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Adverse Outcomes and Effects of Hypothyroidism among pregnant women

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REVIEW

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Introduction

There is now a large literature describing associations between maternal subclinical hypothyroidism and adverse obstetric and neonatal outcomes in observational studies. Although associations of subclinical hypothyroidism with outcomes such as miscarriage, premature delivery gestational hypertension, gestational diabetes, and placental abruption have been reported, associations have differed across studies, and some large cohorts have not reported any adverse effects at all. The heterogeneity of study results is likely due to differences in the definitions of subclinical hypothyroidism used, in the size of studies (and thus the adequacy of power to examine rare outcomes), and in the timing of maternal thyroid function testing during gestation. Whether or not studies excluded women with positive thyroid autoantibodies may also have influenced results; evidence suggests that women with thyroid autoimmunity may experience a higher risk for miscarriage at lower TSH threshold Recently, several systematic reviews and meta-analyses have examined associations between maternal subclinical hypothyroidism and adverse obstetric outcomes.

A 2011 meta-analysis of three studies, including 1010 sub-clinically hypothyroid women, demonstrated an increased risk of perinatal mortality in women with subclinical hypothyroidism compared to euthyroid controls (2.7, 95% CI 1.6–4.7). However, in the same systematic review, meta-analyses did not show associations between subclinical hypothyroidism and either pregnancy-induced hypertension or preterm delivery.

In contrast, Jouyandey. reviewed 241 articles on case-based screening for thyroid disease in pregnancy and their meta-analysis showed poor sensitivity of “case-based screening” when using risk factors such as higher age, BMI and family history of thyroid dysfunction to predict unknown (overt) thyroid dysfunction: on average, 49% of the cases were missed. In a study by Pop.that included the Completion of a draft questionnaire with “classical” symptoms of hypothyroidism at 12 weeks of gestation by 2198 healthy pregnant women from an iodine-sufficient area. They concluded that “symptoms and signs during early pregnancy will not help a clinician detect women at risk of thyroid hypofunction and should not be used as a risk factor for case-finding strategy to detect women with thyroid function abnormalities that require immediate treatment. They concluded that symptoms and signs during early pregnancy will not help a clinician detect women at risk of thyroid hypofunction and should not be used as a risk factor for case-finding strategy to detect women with thyroid function abnormalities that require immediate treatment.

This was confirmed by a recent large population-based study in the Netherlands including 3993 men and 5498 women showing no significant differences in symptom levels between those with and without elevated or suppressed TSH levels.

Outcomes of pregnancy with thyroid dysfunction

Studies showed subclinical hyperthyroidism is not associated with adverse pregnancy outcomes. There are also studies suggesting that there might be a risk of decreased intelligence and motor scores also in the offspring.

Multiple studies have reported an association of SCH with an increase in the risk of adverse pregnancy and neonatal outcomes including pregnancy loss, preterm delivery, gestational diabetes, gestational hypertension, preeclampsia, placental abruption, premature rupture of membranes, intrauterine growth restriction, low birth weight, small for gestational age, low Apgar score, and neonatal death.

The studies' results indicate that the identification of subclinical hyperthyroidism and treatment during pregnancy is unwarranted. Although subclinical hyperthyroidism has long-term sequelae on patients, that include osteoporosis, cardiovascular morbidity, and progression to overt thyrotoxicosis or thyroid failure.

In a retrospective cohort of 14 overtly hypothyroid pregnant women, reported complications included anemia in 31%, preeclampsia in 44%, placental abruption in 19%, postpartum hemorrhage in 19%, low birth weight in 31%, and fetal death in 12%. In another retrospective analysis which included 23 overtly hypothyroid women, overt hypothyroidism was associated with increased risk for gestational hypertension, preeclampsia, and low birth weight.

Presently, there is no convincing evidence that subclinical hyperthyroidism should be treated during pregnancy. According to one large study to assess the effects of Hyper on pregnancy, showed that SHyper (1.7%) was not associated with adverse pregnancy or neonatal outcomes.

The impact of subclinical hypothyroidism on pregnancy outcomes remains controversial. While some observational studies showed subclinical hypothyroidism increases adverse pregnancy outcomes such as preterm labor, miscarriage, gestational hypertension, placental abruption, fetal distress, preeclampsia and gestational diabetes, others reported no significant associations. Existing literature supports an association between subclinical hypothyroidism and adverse perinatal outcomes, such as preeclampsia, preterm birth, abruption placentae, and gestational diabetes; however, evidence for a treatment benefit are sparse.

