Subclinical Hypothyroidism in Pregnancy

Abstract

It is always been controversial whether to treat subclinical hypothyroidism (SCH) or not. In last decade many clinical studies have been published about the adverse outcome with SCH in pregnant women. Due to lack of randomized prospective clinical trials, it is difficult to formulate the consensus on creating guidelines managing SCH. Here we discuss some of the data available in this regard.

Keywords: Subclinical hypothyroidism; Pregnancy; TSH; Levothyroxine

Mini Review

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Introduction

Hypothyroidism is the most common pregnancy-related thyroid disorder. Subclinical hypothyroidism is more common than is overt hypothyroidism. For patients with SCH, recommendations for therapy differ between various professional groups as a result of inconsistent data from both observational studies and clinical trials regarding the benefits for the mother or the child.

Discussion

The 20-year follow-up of the Whickham cohort [1] provided incidence data of SCH as 3.5 per 1000 women and 0.6 per 1000 men. Thyroid diseases affect up to 5% of all pregnancies. 0.3-0.5% is overt and 2.0-2.5% is SCH [2,3]. Iodine deficiency is the most common cause worldwide for pregnancy hypothyroidism whereas chronic autoimmune thyroiditis remains most common cause in iodine sufficient region. TSH level >10 mIU/l indicates overt hypothyroidism, irrespective of free T4 concentrations and usually patients have clinical symptoms [2,3]. SCH is diagnosed when TSH is elevated but <10 mIU/l and free T4 concentrations are normal [2,3]. It is almost always asymptomatic. Fatigue and constipation are frequently observed in pregnancy and their presence does not necessarily indicate SCH.

High circulating estrogen levels in first half of pregnancy increases concentrations of thyroid binding globulin [4] and rise in placental type II and type III deiodinases increase metabolism of T4 in the second and third trimesters. All these changes lead to an increase in the size of the thyroid gland in 15% of pregnant women, which returns to normal in the post-partum period. High prevalence of hypothyroidism in pregnancy tempted clinicians for universal screening but, rationality is still under scrutiny before recommendations for rampant use is made.

Universal screening can detect 30% of women with overt or subclinical hypothyroidism which can be missed if only high-risk women were screened [5]. There is a huge controversy over the treatment of SCH in asymptomatic nonpregnant population. However, present data discourage indiscriminate use of thyroxine supplementation in this group. Nevertheless, same cannot be applied in the case of pregnancy as increased maternal TSH concentrations have been associated with increased risk of fetal losses [6-13], gestational hypertension [11,14-17], placental abruptions [15,18], preterm birth [12,13,18-21] and poor neurological development in the offspring [13,22,23]. In various studies, subclinical hypothyroidism was found associated with cesarean sections [11], gestational diabetes [18,24], breech presentation [25,26], infants being small for gestational age [12], fetal distress [13], neonates needing intensive care treatment [18,20] and respiratory distress syndrome [20]. However, some studies have found no association between adverse perinatal outcomes and hypothyroidism [27-32].

There is a debate about whether to treat all pregnant women with subclinical hypothyroidism. Women with SCH are more likely to have TPO antibody positivity compared to euthyroid women (31% compared to 5%) [33]. Up to 40% of women with positive thyroid antibodies develop hypothyroidism during or immediately after pregnancy [34]. Most studies evaluating the association between SCH and pregnancy outcomes was based on first trimester measures of thyroid function. Therefore, more information is needed to determine whether hypothyroidism detected in the first trimester will progress. In a study evaluating treatment for SCH, 44% of women with initially high TSH had normal thyroid function tests in a repeat sample taken 1 week later [35].

In non-pregnant overt hypothyroidism, full replacement doses of levothyroxine are calculated by formula 1.6 µg/kg/day. In developing countries like India, clinician hardly prescribes levothyroxine in such doses. Overcorrection is not infrequent and loss of follow-up with good compliance can reverse the scenario. Keeping in mind about the potential untoward effect of SCH in pregnancy it will be prudent to treat such cases. Present data revealed that those with baseline TSH up to 4.2 mIU/l required smaller levothyroxine doses (1 µg/kg/day) than those with baseline TSH 4.2-10 mIU/l (1.42 µg/kg/day) to achieve euthyroidism [36]. When treating women with subclinical hypothyroidism with steady doses of levothyroxine based on their baseline TSH levels, 79, 82 and 90% of women with baseline TSH 2.5-5.0 mIU/l, 5.0-8.0 mIU/l and higher than 8.0 mIU/l, respectively, reached euthyroidism with respective levothyroxine

doses of 50, 75 and 100 µg/day [35]. Either approach seems to be appropriate in reaching euthyroidism. The thyroxine dose should be titrated to reach a serum TSH value <2.5 mIU/liter, while maintaining free T4 levels in the high normal range. Women should be followed up every 4-6 weeks with free T4 and TSH value, till delivery, to facilitate periodic adjustment of levothyroxine supplementation. Various clinical studies revealed that different levothyroxine products might have more than 12.5% difference in levothyroxine doses [37,38]. Many a time pharmacist changes brand without the knowledge of clinician. This may be a reason for failure to control hypothyroidism which may lead to adverse events on occasions. Levothyroxine should be ingested in the morning at least 60 min before eating [39]. Routinely prescribed iron and calcium supplements may interfere with levothyroxine absorption, so 4 to 6 hours gap can ensure adequate absorption [39].

There is currently insufficient evidence to show clear benefits of treating subclinical hypothyroidism [40]. In one trial randomizing women to case finding or universal screening for thyroid disease during pregnancy, 91.2% of all women with undiagnosed and untreated hypothyroidism had at least one adverse outcome, whereas the rate was 35% among those with diagnosed and treated hypothyroidism [41]. However, levothyroxine treatment of SCH has been shown to reduce miscarriages in some [42] but not all studies [43]. In a randomized trial, the infants of women with untreated thyroid hypofunction had similar intelligence quotient as those of women treated with levothyroxine [44].

Conclusion

Systematic review and meta-analysis of available data in this regard have sufficient evidence of poor maternal and neonatal outcomes. The effectiveness of treatment in this settings is largely unknown. The general consensus is that the universal screening, early confirmation of diagnosis and prompt treatment along with regular post-partum follow up, may ensure favorable maternal and fetal outcomes.

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