Original Article

Subclinical hypothyroidism in pregnancy: An emerging problem in Southern West Bengal: A cross-sectional study

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Abstract

Background: Prevalence of subclinical hypothyroidism (SCH) in pregnancy varies widely in different parts of our country, but it has multiple adverse outcomes in both the mother and fetus. **Objectives:** This study was conducted to evaluate the prevalence of SCH in pregnant women during the first trimester and to identify the prevalence of thyroid autoimmunity in pregnant women. **Materials and Methods:** This cross-sectional study (March 2014 to February 2015) was conducted among the pregnant women attending antenatal clinic in their first trimester at a tertiary care center. Morning samples of study participants were analyzed for free thyroxin (FT4), thyroid stimulating hormone (TSH), and thyroid peroxidase antibody (TPO Ab). Data expressed as mean ± standard deviation and percentage (%) as applicable. **Results:** Of the 510 subjects, 168 had TSH value >2.5 μIU/ml (32.94%) with normal FT4 and they were diagnosed as SCH. TSH level >4.5 μIU/ml was estimated in 13.92% (71) of the subjects. TPO Ab was positive in 57 (33.93%) of subclinical hypothyroid and 5 (1.47%) of normal subjects. 70.42% (50) of the subjects with TSH >4.5 μIU/ml had positive TPO Ab. **Conclusions:** Prevalence of SCH is high in South Bengal and routine thyroid screening at the first antenatal visit should be done to reduce the social and financial burden caused by SCH.

Key words: Autoimmunity, first trimester, pregnancy, subclinical hypothyroidism

INTRODUCTION

Subclinical hypothyroidism (SCH) is characterized by increased serum thyroid stimulating hormone (TSH) and normal serum free thyroxin (FT4).[1] Prevalence of SCH in pregnancy varies widely worldwide.[2] In our country, prevalence of SCH varies from 2.8% in south India to 14.3% in northern part of the country.[3,4] SCH usually does not have any symptoms or sign in nonpregnant women but associated with multiple adverse outcomes in the mother and fetus including spontaneous abortion, preeclampsia, gestational hypertension, gestational diabetes, preterm delivery, and decreased intelligence quotient (IQ) in the offspring.[5,6] Though controversy exists, a study by Negro *et al.*, in 2010 has shown that treatment of SCH in pregnancy decreases adverse outcome.[7]

To prevent the adverse outcome of SCH on both mother and fetus, maternal serum TSH and FT4 assay is essential

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and to assess the cost-effectiveness of routine FT4 and TSH assay in a low resourceful country like ours it is necessary to determine the prevalence of SCH. To the horizon of our knowledge, no data about the prevalence of SCH in pregnant patients in South Bengal has been published. Our institute is a tertiary referral center (Medical College) of two districts of South Bengal and caters a large population of four districts of South Bengal. Therefore, the aim of this study was to assess the prevalence of SCH in pregnant women during the first trimester and to identify the prevalence of thyroid autoimmunity in pregnant women.

MATERIALS AND METHODS

After obtaining Ethical Committee clearance, a cross-sectional study of 12 months duration (From March 2014 to February 2015) was conducted by the Department of Obstetrics and Gynecology in collaboration with the department of Biochemistry at our institution. Seven hundred and three (703) pregnant women attending antenatal outpatient department (OPD) on a particular day of the week (Tuesday) throughout the study period in their first trimester for their first antenatal check-up was initially approached. History was taken in detail including present, past, obstetric, family, and personal history. None of the patients had previously diagnosed thyroid disorder (hypo- or hyper-thyroidism). All the patients were enquired about their family income to classify their socioeconomic status. Patients having family income of ten thousand rupees or less per month were classified as poor or lower middle socioeconomic status, those having family income of more than 10,000-25,000 belonged to middle class and those having more than 25,000 per month were included in the higher middle class. General survey including vital parameters such as pulse and blood pressure (by mercury sphygmomanometer) measurement was done in all patients. A complete physical and obstetrical examination was also done. Apart from recommended routine antenatal investigations (blood investigations and ultrasonography) blood for FT4, TSH and thyroid peroxidase antibodies (TPO-Ab) were advised. Five hundred and ten (510) patients returned with the report and after obtaining informed patient consent they were included in the study. Reference range used for FT4 and TSH are 0.8-1.7 ng/dl and 0.1-2.5 μIU/ml respectively.[8] All the women having normal FT4 with TSH >2.5 μIU/ml were diagnosed as SCH in this study. Blood samples were collected in OPD setting between 0900 and 1100 h in empty stomach. Serum FT4 and TSH estimation were done by Advia Centaur XP Siemens kit (ADVIA Centaur® ReadyPack) dedicated equipment using chemiluminescent immunoassay technique, and the anti-TPO assay was carried out by using Hycor kits by ELISA method using Elisa microplate reader (Goodhealth Inc.). All the tests were performed at the institutional biochemistry laboratory by qualified technicians under the supervision of clinical biochemist. Complete blood count, serum creatinine, and liver function test were also done to exclude renal and hepatic dysfunction. Data expressed as mean ± standard deviation and percentage (%) as applicable. Statistical analysis was performed using Statistical Package for the Social Sciences (SPSS Inc., Chicago, IL, USA), version 12.0.

