Subclinical hypothyroidism: Identification and treatment in pregnancy.

Hemanta Kumar Pradhan*

Obstetrics and Gynecology Department, All India Institute of Medical Sciences, Jodhpur, Rajasthan, India

Abstract

Deranged thyroid function tests are commonly encountered in pregnancy. Thyroid dysfunction is the second most frequent endocrine diseases among reproductive-aged women. Study in hypothyroidism has increased over the past few years as it affects development and growth in the offspring and can cause adverse effects on pregnancy outcome. A lot of research has been going on recently on the impact of subclinical hypothyroidism (SCH) on pregnancy outcome. Although the effect of clinical hypothyroidism on pregnancy is well known and replacement therapy is strongly recommended, but doubt exists about the effects of subclinical hypothyroidism and its need for replacement in pregnancy. This has led to much health organization to recommend routine thyroid screening in pregnancy.

Keywords: Pregnancy, Hypothyroid, Subclinical, Treatment

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Introduction

Thyroid disorders are the commonly detected endocrinopathies during pregnancy. It seems that prevalence of hypothyroidism is more in Asian countries compared with the West [1,2]. The majority of cases of hypothyroidism are considered to be subclinical type. In west, the prevalence of hypothyroidism is estimated to be 2-3% and 0.3-0.5% for subclinical and overt hypothyroidism respectively [2-4]. In India, the prevalence ranges from 4.8% to 11% [5,6]. Although clinical hypothyroidism during pregnancy is clearly associated with adverse fetal outcome, screening and treating subclinical hypothyroidism during pregnancy are subjects of on-going debate.

Physiological changes in thyroid gland during pregnancy

Anatomically the thyroid gland undergoes mild to moderate generalized enlargement during pregnancy caused by glandular hyperplasia as well as hypertrophy and increased vascularity to meet maternal and fetal needs. Such enlargement is not considered to be pathological but significant thyromegaly or any goiter should be investigated.

Pregnancy complicates the diagnosis by causing a number of changes in thyroid physiology. Thyroid binding globulin(TBG) is one of the several proteins that transport thyroid hormones in blood increases in pregnancy because of estrogen mediated decreased clearance [7] enhanced hepatic synthesis and a reduced degradation rate because of oligosaccharide modification [8]. TBG has the highest affinity for T4 as compare to T3. Increased level of TBG leads to lowered free T4 which result in elevated TSH secretion by pituitary and consequently enhanced production of thyroid hormone. The net effect of elevated TBG lead to a new equilibrium between bound and free thyroid hormones. So overall production of thyroid hormones remains elevated throughout pregnancy but free levels generally stay the same or are slightly decrease. hCG has a weak TSH activity because it shares similarity with TSH and can bind and transduce signal from TSH receptor on the thyroid epithelial cells results in increase release of T3 and T4, which lead to suppression of TSH.

Iodine requirement increases rapidly by approximately 50% during pregnancy [7] as the thyroid gland takes up iodine more rapidly and renal excretion increases particularly in first trimester [9] so more intake is required to maintained homeostasis. According to the WHO, daily iodine intake during pregnancy and lactation should be atleast 250 μg and should not exceed 500 μg [10]. This may be achieved by administering iodine supplements in the form of potassium iodide often as vitamin supplements. Adequate iodine intake during pregnancy should be preferably achieved before conception.

Diagnosis of sub-clinical hypothyroidism

Diagnosis of SCH can only be diagnosed on the basis of laboratory tests results as it has no or very few symptoms that are non-specific and often mimic some of the normal symptoms that a woman experiences during pregnancy [11]. In pregnancy subclinical hypothyroidism (SCH) is defined by a serum thyroid-stimulating hormone (TSH) concentration higher than the upper limit of the pregnancy related reference range associated with a normal serum thyroxine; either total (TT4) or free (FT4) concentration. This is in contrast to overt hypothyroidism is defined as elevated TSH with decrease FT 4 concentration below normal or TSH concentration higher than 10 mU/l irrespective of FT 4 levels [12,13].

Reference range for TSH should be standardized for diagnosis. The ATA 2011 and the ES 2012 guidelines recommend that the normal TSH reference range should be 0.1-2.5 mIU/L, 0.2-3.0 mIU/L, and 0.3-3.5 mIU/L in the first, second, and third trimesters of pregnancy, respectively [12,13]. However, these reference ranges are probably not valid worldwide, because recent publications indicate that values vary with geographic region and ethnic origin. Where this reference range is not available, attempts should be made to establish an appropriate reference range. If trimester-specific reference ranges for TSH are not available in that laboratory, above upper limits reference range are recommended.

