity has intrinsic thyrotrophic activity causing thyroid stimulation.[5] During pregnancy estrogen promotes production of a more highly sialylated T4-binding globulin isoform that is less rapidly degraded, resulting in increased serum T4-binding globulin and T4 concentrations.[6] Normal suppression of thyroid stimulating hormone (TSH) during pregnancy is often misdiagnosed as subclinical hyperthyroidism. Greater concern is that there is a potential failure to identify women with early hypothyroidism because of suppressed TSH.[5]

Laboratory reference intervals for thyroid function tests have traditionally been derived from non-pregnant subjects who are free from thyroid disease. So their validity in pregnant women is debatable as

pregnancy produces profound physiological changes in the mother, which in turn complicate the interpretation of maternal thyroid function tests. Interpretation of thyroid function test in pregnant women using non-pregnant reference intervals could potentially result in misclassification of a significant percentage of results to the tune of 5.6–18.3%.[7] This study was done to find out the discrepancy in thyroid status of pregnant women in Manipur by comparing the trimester specific range as published by American Thyroid Association (ATA) guidelines with the non-pregnant/ laboratory reference range.

MATERIALS AND METHODS

The cross-sectional study was undertaken after the approval of the Institutional Ethics Committee (IEC). Pregnant women more than 18 years of age with singleton intrauterine gestation, who gave a valid written consent, were included in the study.

Exclusion criteria: Patients who were already on oral thyroxine replacement or anti-thyroid treatment or on any drugs which affect the thyroid metabolism and who had clinically visible or palpable goiter or any autoimmune disorder were excluded from the study. Also, patients with family history of thyroid diseases or any autoimmune disorder were excluded. Patients with history of hyperemesis gravidarum were also excluded from the study.

The sample size was calculated with the precision of 95%, absolute error of 0.5. Variables in the study were gestational age, thyroid stimulating hormone (TSH), total thyroxine (TT4), and total triiodothyronine (TT3). The thyroid hormones (TSH, TT4 and TT3) were analyzed by Chemiluminescence assay using ADVIA Centaur manufactured by SIEMENS, New York, USA. The intra- and inter-assay coefficient of variation was 0.1 (10%).

According to the ATA guidelines, the pregnancy reference range of TSH are 0.1-2.5, and 0.2–3.0 and 0.3–3.0 mIU/L in the first, second and third trimesters, respectively.[8] The upper and lower limit of the manufacturer/non-pregnant reference range are TSH: 0.35–5.50 mIU/L; TT4: 4.5–12.6 μg/dl; TT3: 60–181 ng/dl.

Trimester-specific reference ranges for TSH were used to classify pregnant women into four groups: (1) Overt hypothyroidism (OH); (2) Subclinical hypothyroidism (SCH); (3) Low TSH and (4) Normal. A classification was made also according to the lower and upper ranges provided by the manufacturer for thyroid hormones.

RESULTS

In this cross-sectional study, 377 cases with singleton intrauterine gestation were evaluated. The thyroid status of these pregnant women was analyzed using ATA guideline 2011 as shown in Table 1.

The thyroid status of pregnant women was further assessed using the manufacturer's reference, which is not based on pregnant women [Table 2].

Then we compared the prevalence of subclinical hypothyroidism in these women using the manufacturer's reference range and the ATA reference range. This is a huge discrepancy in the prevalence of subclinical hypothyroidism as shown in Table 3. So if we rely on the manufacturer's reference range a large section of pregnant women with subclinical hypothyroidism will be passed off as normal with potential adverse outcome to the fetus and pregnancy.

