Review Article

Subclinical hypothyroidism in female

Pinkee Saxena

Department of Obstetrics and Gynaecology, Deen Dayal Upadhyaya Hospital, Hari Nagar, New Delhi, India

Abstract Hypothyroidism is commonly seen in women in the reproductive age group. Overt hypothyroidism is associated with maternal and fetal complications and hence needs to be treated. However there is no uniform consensus whether or not a women with subclinical hypothyroidism should be treated or not. Review of literature was done using pubmed and online database search. ACOG does not recommend treating all cases of SCH in pregnancy. Other endocrine organizations do recommend treating SCH in pregnancy. Since there is lack of clear guidance treatment must be individualised for each patient.

Keywords: Infertility, pregnancy, subclinical hypothyroidism

Address for correspondence: Dr. Pinkee Saxena, MD (Obstetrics & Gynaecology), FICOG, FICMCH, Specialist Obs & Gyn, 534 Mandakini Enclave, Alaknanda, New Delhi - 110019, India.
E-mail: drpinkee@hotmail.com

INTRODUCTION

Pregnancy induces changes in the thyroid gland and its function. It leads to increase in the production of thyroxine (T_4) and triiodothyronine (T_3) by 50%. This in turn results in increased iodine requirement by 50%. These physiological changes of pregnancy on thyroid gland may result in manifestation of hypothyroidism in pregnant women. Placental human chorionic gonadotropin also has an influence on thyrotropin (TSH) levels and results in decreased TSH levels throughout pregnancy.

Hypothyroidism can either be overt or subclinical. It is well known that overt hypothyroidism (OH) has potential maternal and fetal complications and hence needs to be treated. However there is no uniform consensus whether or not a woman in the reproductive age group with subclinical hypothyroidism (SCH) should be treated or not.

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SUBCLINICAL HYPOTHYROIDISM (SCH)

OH is defined as an elevation in serum TSH during pregnancy more than the defined pregnancy-specific reference ranges (TSH >2.5 mIU/L) with a decreased free thyroxine (FT_4) concentration. Women with TSH levels of 10.0 mIU/L or above are considered to have OH[1] irrespective of their FT_4 levels.

SCH is defined as a TSH level greater than the upper limit of normal range (4.5–5.0 mIU/L) with normal FT_4 levels. The incidence of SCH in the reproductive-age population is approximately 2–2.5%.[1]

The diagnosis of SCH[2] should be made on trimester-specific reference ranges for TSH and T_4 (total or free) for given laboratory. If TSH trimester-specific reference ranges are not available in that laboratory, the following reference range upper limits should be considered: first trimester, 2.5 mU/l; second trimester, 3.0 mU/l; third trimester, 3.5 mU/l. Serum TSH must be measured in early pregnancy. If TSH is elevated, then the

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next step should be to determine serum FT_4 and thyroid peroxidase antibodies (TPOAb) levels. This will enable to identify the type of hypothyroidism. For cases in which TSH is elevated with negative TPOAb, thyroglobulin antibody (TgAb) should be measured. Thyroid ultrasound may be required to further evaluate the thyroid gland in some cases.

Causes of hypothyroidism differ in developed and developing countries. In the former, chronic autoimmune thyroiditis is the leading cause of hypothyroidism while in the later severe iodine deficiency accounts for majority of cases. Thyroid auto-antibodies are elevated in about 50% of pregnant women with SCH and in more than 80% with OH.

EFFECT OF SCH

Infertility

The incidence of SCH is similar in infertile women and the general female population. However, it is seen that the mean TSH level may be slightly higher in infertile women. Lincoln *et al.*[3] studied 704 infertile women receiving treatment for infertility. They found an elevated TSH level in 2.3% of women, of which 69% (11 of 16) women with hypothyroidism had ovulatory dysfunction. On treatment with levothyroxine, successful pregnancies were reported in 7 of 11 (64%) patients. Abalovich *et al.*[4] in their study reported an increased risk of unexplained infertility in women with SCH. Few studies that have analyzed the relation between thyroid antibodies and unexplained subfertility, have reported that subfertility was more frequently seen in antibody-positive women (Abalvich *et al.*,[4] Bellver *et al.*,[5] and Poppe *et al.*[6]).

In a retrospective study, done on 355 infertile Finnish women, the authors reported an elevated serum TSH in 4% of infertile women who had no previous known history of thyroid dysfunction.[7] The prevalence was highest in those with ovulatory dysfunction (6%) and unexplained infertility (5%). SCH was, however, not found to be increased in infertile patient with other cause of infertility, including tubal block, etc.