TSH should be measured at the beginning of pregnancy before 10 week of gestation if screening is performed if possible preferably before conception.

The most common cause of hypothyroidism in developing countries is severe iodine deficiency, whereas in developed countries it is autoimmune thyroiditis. Thyroid autoantibodies are detected in about half of pregnant women with subclinical hypothyroidism and in more than 80% with overt hypothyroidism. Therefore FT4 with circulating antibodies against TPO & TG should be measured in patients with subclinical hypothyroidism to establish overt hypothyroidism along with autoimmune thyroid disease [12-16]. A negative test for both the antibodies virtually excludes AITD as 98% of patients are positive for either antibody. Anti TPO-Ab is specific and sensitive than TG Ab in diagnosis of autoimmune hypothyroidism. Elevated TSH with TPO antibodies is the gold standard for diagnosis of chronic hypothyroidism (Hashimoto's thyroiditis). Women with isolated TG-Ab had significantly higher serum thyrotropin concentrations than those without autoimmune thyroid disease [17].

Finally, it is important to consider that as the immune system is suppressed during pregnancy, thyroid antibody titers decrease on average by 60% in the second half of pregnancy [18]. So in the presence of elevated TSH values and negative thyroid antibodies specially after first trimester thyroid ultrasonography may be helpful to evaluate hypo-echogenicity or an inhomogeneous echo pattern in thyroid gland and subsequent diagnosis [19]. Usually in these women with autoimmune thyroid disease with negative thyroid antibodies and increased TSH, immunologic rebound occur during the first six months postpartum.

A study was carried out by Marwaha et al. [20] in 2008 to establish reference range for thyroid profile in Indian normal pregnant women. The trimester wise values in first, second and third trimester were FT3

(0.149-0.455, 0.248-0.445, 0.256-0.436 ng/dL), FT4 (0.932-1.51, 0.736-1.521, 0.86-1.45 ng/dL) and TSH (0.6-5, 0.44-5.78, 0.74-5.7 mIU/L).

Mankar et al. [21] also recently in 2016 publish reference range for thyroid function test in Indian normal pregnant women. Reference range for first trimester TSH:0.24-4.17 (mIU/L), FT3:0.29-3.1(ng/dL) and FT4:1-2.2(ng/dL). For second trimester reference range for TSH, FT3 and FT4 are 0.78-5.67 mIU/L, 0.27- 3.34 ng/dL,0.45-2.24 ng/dL. For third trimester reference range for TSH, FT3 and FT4 are 0.47-5.78 mIU/L,0.24-3.61 ng/dL,0.47-5.1 ng/dL.

These studies are also matches with survey done in India by Kumar et al. [22].

SCH and maternal-fetal complication

Various studies showed that there is a considerable risk of developing antenatal complication when the thyrotropin levels increases. This may progress to overt hypothyroidism in about 2.5% cases annually [23].

Incidence of preeclampsia, eclampsia have also been reported to higher in SCH (15%) as compared to normal population (7.9%) [24].

In a study by Chen et al. [25], incidence of gestational hypertention was 1.8% in normal and 3.5% in SCH mothers, PROM 4.97% and 8.6%, GDM 3.74% and 2.15%, preterm delivery 3.5% and 3.504% among normal and SCH mothers respectively. A significant association between SCH and severe pre-eclampsia was also observed by Mohanty et al. [3].

Study by Liang-Miao Chen, showed that fetal distress was 3.6% and 1.7%, low birthweight was 5.1% and 2%, IUGR was 2.7% and 0.7%, fetal death was 1.8% and 0.2% in SCH and healthy mothers respectively [25]. Two fold increase of incidence of preterm birth was also seem by Casey et al. in another study [26]. Women with TSH values more than 10 mU/L had significantly increased incidence of stillbirth [14].

Haddow et al. [27] reported that children of women whose TSH levels were elevated during the midtrimester of pregnancy had a slight but significant reduction in intelligence quotient scores between 7 and 9 years of age when compared with infants of euthyroid women.

The association between SCH in pregnancy and impaired neuropsychological development of the offspring is inconsistent but which may be related to the effects of prematurity as a result of SCH.