Table 1: The thyroid status as per ATA guidelines

Trimester (number)	OH *n* (%)	SCH *n* (%)	Low TSH *n* (%)	Euthyroid state *n* (%)
First (110)	1 (0.9)	41 (34.4)	2 (1.8)	66 (62.9)
Second (149)	1 ((0.7)	47 (31.5)	0	101 (67.8)
Third (118)	0	36 (30.5)	0	82 (69.5)
Total (377)	2 (0.53)	124 (32.1)	2 (0.6)	249 (66.7)

OH: Overt hypothyroidism, SCH: Subclinical hypothyroidism, TSH: Thyroid stimulating hormone

Table 2: The thyroid status as per laboratory/non-pregnant reference range

Trimester (number)	OH *n* (%)	SCH *n* (%)	Low TSH *n* (%)	Euthyroid state *n* (%)
First (110)	1 (0.9)	4 (3.6)	5 (4.5)	100 (91.9)
Second (149)	1 (0.7)	4 (2.6)	1 (0.7)	143 (96.7)
Third (118)	0	8 (6.8)	0	110 (93.2)
Total (377)	2 (0.53)	16 (4.3)	6 (1.7)	343 (93.7)

OH: Overt hypothyroidism, SCH: Subclinical hypothyroidism, TSH: Thyroid stimulating hormone

Table 3: Misdiagnosed SCH patients on comparing the ATA and non-pregnant reference

Trimester (*n*)	SCH *n* (%)	SCH *n* (%)	Misdiagnosed patients *n* (%)
First (110)	41 (34.4)	4 (3.6)	39 (35.4)
Second (149)	47 (31.5)	4 (2.6)	43 (28.8)
Third (118)	36 (30.5)	8 (6.8)	28 (23.7)
Total (377)	124 (32.1)	16 (4.3)	110 (29.3)

OH: Overt hypothyroidism, SCH: Subclinical hypothyroidism, TSH: Thyroid stimulating hormone

DISCUSSION

Pregnancy is a period that places great physiological stress on both the mother and the fetus. When pregnancy is compounded by endocrine disorders such as hypothyroidism, the potential for maternal and fetal adverse outcomes can be immense.[2-5] Untreated maternal hypothyroidism and subclinical hypothyroidism in pregnancy is associated with adverse fetal and obstetric outcomes[9,10] which can be ameliorated by adequate levo-thyroxine therapy.[11]

Higher maternal TSH levels even within the normal reference range are associated with an increased risk of miscarriages, fetal and neonatal distress[12] as well as preterm delivery.[13]

According to the ATA guideline published in October 2011, OH is defined as an elevated TSH (>2.5 mIU/L) in conjunction with a decreased FT4 concentration. Women with TSH levels of 10.0 mIU/L or above, irrespective of their FT4 levels, are also considered to have OH. SCH is defined as a serum TSH between 2.5 and 10 mIU/L with a normal FT4 concentration.[8]

In this study, there was one OH patient each in the first and second trimesters as per ATA guidelines. The prevalence of subclinical hypothyroidism was 34.4, 31.5 and 30.5%, in the respective trimesters with an overall percentage of 32.1%. Only two patients had low TSH in the first trimester alone. A similar study done in Italy, 12.3% and 2.6% had hypothyroidism (OH and SCH) and low TSH, respectively.[14]

In this study when the laboratory/non-pregnant reference was used, the prevalence of SCH was 3.6, 2.6 and 6.8%, in the respective trimesters. The overall prevalence was 4.3% in all three trimesters together. These results emulate the Indian and the western reports.

In this study 33, 29.5 and 23.7% were misclassified as normal women when the laboratory/non-pregnant reference was used. An overall of 29.3% in all trimesters together were misclassified as normal thyroid hormones. The prevalence of hypothyroidism (OH and SCH) in pregnancy ranges from 2–5% according to the western literature when non-pregnant reference was taken.[15]

In a study done by Gayathri *et al*., the prevalence of SCH was 2.8% when the non-pregnant reference range was used. When the criterion of TSH less than 2.5 was used, the prevalence of SCH increased markedly to 18.98%. In all, 16.2% were misdiagnosed as normal in their study.[16] Study done by Altomare *et al*. had mentioned that using non-pregnant reference range for TSH, 10.6% of women were misclassified.[14] But in this study the misclassified cases were more than that of the previous Indian study and western study by Altomare *et al*. This may be because of inadequate intake in our population though in this study we did not estimate urinary iodine. The Indian study showed a misdiagnosis of 16.8% patients.[16]