Studies evaluating the impact of thyroid function tests in women undergoing assisted reproductive technology (ART) show conflicting report. A recent retrospective study[8] evaluated *in vitro* fertilization (IVF) patients and the association between abnormal TSH and early pregnancy loss. They concluded that miscarriage rate in IVF patients appears to have no relation to TSH levels. In a meta-analysis of seven studies done to evaluate the relation of thyroid antibodies in IVF outcome, it was noted that of 1760 women undergoing IVF for different indications, no association could be found between the presence of thyroid antibodies and the clinical pregnancy rates after IVF.[9]

In another meta-analysis[10] the effect of antithyroid antibody status alone on pregnancy outcomes in euthyroid women undergoing ART was evaluated. It was found that in subfertile euthyroid women whose SCH status is unknown, antithyroid antibody was associated with increased miscarriage rate and decreased delivery rate, but was not related to pregnancy rate. In subfertile euthyroid women without SCH, the present study did not detect a significant effect of antithyroid antibody status on pregnancy rate, miscarriage rate, and delivery rate.

Mintziori *et al.*[11] suggested thyroid screening in infertile women undergoing IVF. They said that in cases of SCH, where the TSH levels are more than the threshold value of 4.0 or 4.5 μIU/ml before IVF, levothyroxine replacement should be given. The same intervention might also be justified in women undergoing IVF with TSH concentration more than 2.5 μIU/ml.

Miscarriage

OH is associated with an increase in miscarriage rate. However, data regarding its association with SCH are unclear. Negro *et al.*[12] published data suggesting that SCH increases the risk of pregnancy complications in anti-thyroid peroxidase antibody positive (TPOAb+) women. In a prospective, randomized trial of >4000 women, all pregnant women were screened for TSH and TPOAb levels. In the study group, thyroid replacement therapy was started for pregnant women with TPOAb positive and TSH >2.5 mIU/L. In a control population, no LT_4 was provided to this group. It was seen that in women who received levothyroxine a significant decrease in pregnancy complications was noted. Also a significant increased rate of miscarriage was reported in pregnant women who were TPOAb negative with TSH levels between 2.5 and 5.0 mIU/L compared to those with TSH levels below 2.5 mIU/L (6.1% vs. 3.6%). Liu *et al.*[13] in their prospective study reported that women with SCH and thyroid autoimmunity (TAI) are at an increased risk of miscarriage between four and eight gestational weeks. Women with a combination of SCH and TAI were found to have the highest risk and earlier gestational ages of miscarriage.

However, some studies indicate contrasting results. Cleary-Goldman *et al.*[14] studied 10,990 pregnant women in first and second trimester of pregnancy and reported that subclinical maternal hypothyroidism had no adverse effect on these women.

In another study, Ashoor *et al.*[15] evaluated TSH and FT_4 levels in 202 singleton pregnancies at 11–13 weeks, which eventually, subsequently resulted in miscarriage or fetal death and compared with TSH and FT_4 levels with those of 4318 normal pregnancies. They reported that women whose pregnancy resulted in either miscarriage or fetal loss had increased TSH levels above the 97.5th percentile (5.9% vs. 2.5%) and FT_4 levels below the 2.5th percentile (5.0% vs. 2.5%).

At present, evidence suggests that SCH is associated with increased risk of miscarriage.

Adverse obstetric outcomes

Studies suggest that SCH increases the risk for obstetric complications such as placental abruption, preterm birth, preterm premature rupture of membranes, fetal death, gestational diabetes, and pre-eclampsia. In a large, observational study of 25,756 pregnant women, 2.3% were found to have elevated TSH at 15 weeks' gestation.[16] When compared, it was found that 1% of women with elevated TSH experienced placental abruption as compared to 0.3% with a normal TSH. Also preterm delivery was seen in 4% women who had elevated TSH and in 2.5% with normal TSH. Thyroid antibodies in the meta-analysis were associated with an increased risk of preterm delivery. One study found a significantly higher fetal death rate in the 2.2% of 9403 women, who had elevated TSH levels more than 6 mIU/L compared to women whose TSH was 3.8 mIU/L (12.5%).[17]

Association between SCH and pre-eclampsia and gestational hypertension has been shown by few studies. A retrospective study[18] on 24,883 pregnant women reported hypertension in pregnancy in 10.9% women with SCH and in 8.5% women with normal TSH. This study showed a significant association between SCH and severe pre-eclampsia. In another meta-analysis,[9] women with SCH were found to have increased risk to develop pre-eclampsia when compared to euthyroid women.