Screening for SCH in pregnancy

Screening is a process of identifying apparently asymptomatic individuals who are at an increased risk of a disease. Criteria for screening include the presence of a well-defined disease with known incidence prevalence. The test should be readily available and identification of the condition should result in a beneficial intervention. The test should be simple, safe and cost effective with reliable cut-off values. The cost of test relative to benefit should be known. The universal screening of asymptomatic pregnant women for hypothyroidism in pregnancy is controversial. Because of insufficient evidence and because the criteria for universal screening are not all satisfactory, most professional societies essentially from iodine sufficient countries recommend targeted case finding rather than universal screening.

Most of the guidelines recommended measurement of serum TSH in pregnant women in the following condition.

1. Sign and symptom suggestive of thyroid hypo function

2. Previous h/o thyroid surgery

3. Personal h/o thyroid disease including known goiter or thyroid antibodies

4. Family history of thyroid disease

5. Women with h/o autoimmune disorders including pernicious anemia, SLE,systemic sclerosis,sjogren's syndrome, type 1 diabetes

6. Previous history of miscarriage or preterm preterm delivery

7. History of head and neck radiation

8. Morbid obesity (BMI $\geq$ 40)

9. Women aged $\geq$ 30 as the prevalence of thyroid hypofunction increases with age

10. Women on medication like amiodarone and lithium

Confusion about the need for universal screening for thyroid dysfunction during pregnancy is going on. Guidelines from AACE, the Society of Maternal-Fetal Medicine, the American College of Obstetrics and Gynecology, the Cochrane Collaboration, and the ATA do not recommend universal screening for SCH because of the lack evidence based

benefit. Although there are still no well-controlled studies to justify universal screening, some endocrinologist recommend universal screening in pregnancy or those planning to become pregnant because of the beneficial effects of levothyroxine treatment on unknown overt hypothyroidism on obstetric outcome and the fact that the targeted approach will miss a large percentage of women with SCH, especially in mildly iodine-deficient women [14,28].

Those who favor universal screening cite the increased prevalence of hypothyroidism (overt and subclinical) during pregnancy, the inexpensive nature of the treatment (levothyroxine), the wide availability of an inexpensive screening test (TSH measurement) and the cost effectiveness of a screening strategy.

As discussed earlier, many studies and meta-analyses have documented an association between subclinical hypothyroidism and gestational diabetes, miscarriage, preterm delivery, gestational hypertension, pre-eclampsia, and impaired neuropsychological development of the offspring. However, only two randomised controlled trials have been published that have investigated the potential benefits of treating maternal subclinical hypothyroidism. Case finding as a strategy for identifying women with thyroid disease during pregnancy has limitations. Firstly, data from prospective studies have shown that when risk factors for thyroid disease are used, case finding will miss between 33% and 81% of pregnant women with hypothyroidism [28-31]. Secondly, a large number of risk factors need to be evaluated in a case finding strategy are controversial also which is time consuming. Thirdly, study reported that obstetricians providing the majority of pregnancy related care have limited knowledge about the association between thyroid disease and pregnancy. Again both the ATA 2011 and ES 2012 guidelines recommend screening all women over the age of 30 years as prevalence of hypofunction of thyroid occure as age advances.

Management of Hypothyroidism

The decision on whether to treat subclinical hypothyroidism diagnosed during pregnancy is controversial. The question is whether identification and thyroid hormone supplementation of women with subclinical hypothyroidism would prevent or modify any of these adverse outcomes. The ATA 2011 and the ES 2012 guidelines, but not the American College of Obstetricians and Gynecologists guidelines, recommend initiating levothyroxine therapy in these patients.

It is important to note that therapy should start before 10 weeks of gestation as after that gestation it would not eliminate any already established fetal neurodevelopmental impairment from hypothyroxinemia. Pop and colleagues have provided evidence that treatment may be ineffective if given after this time [32].

The recommended treatment of maternal hypothyroidism is administration of oral levothyroxine. It is strongly recommended not to use other thyroid preparations such as T3 or desiccated thyroid, which cause lowering of serum T4 levels. In patients with morning sickness usually common in early pregnancy the administration of levothyroxine at late night may be a valid option.

Women who have already treated with thyroxin for thyroid hypo function before conception, the amount of increase in levothyroxine may vary from 25 to 50%, depending on the etiology of hypothyroidism and prepregnancy TSH level. TSH values should be checked every 4-6 weeks during the first trimester and once during the second and third trimesters, and the levothyroxine dose should be adjusted within the trimester-specific reference range. Following delivery the levothyroxine dose should be reduced to the preconception dose.