A study done by Klein *et al*. had shown SCH prevalence of 2.5% with 0.3% of OH.[17] The prevalence of OH is 0.5% and the prevalence of OH is 0.3% in pregnancy.[18] In this study the prevalence of OH was 0.53%. Further, when the laboratory/non-pregnant reference range was used, 1% of normal patients were misdiagnosed to be having subclinical hyperthyroidism. These patients were normal as per ATA guidelines. This is because of the structural similarity between the hCG and TSH.[5]

If the non-pregnant reference intervals are used to interpret the thyroid status inpregnant women there was misclassification of thyroid status in 6.1–31.0% of women.[19] In China, the percentage of potentially misclassified cases of subclinical hypothyroidism and hypothyroxinemiain pregnant women was decreased by using the gestational age-specific reference intervals.[20] There is similar data from Malaysia.[21]

In the Australian study by Gilbert *et al*., if the non-pregnant TSH reference range was applied to the study participants, 344 women (16.0%) whose serum TSH concentration was within the first-trimester-specific reference range would be misclassified as having subclinical hyperthyroidism, and 98 women (4.5%) with a TSH concentration above the first-trimester-specific upper reference limit would not be identified.[22]

Untreated maternal hypothyroidism can lead to preterm birth, low birth weight, and respiratory distress in the neonate. Enough evidence has been accumulated over the years about the role of thyroxine in normal development of the fetal brain. A number of pioneering studies by Haddow *et al*.[2] and Pop *et al*.[3] have conclusively proved that children born to mothers with hypothyroidism had a significantly increased risk of impairment in IQ scores, neuropsychological developmental indices and learning abilities. Children born to untreated hypothyroid women had an IQ score that was 7 points below the mean IQ of children born to healthy women and women given thyroxine supplements. This risk applies to children born not only of untreated women, but also women with suboptimal supplementation.[2-4,23,24]

We conclude that gestational specific reference range should be used in interpreting the thyroid hormones during pregnancy to prevent misclassification of patients, as hypothyroidism has a detrimental effect on both mother and the developing fetus.