Given the conflicting data, universal thyroid screening remains a topic of controversy. There are controversial recommendations for screening of asymptomatic patients during pregnancy and in the preconception period. For example, the ACOG does not recommend Universal screening in pregnancy, while there is no consensus in the Endocrine Society, while the AAGE recommends “Aggressive case finding” but not universal screening.

A study by Aljohani et al. (2013) in Saudi Arabia showed that patients with subclinical hypothyroidism have higher vitamin D level than healthy people. Gestational diabetes mellitus (GDM) with normal pre-pregnancy glucose metabolism only occurs during pregnancy. The incidence of gestational diabetes (GDM) has increased significantly in recent years. For example, as early as 2006, Akbar et al. (2006) have conducted a study that involved 200 Saudi patients has found that subclinical hypothyroidism and hypothyroidism were the commonest thyroid dysfunction and concluded that thyroid autoimmunity and dysfunction were significantly higher in diabetics compared to controls and that thyroid dysfunction and autoimmunity are common in Saudi type 2 diabetics.

Recently, Al Shanqeeti et al. (2018) has estimated the prevalence of SCH in pregnant women to be (13%). However, they found that age, fast blood sugar, systolic blood pressure, obesity, diabetes, and GDM were not significantly associated with subclinical hypothyroidism ($p>0.05$) and higher prevalence of subclinical hypothyroidism was found in pregnant women.

GDM and SCH pregnant women have higher Vit. D deficiency occurrence than normal pregnant women. Thyroid stimulating hormone and blood glucose levels in pregnant women are negatively correlated with Vit. D levels. While receiving retreatment, GDM and SCH pregnant women should actively replenish Vit. D to protect maternal and child health.

A Systematic Review and Meta-analysis by Maraka (2016) on Subclinical Hypothyroidism in Pregnancy that included Eighteen cohort studies at low-to-moderate risk of bias. They found that, compared to euthyroid pregnant women, pregnant women with SCH were at higher risk for pregnancy loss (RR 2.01, CI 1.66 to 2.44), placental abruption (RR 2.14, CI 1.23 to 3.70), premature rupture of membranes (RR 1.43, CI 1.04 to 1.95), and neonatal death (RR 2.58, CI 1.41 to 4.73).

A multi-center randomized trial assessed the impact of levothyroxine on the cognitive function among children of women who had TSH greater than 97.5th percentile or free T4 lower than 2.5th percentile, or both, during pregnancy The treatment had no effect on the mean offspring IQ at 3 years or the proportion of children with IQ below 85. A post hoc analysis for the subgroup of pregnant women who met the criteria for SCH had the same non-significant results. Maraka et al. (2016) concluded that The extant body of evidence supports an association of SCH during pregnancy with multiple adverse maternal and neonatal outcomes, but there is paucity of evidence for the value of levothyroxine therapy to mitigate this association.

Effects of treatment of subclinical hypothyroidism on the fetus and offspring

The Stagnaro-Green et al. study (2011) of two prospective randomized trials assessing the impact of levothyroxine on offspring IQ in women with subclinical hypothyroidism with TSH values ≥2.5 mIU/L or isolated hypothyroxinemia, found no significant effect. It has been suggested that subclinical hypothyroidism during pregnancy is associated with impaired cognitive development in offspring and treatment may improve neurocognitive outcomes. However, data available from RCTs does not support this hypothesis.

Lazarus et al., conducted a well-designed randomized controlled trial (RCT) of pregnant women (gestation approximately 16 weeks) to find the treatment effect on intelligence quotient (IQ) at 3 years of age in children; women were assigned to a screening and a control group; all positive screening women were prescribed 150 µg of LT4 per day; they showed that antenatal screening and

maternal treatment for hypothyroidism did not result in improved cognitive function in children at 3 years of age, as the mean IQ and the proportion of children with IQ levels below 85 did not differ significantly between the children of the mothers treated during pregnancy and the children of those who were not treated.

No randomized clinical trials have been performed to demonstrate treatment benefits in pregnancy, and it would be considered unethical to conduct a placebo-controlled trial in overtly hypothyroid women. However, in retrospective analyses, adequate levothyroxine treatment decreases rates of preterm delivery and miscarriage.