Reid *et al.*[19] reviewed studies to evaluate the role of treatment with levothyroxine for SCH. They found that levothyroxine treatment in women with TPOAb did not decrease pre-eclampsia significantly when compared to controls. However, a reduction in preterm birth and miscarriage was noted in women receiving levothyroxine therapy.

The association between SCH and gestational diabetes mellitus (GDM) is controversial. Toulis *et al.*[20] in their meta-analysis evaluated the of risk of GDM in pregnant women with SCH. They reported a modestly increased risk of GDM in pregnant women with SCH compared to euthyroid pregnant women. They said that compared to a euthyroid population, for every 43 pregnant women with SCH, there would be one case of GDM. These results, however, need to be evaluated further.

Fetal

Perinatal mortality was not increased in study of Negro *et al.*[12] In another meta-analysis, increased risk of perinatal mortality was seen in subclinical hypothyroid patients when compared to normal.[9] Studies regarding Apgar score in women with SCH are conflicting. Negro *et al.*[12] in their study said that the risk of a low Apgar score (>3) after 5 min was comparable in hypothyroid and euthyroid patients. Another study on 598 patients and 16,011 controls, indicated an increased risk for low Apgar score in patients with SCH.[5] Studies have reported that risk of congenital malformations is not increased in foetuses of pregnant women with SCH or in pregnant women having TAI.[16]

The detrimental effect of SCH on fetal neurological development is less clear. Haddow *et al.*[21] reported reduction in intelligence quotient (IQ) among children born to untreated hypothyroid women when compared with euthyroid controls. They reported a 7-point lower IQ in children of hypothyroid women than in control. Klein *et al.*[22] in their study showed that an inverse correlation exists between severity of maternal hypothyroidism and intelligence score in children. Association between maternal SCH and adverse fetal neurological development is not definitive though biologically plausible.

TREATMENT OF SCH

SCH has been associated with adverse maternal and fetal outcomes. There is lack of well controlled randomized trials. There is inadequate evidence to recommend for or against universal LT_4 treatment in TPOAb negative pregnant women with SCH.[1]

Women who are positive for TPOAb and have SCH should be treated[1] with LT_4.

The recommended treatment of maternal hypothyroidism is administration of oral levothyroxine. The goal of levothyroxine treatment is to normalize maternal serum TSH values within the trimester-specific pregnancy reference range. Levothyroxine in a patient diagnosed with SCH first time in pregnancy should be started in dose of 1.20 μg/kg/day.

Women with SCH in pregnancy, who are not initially treated with levothyroxine, should be monitored for progression to OH. Serum TSH and FT_4 should be done every 4 weeks until 16–20 weeks gestation and then at least once between 26 and 32 weeks gestation.[1]

In hypothyroid women on treatment with levothyroxine preconception, the amount of increase in levothyroxine may vary from 25 to 50%, depending on the aetiology of hypothyroidism and prepregnancy TSH level. TSH values should be checked every trimester and dose accordingly adjusted to maintain TSH to <2.5 mU/l. Following delivery, the levothyroxine dose should be reduced to the preconception dose. Women diagnosed with SCH during pregnancy with TSH less than 5 mU/l and negative TPOAb do not require levothyroxine after delivery. They must be re-evaluated periodically later on.

Screening

The American College of Obstetricians and Gynecologists (ACOG)[1] does not recommend universal screening for thyroid disorder in pregnancy. The American Association of Clinical Endocrinologists (AACE)[23] also does not recommend universal screening for pregnant patients or those planning pregnancy including IVF, but suggests aggressive case finding instead. However the American Society for Reproductive Medicine[24] does recommend testing for TSH in infertile women. Simple correction of TSH levels in infertile women can lead to pregnancy and avoid unnecessary investigations and procedure at times.

CONCLUSION

There is consensus that OH should be treated for both maternal and fetal benefit, but whether SCH should be treated is controversial. Although the risks for maternal and fetal complications are not conclusive, evidence do suggests a possible risk for adverse outcomes. ACOG does not recommend treating all cases of SCH[1] in pregnancy. Other endocrine organizations, such as the European Thyroid Association,[2] Endocrine Society, and the American Association of Clinical Endocrinologists, do recommend treating SCH in pregnancy. There is a lack of clear guidance from the literature in treatment of SCH. Till robust evidences follow, it is reasonable to leave the treatment decision up to the clinician and patient.

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Conflicts of interest

There are no conflicts of interest.

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