RESULTS

The mean age of patients and mean gestational age were 18.7 ± 3.52 years and 7.6 ± 1.12 weeks respectively. Systolic and diastolic blood pressure in the present study was estimated to be 108.5 ± 7.34 and 63.7 ± 5.83 mmHg respectively. All the study subject belonged to either poor or lower middle socioeconomic status with family income of <10,000 rupees/month. Of 510 women, two had blood pressure more than 140/90 mmHg. None of the subjects had kidney or liver dysfunction. Four subjects had TSH values >10 μIU/ml (among these two have high blood pressure), two among them had FT4 less than normal and were diagnosed as overt hypothyroidism. Hence effectively 504 women undergo final analysis.

Out of the 510 subjects 168 had TSH value >2.5 μIU/ml (32.94%) with normal FT4 and they were diagnosed as SCH. TSH level >4.5 μIU/ml was estimated in 13.92% (71) of the subjects. TPO Ab was positive in 57 (33.93%) of SCH and 5 (1.47%) of normal subjects. 70.42% (50) of the subjects with TSH >4.5 μIU/ml had positive TPO-Ab. All the four subjects with TSH>10 μIU/ml were TPO-Ab positive. The level of TSH and FT4 of the whole study population was estimated to be 1.94 ± 4.45 μIU/ml and 1.05 ± 0.23 ng/dl respectively. Parameters related to thyroid dysfunction are given in Table 1.

DISCUSSION

During pregnancy production of thyroid hormones and requirement of iodine is increased by approximately 50% and

Table 1: Thyroid dysfunction in first trimester pregnant women

Parameters	Percentage (*n*)
Subclinical hypothyroidism (TSH >2.5 μIU/ml)	32.94 (168)
Subjects with TSH >4.5 μIU/ml	13.92 (71)
TPO Ab positive subjects	12.15 (62)
TPO Ab positive in SCH	33.93 (57)
TPO Ab positive in euthyroid subjects	1.47 (5)
TPO Ab positive in subjects with TSH >4.5 μIU/ml	70.42 (50)

TSH: Thyroid stimulating hormone, TPO Ab: Thyroid peroxidase antibody, SCH: Subclinical hypothyroidism

thyroid gland enlarges by 10% or more.[9,10] Thus, pregnancy creates a challenge for the thyroid, particularly where thyroid reserve is limited, or iodine deficiency is present.

National Association of Clinical Biochemistry have stated that it is likely that in future the upper limit of euthyroid reference range of serum TSH will be reduced to 2.5 μIU/ml from 4.5 μIU/ml for all adults, because more than 95% of normal euthyroid volunteers have serum TSH values between 0.4 and 2.5 μIU/ml.[11] However, the American Association of Clinical Endocrinologists has continued to recommend 4.5 μIU/ml as the upper limit of normal TSH value, although some individuals within the range of 2.6-4.5 μIU/ml may have subclinical thyroid disease, there is a lack of evidence of adverse outcome in this group.[1] However, American Thyroid Association Guidelines (2011) recommends 2.5 μIU/ml as the upper limit of TSH in the first trimester of pregnancy.[12] Recent Endocrine Society guidelines also suggested 0.1-2.5 μIU/ml as the "normal" range for TSH values in the first trimester and <3 μIU/ml in the second and third trimester, so in this study we have taken TSH value of 2.5 μIU/ml as cut-off to exclude to SCH in the first trimester.[7]

However, it is to be remembered that both the Endocrine Society and the American Thyroid Association recommend that each geographic area define the normal values for TSH for each of the three trimesters, and the cut-off of a TSH of 2.5 μIU/ml should only be used in the absence of local normative data, which is applicable in our scenario.[7,12] There are no data available to define the normal reference range for thyroid hormones in normal pregnant women in eastern India, only one study done in 2008 by Marwaha *et al*. in northern India is available where cut-off for TSH value is 5 μIU/ml in the first trimester.[13] However, this reference range is defined only on the data of 107 pregnant women and represents the population of north India.

In 2007, Gayathri *et al*. reported the prevalence of SCH 2.8% among the pregnant women in Chennai and 57.1% of the hypothyroid patients had positive TPO antibody.[3] Aggarwal *et al*. found the prevalence of SCH to be 10.9% among the pregnant women in a study conducted in an apex institute of north India and TPO antibody positivity was 59% among the hypothyroid mother in this study.[14] Thus, it is evident that the prevalence of SCH varies widely in a different part of the country among the pregnant women.