In newly diagnosed patients with SCH in pregnancy, a starting dose of 1.20 μg/kg/day is usually given for TSH ≤ 4.2 mIU/L, 1.42 μg/kg/day with TSH ≥ 4.2-10 mIU/L and 2.33 μg/kg/day for overt hypothyroidism [33]. Women diagnosed with SCH during pregnancy with negative TPOAb usually discontinue levothyroxine after delivery and have thyroid function checked 6 weeks, 6 month and 1 year respectively after delivery to ascertain the continuing requirement for levothyroxine therapy. But SCH with positive anti TPO antibody required thyroid function test in regular interval as these patients were increased risk for overt hypothyroidism. Women with TPOAb and TSH greater than 5 mU/l in pregnancy were more likely to have persistently elevated TSH.

For better absorption levothyroxine should be taken in empty stomach. Many medication including iron, calcium, antacid and PPI interfere with its absorption. Several foods like milk, coffee, soya products and papaya decrease absorption.

For monitoring patient on levothyroxine, blood should be collected before taking medication in empty stomach.

Discussion

TSH is the most reliable test for diagnosing hypothyroidism but pregnancy presents a challenge for establishing reliable reference ranges and cutoffs [34]. Therefore it is necessary to establish a reference range of thyroid hormone for all the three trimester of pregnancy separately. The normal range of thyrotropin varies according to geographic region and ethnic background. In the absence of local normative data, the recommended upper limit of thyrotropin is 2.5 mIU/L, 3.0 mIU/L and 3.5 mIU/L in the first, second and third trimester respectively.

During pregnancy TSH levels are lower compare to normal population and more so in first trimester. Towards the end of first trimester when hCG levels are highest, significant fraction of TSH activity is from hCG which lead to reduction in the levels of TSH.

Thyroid hormones have great impact on fetal development and growth. Human fetus acquires the ability to synthesize thyroid hormone at roughly 12 weeks of gestation. SCH is increasingly being recognized as a cause of developmental disease [35]. Multiple evidences suggest adverse pregnancy outcome in SCH is inconsistent and conflicting. Equally, treatment with thyroxin has not been shown to be definitely beneficial. While results of on-going trials are awaited, thyroxin treatment is recommended in the absence of evidence of harm. However, the possibility of overtreatment in pregnancy should be considered. Monitoring for iatrogenic hyperthyroidism with a repeat TSH four to six weeks apart after any change in thyroxin dose should be considered and be aware that most of these women will not need ongoing thyroid replacement after pregnancy [36].

In 2011, the ATA guidelines [12] mentioned that subclinical

hypothyroidism has been associated with adverse maternal and fetal outcomes, and recommended that women with positive antibodies against thyroid peroxidase or thyroglobulin and subclinical hypothyroidism should be treated with LT4. The same guidelines also recommended LT4 replacement in women with antibody negative subclinical hypothyroidism; although the evidence levels were very low both for obstetrical and neonatal neurological outcome.

Conclusion

Various studies suggest that the prevalence of SCH in India seems to be considerably higher than other parts of the world. Most of the study indicate subclinical hypothyroidism has been associated with multiple negative outcomes, including pregnancy loss, preterm delivery, gestational diabetes, and gestational hypertension including severe preeclampsia.

The mechanism by which thyroid hormone deficiency leads to preterm labor, placental abruption or other pregnancy complications is not known but one hypothesis suggest that thyroid hormone is necessary for normal placental development. There is evidence that preterm delivery and vascular diseases such as preeclampsia and placental abruption may be related to faulty early placentation. Although impaired neurologic development in the offspring is controversial but it may be assume due to prematurity which is commonly associated with SCH.

It is recommend that diagnosis and treatment of subclinical hypothyroidism in pregnancy is based on TSH above the upper limit of a local gestation specific reference range (rather than a universal 2.5 mU/L). Where this reference range is not available, attempts should be made to establish an appropriate reference range.

The majority of cases of subclinical hypothyroidism in pregnancy are transient, so treatment with L thyroxine in these patients should be reviewed because it may not be warranted outside of pregnancy. However, if the clinician chooses to replace with thyroid hormone in pregnant women with subclinical hypothyroidism by virtue of the potential benefits outweighing the potential risks as recommended by the international task force, the treatment should be monitored closely by monthly measurements of thyroid function, and treatment adjusted accordingly in order to maintain normal biochemical variables.

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***Correspondence to:**

Hemanta Kumar Pradhan
Obstetrics and Gynecology Department
All India Institute of Medical Sciences
Jodphur, India
Tel: 9166286880
E-mail: drhemantakumar@gmail.com