REFERENCES

1. De Escobar GM, Obregon MJ, del Rey FE. Maternal thyroid hormones early in pregnancy and fetal brain development. Best Pract Res Clin Endocrinol Metab 2004;18:225-48.
2. Haddow JE, Palomaki GE, Allan WC, William JR, Knight GJ, Gagnon J, *et al*. Maternal thyroid deficiency during pregnancy and subsequent neuropsychological development of the child. N Engl J Med 1999;341:549-55.
3. Pop VJ, Brouwers EP, Vader HL, Vulsma T, van Baar AL, de Vijlder JJ. Maternal hypothyroxinaemia during early pregnancy and subsequent child development: A 3 year follow-up study. Clin Endocrinol (Oxf) 2003;59:282-8.
4. Williams GR. Neurodevelopmental and neurophysiological actions of thyroid hormone. J Neuroendocrinol 2008;20:784-94.
5. Cunningham FG, Leveno KJ, Bloom SL. Maternal physiology. In: Dashe JS, Alexander MJ, Hoffman BL, Sheffield JS, Mahendro MS, Casey BM, editors. Obstetrics. 23rd ed. New York: McGraw-Hill; 2010. p. 107-35.
6. Burrow GN, Fisher DA, Larsen PR. Maternal and fetal thyroid function. N Engl J Med 1994;331:1072-8.
7. Stricker R, Echenard M, Eberhart R, Chevailler MC, Perez V, Quinn FA, *et al*. Evaluation of maternal thyroid function during pregnancy: The importance of using gestational age-specific reference intervals. Eur J Endocrinol 2007;157:509-14.
8. Stagnaro-Green A, Abalovich M, Alexander E, Azizi F, Mestman J, Negro R, *et al*. Guidelines of the American Thyroid Association for the diagnosis and management of thyroid disease during pregnancy and postpartum. American Thyroid Association Taskforce on Thyroid Disease during Pregnancy and Postpartum. Thyroid 2011;21:1081-125.
9. Casey BM, Dashe JS, Wells CE, McIntire DD, Byrd W, Leveno KJ, *et al*. Subclinical hypothyroidism and pregnancy outcomes. Obstet Gynecol 2005;105:239-45.
10. Negro R. Thyroid insufficiency during pregnancy: Complications and implications for screening. Expert Rev Endocrinol Metab 2008;32:1-10.
11. Negro R, Formoso G, Mangieri T, Pezzarossa A, Dazzi D, Hassan H. Levothyroxine treatment in euthyroid pregnant women with autoimmune thyroid disease: Effects on obstetrical complications. J Clin Endocrinol Metab 2006;91:2587-91.
12. Benhadi N, Wiersinga WM, Reitsma JB, Vrijkotte TG, Bonsel GJ. Higher maternal TSH levels in pregnancy are associated with increased risk for miscarriage, fetal or neonatal death. Eur J Endocrinol 2009;160:985-91.
13. Stagnaro-Green A, Chen X, Bogden JD, Davies TF, Scholl TO. The thyroid and pregnancy: A novel risk factor for very preterm delivery. Thyroid 2005;15:351-7.
14. Altomare M, La Vignera S, Asero P, Recupero D, Condorelli RA, Scollo P, *et al*. High prevalence of thyroid dysfunction in pregnant women. J Endocrinol Invest 2013;36:407-11.
15. LeBeau SO, Mandel SJ. Thyroid disorders during pregnancy. Endocrinol Metab Clin North Am 2006;35:117-36.
16. Gayathri R, Lavanya S, Raghavan K. Subclinical hypothyroidism and autoimmune thyroiditis in pregnancy-a study in south Indian subjects. J Assoc Physicians India 2009;57:691-3.
17. Klein RZ, Haddow JE, Faix JD, Brown RS, Hermos RJ, Pulkkinen A, *et al*. Prevalence of thyroid deficiency in pregnant women. Clin Endocrinol (Oxf) 1991;35:41-6.
18. Stagnaro-Green A. Overt hyperthyroidism and hypothyroidism during pregnancy. Clin Obstet Gynecol 2011;54:478-87.
19. Wang QW, Yu B, Huang R, Cao F, Zhu Z, Sun D, *et al*. Assessment of thyroid function during pregnancy: The advantage of self-sequential longitudinal reference intervals. Arch Med Sci 2011;7:679-84.
20. Shan ZY, Chen YY, Teng WP, Yu XH, Li CY, Zhou WW, *et al*. A study for maternal thyroid hormone deficiency during the first half of pregnancy in China. Eur J Clin Invest 2009;39:37-42.
21. Thevarajah M, Chew YY, Lim SC, Sabir N, Sickan J. Determination of trimester specific reference intervals for thyroid hormones during pregnancy in Malaysian women. Malays J Pathol 2009;31:23-7.
22. Gilbert RM, Hadlow NC, Walsh JP, Fletcher SJ, Brown SJ, Stuckey BG, *et al*. Assessment of thyroid function during pregnancy: First-trimester (weeks 9–13) reference intervals derived from Western Australian women. Med J Aust 2008;189:250-3.
23. Nambiar V, Jagtap VS, Sarathi V, Lila AR, Kamalanathan S, Bandgar TR, *et al*. Prevalence and impact of thyroid disorders on maternal outcome in Asian-Indian pregnant women. J Thyroid Res 2011;2011:429097.
24. Sahay RK, Nagesh VS. Hypothyroidism in pregnancy. Indian J Endocrinol Metab 2012;16:364-70.

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