A recent study in 2014, conducted in Delhi by Dhanwal *et al*. has cited even higher prevalence of SCH (13.8%) among the pregnant women and a good number (57%) among them were TPO antibody positive.[4] All the studies mentioned above used cut-off value of TSH >4.5 μIU/ml to diagnose SCH.

In our study, we have found 32.94% of the pregnant mothers to be subclinical hypothyroid which is much higher than any other study conducted in India because we have reduced the cut-off for TSH to 2.5 μIU/ml. 13.92% of the subjects had TSH value >4.5 μIU/ml in this study, which is comparable to the study by Dhanwal *et al*.[4] Thus, it is found that when the cut-off for TSH value was reduced to 2.5 μIU/ml the prevalence of SCH was increased by more than 2 times.

TPO Ab positivity was found in 12.15% of the study population and 33.93% of the SCH pregnant women, which is slightly less than the other studies.[3,4] This is probably due to change in the reference range of TSH for SCH. It is observed in this study that 70.42% of the subjects with TSH >4.5 μIU/ml had TPO-Ab positive, which is even more than the previous studies.[3,4,14]

In our study, a small percentage of the euthyroid population had positive TPO-Ab (1.47%) in early pregnancy. This subgroup of the population is at increased risk of developing hypothyroidism and should be monitored every 4-6 weeks.[15,16]

Thyroid autoantibodies are positive in 5-15% of women during childbearing age and chronic autoimmune thyroiditis is the main cause of hypothyroidism, apart from iodine deficiency.[17] Other causes include radioiodine ablation or surgery for hyperthyroidism, thyroid tumor surgery, congenital hypothyroidism, and rarely, lymphocytic hypophysitis.[8]

Iodine is essential for the synthesis of T4, which is necessary for fetal brain development. Fetus is solely dependent on maternal T4 before the development of the fetal thyroid at 13-15 weeks of gestation; maternal iodine is still required for fetal thyroid hormone synthesis thereafter. During pregnancy, thyroid hormone synthesis increases by 20-40%, compensating for estrogen-induced thyroid binding globulin and increased iodine clearance.[8] Therefore, maternal iodine intake must be increased during pregnancy. Iodine stores should be replenished at conception with an iodine intake >150 μg/day.[18] Hence, iodine supplementation of iodine 150-200 μg/day in the form of potassium iodide or iodate may be considered in our country particularly in iodine deficient state like West Bengal.[19]

SCH has several ill-effects on both mother and the baby if goes untreated. Women with untreated SCH are 3 times and 1.8 times more likely to develop placental abruption and experience preterm labor, respectively.[5,20] SCH is also responsible for gestational hypertension whereas 36.1% of the women with overt hypothyroidism develops

gestational hypertension. The incidence of low birth weight is markedly increased in the case of overt as well as SCH. Fetal neurological development and cognitive function can be influenced by the thyroid status of the mother.[21] Contradictory observation also made by Lazarus *et al.* where they have found no benefit on IQ of the fetus when treated for SCH.[22]

Women with mild or overt hypothyroidism results in preterm delivery in 80% of the pregnancies whereas with adequate thyroxin replacement in early pregnancy preterm delivery can be reduced to 10%.[23] Women in the euthyroid state but with thyroid autoimmunity are twice likely to experience spontaneous miscarriage probably due to generalized activation of the immune system or transplacental transfer of thyroid receptor blocking antibodies.[9,24,25] There is weak evidence that administration of T4 may prevent miscarriage due to thyroid autoimmunity.[26]

The Indian guideline is still not clear about treating women with TSH between 2.5 and 4.5 μIU/ml, but Indian Thyroid Society guidelines have suggested that universal screening for thyroid profile during pregnancy at the first antenatal visit should be the norm.[27]

From the data available until date, it is evident that treatment of SCH in pregnancy leads to better outcome. One large National Institute of Health funded clinical trial is ongoing (likely results in 2016) and if universal screening of pregnant women becomes the standard in its recommendation, there will be a huge increase in the number of pregnant women requiring levothyroxine treatment.[27]

The absence of reference values for SCH in the eastern India and restriction of the study population to four districts of South Bengal are the limitations of the present study. A multicenter study involving all the tertiary centers of South Bengal is necessary to overcome this limitation.

CONCLUSION

We can conclude from the present study that the prevalence of SCH is high in South Bengal and routine thyroid screening at the first antenatal visit should be done to reduce the social and financial burden caused by SCH.

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Conflicts of interest

There are no conflicts of interest.