Evidence for Treatment Benefit in Overt Hypothyroidism is still missing. No randomized clinical trials have been performed to demonstrate treatment benefits in pregnancy, and it would be considered unethical to conduct a placebo-controlled trial in overtly hypothyroid women. However, in retrospective analyses, adequate levothyroxine treatment decreases rates of preterm delivery and miscarriage, and animal studies strongly suggest that treatment of overtly hypothyroid pregnant women is likely to improve child neurodevelopment. There is universal agreement that overt hypothyroidism in pregnancy should be treated with thyroid hormone replacement. In a 2016 meta-analysis of seven studies, Gong et al. (2016) reported that risk for gestational diabetes was increased in subclinically hypothyroid women (OR 1.558; 95% CI 1.292–1.877). Also, in 2016 Tong and colleagues performed a meta-analysis of seven studies and reported a significant association of subclinical hypothyroidism with intrauterine growth restriction (OR 1.54, 95% CI 1.06–2.25).

In 2016 Maraka and colleagues completed a systematic review including 18 studies, which together incorporated 3995 pregnant women with subclinical hypothyroidism. Although significant associations between subclinical hypothyroidism and pregnancy loss, placental abruption, premature rupture of membranes, and neonatal death were seen in the pooled analyses, there were no significant associations with other outcomes such as premature delivery, preeclampsia, gestational hypertension, and low birth weight. Most recently, in 2017, Zhang and colleagues performed a meta-analysis of 7 studies which included 3137 untreated sub clinically hypothyroid women and found that women with subclinical hypothyroidism had a higher prevalence of miscarriage (RR = 1.90, 95% CI1.59–2.27) than women who were thyroid. Taken together, these data strongly suggest that maternal subclinical hypothyroidism is associated with multiple adverse obstetric outcomes, although the underlying mechanisms remain unclear.

Treatment of Hypothyroidism in Pregnancy

For all women with overt hypothyroidism, and for those women with subclinical hypothyroidism in whom therapy is elected, the recommended treatment is levothyroxine. Thyroid replacement with desiccated thyroid, or with liothyronine alone or in combination with levothyroxine, is not recommended in pregnancy because it is primarily T4, rather than T3, that crosses the placenta in early pregnancy and thus these treatments confer a risk of selective fetal hypothyroidism even when the maternal TSH is normal . It is recommended that levothyroxine therapy should be titrated in order to maintain a maternal serum TSH <2.5 mIU/L both preconception and during gestation. A retrospective study has demonstrated that levothyroxine-treated women with first-trimester TSH values >2.5 mU/L had a higher risk of miscarriage compared to women with TSH values of 0.2–2.5 mU/L. Preconception counseling is important for all women with known hypothyroidism. The majority of women on levothyroxine, even if adequately treated prior to conception, will need dose increases to maintain euthyroidism throughout gestation. Thyroid hormone requirements increase starting in weeks 4–6 of gestation and gradually increase until about weeks 16–20. Levothyroxine requirements are dependent in part on the underlying cause of hypothyroidism, with women who are athyreotic due to thyroidectomy or radioactive iodine ablation most likely to require increased doses during gestation. It is recommended that levothyroxine doses be empirically increased by 25–30% as soon as pregnancy is diagnosed.

One way to achieve this is by instructing women to increase from seven to nine levothyroxine tablets per week as soon as pregnancy is confirmed. In all levothyroxine-treated women, serum TSH should be assessed every 4 weeks during the first half of gestation and at least once around week 30. Following delivery, levothyroxine doses can be decreased to preconception levels, with serum TSH testing performed at approximately 6 weeks postpartum. Maraka et al. (2016) concluded that the value of levothyroxine therapy in preventing these adverse outcomes remains uncertain

Conclusion

More evidence is required to assess the benefits/advantages and disadvantages of the two different screening strategies for thyroid dysfunction before and during pregnancy, looking for maternal, neonatal and offspring's health outcomes. We also need to know how the diagnosis of subclinical hypothyroidism could affect quality of life during pregnancy. Overall, it seems that the time has come for universal screening for thyroid disorders during and even before pregnancy. A thyroid screening program

during pregnancy should be based on systematic evaluation of several factors, including the burden of the thyroid disorders in pregnant women, the cost effectiveness of the screening intervention, and how well a given screening test performs in the target population; its performance can be judged by how many individuals must be screened to prevent one pregnancy complication, balanced with how many pregnant women who undergo screening have a positive or abnormal test result when the treatment has no effect.

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