REFERENCES

1. Surks MI, Ortiz E, Daniels GH, Sawin CT, Col NF, Cobin RH, *et al.* Subclinical thyroid disease: Scientific review and guidelines for diagnosis and management. JAMA 2004;291:228-38.
2. Hennessey JV, Espaillat R. Subclinical hypothyroidism: A historical view and shifting prevalence. Int J Clin Pract 2015;69:771-82.
3. 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.
4. Dhanwal DK, Prasad S, Agarwal AK, Dixit V, Banerjee AK. High prevalence of subclinical hypothyroidism during first trimester of pregnancy in North India. Indian J Endocrinol Metab 2013;17:281-4.
5. 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.
6. 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.
7. Negro R, Schwartz A, Gismondi R, Tinelli A, Mangieri T, Stagnaro-Green A. Increased pregnancy loss rate in thyroid antibody negative women with TSH levels between 2.5 and 5.0 in the first trimester of pregnancy. J Clin Endocrinol Metab 2010;95:E44-8.
8. De Groot L, Abalovich M, Alexander EK, Amino N, Barbour L, Cobin RH, *et al.* Management of thyroid dysfunction during pregnancy and postpartum: An Endocrine Society clinical practice guideline. J Clin Endocrinol Metab 2012;97:2543-65.
9. van Raaij JM, Vermaat-Miedema SH, Schonk CM, Peek ME, Hautvast JG. Energy requirements of pregnancy in The Netherlands. Lancet 1987;2:953-5.
10. Glinoer D. The regulation of thyroid function in pregnancy: Pathways of endocrine adaptation from physiology to pathology. Endocr Rev 1997;18:404-33.
11. Baloch Z, Carayon P, Conte-Devolx B, Demers LM, Feldt-Rasmussen U, Henry JF, *et al.* Laboratory medicine practice guidelines. Laboratory support for the diagnosis and monitoring of thyroid disease. Thyroid 2003;13:3-126.
12. 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. Thyroid 2011;21:1081-125.
13. Marwaha RK, Chopra S, Gopalakrishnan S, Sharma B, Kanwar RS, Sastry A, *et al.* Establishment of reference range for thyroid hormones in normal pregnant Indian women. BJOG 2008;115:602-6.
14. Aggarwal N, Suri V, Joshi B, Dutta P, Bhanshali A, Mukhopadhyay K. Prevalence and impact of subclinical hypothyroidism on pregnancy — Prospective study from apex institute of North India. Indian J Appl Res 2014;4:404-6.
15. Mandel SJ. Hypothyroidism and chronic autoimmune thyroiditis in the pregnant state: Maternal aspects. Best Pract Res Clin Endocrinol Metab 2004;18:213-24.
16. Alexander EK, Marqusee E, Lawrence J, Jarolim P, Fischer GA, Larsen PR. Timing and magnitude of increases in levothyroxine requirements during pregnancy in women with hypothyroidism. N Engl J Med 2004;351:241-9.
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. WHO Secretariat, Andersson M, de Benoist B, Delange F, Zupan J. Prevention and control of iodine deficiency in pregnant and lactating women and in children less than 2-years-old: Conclusions and recommendations of the technical consultation. Public Health Nutr 2007;10:1606-11.
19. Pandav CS, Yadav K, Srivastava R, Pandav R, Karmarkar MG. Iodine deficiency disorders (IDD) control in India. Indian J Med Res 2013;138:418-33.

20. 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.
21. Leung AS, Millar LK, Koonings PP, Montoro M, Mestman JH. Perinatal outcome in hypothyroid pregnancies. Obstet Gynecol 1993;81:349-53.
22. Lazarus JH, Bestwick JP, Channon S, Paradice R, Maina A, Rees R, *et al*. Antenatal thyroid screening and childhood cognitive function. N Engl J Med 2012;366:493-501.
23. Abalovich M, Gutierrez S, Alcaraz G, Maccallini G, Garcia A, Levalle O. Overt and subclinical hypothyroidism complicating pregnancy. Thyroid 2002;12:63-8.
24. Prummel MF, Wiersinga WM. Thyroid autoimmunity and miscarriage. Eur J Endocrinol 2004;150:751-5.
25. Stagnaro-Green A, Glinoer D. Thyroid autoimmunity and the risk of miscarriage. Best Pract Res Clin Endocrinol Metab 2004;18:167-81.
26. Negro R, Mangieri T, Coppola L, Presicce G, Casavola EC, Gismondi R, *et al*. Levothyroxine treatment in thyroid peroxidase antibody-positive women undergoing assisted reproduction technologies: A prospective study. Hum Reprod 2005;20:1529-33.
27. Jacob JJ. Subclinical hypothyroidism in the first trimester of pregnancy in North India. Indian J Endocrinol Metab 2013;17 Suppl 1:S160-1.