Review Article

Screening for thyroid dysfunction in pregnancy

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Abstract: The most controversial issue in the field of thyroid and pregnancy is whether clinicians should screen all pregnant women for thyroid disease, and the screening should be performed before pregnancy or at the first prenatal visit. This review aimed to discuss updates on the important issue of thyroid screening before conception and during pregnancy and to highlight the gap in evidence that has led to remarkable controversies on this topic. The terms "screening" AND "thyroid" AND "pregnancy" were used to search Medline for English-language papers published from 1990 to the end of January 2018. After reviewing of titles of 482 articles, we focused on high quality and important studies. With respect to the Wilson and Jungner criteria for disease screening, thyroid dysfunction screening before and during pregnancy is still a conflicting issue. Available data suggests that compared to the universal screening, the case finding screening would result in missing cases of thyroid dysfunction. The primary debate is regarding maternal, fetal and offspring benefits of treatment of mothers with subclinical hypothyroidism and/or thyroid autoimmunity. Results of few high-quality studies in this field are in favor of some benefit considering pregnancy outcomes but no significant beneficial impact on fetal and offspring outcomes. Likewise, cost-effectiveness studies support the concept of universal screening. More evidence is required to assess the advantages and disadvantages of two different screening strategies for thyroid dysfunction in pregnancy, focusing on maternal, neonatal and offspring health outcomes following diagnosis and treatment of thyroid dysfunction, especially subclinical hypothyroidism in pregnancy. Moreover, screening strategies need to be individualized for each country according to disease burden, case finding costs and available health services.

Keywords: Screening; thyroid; pregnancy

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Introduction

The most controversial issue in the field of thyroid and pregnancy is whether clinicians should screen all pregnant women for thyroid disease, and if so, should the screening be performed before pregnancy or at the first prenatal visit. Considering the uncertainties surrounding the beneficial effects of treating subclinical hypothyroidism on adverse maternal and fetal outcomes, well-known international societies now believe that generalized screening is not mandatory based on current evidence. They recommend just selective screening of women at high risk of thyroid disease (1,2).

Although majority of criteria for screening of thyroid diseases during pregnancy is fulfilled based on the Wilson and Jungner criteria for disease screening (3), controversy regarding some criteria still exists. There is a dilemma over universal screening and selective screening of women at high risk of thyroid dysfunction before and during pregnancy that remains unresolved. One of the screening criteria is that the treatment must be effective; until today we do not have firm data for the efficacy of treatment in

subclinical hypothyroidism detected during screening programs. Additionally, the cost effectiveness of general screening is a major issue that needs to be discussed and resolved based on the socio-economic status and medical budget of each country. Health organizations are required to set priorities and allocate resources within the constraint of limited funding for each disease; it seems that screening strategies need to be individualized for each country. The American Association of Clinical Endocrinologists (AACE), American Thyroid Association (ATA), Endocrine Society and American College of Obstetrics and Gynecology (ACOG) do not recommend universal thyroid assessment for every pregnant woman, and suggest the targeted high-risk case finding approach (1,2,4,5). The 2011 ATA pregnancy guidelines (6) recommended screening in high risk groups, a recommendation which has not changed over the past 6 years, i.e., is the same in the 2017 ATA pregnancy guidelines (1). These guidelines underscore the criteria mentioned above, i.e., the cost effectiveness and the practicality/feasibility of the screening approach. Studies evaluating the question of "to screen or not to screen for thyroid dysfunction during pregnancy" demonstrate mixed conclusions. Several ongoing investigations and future studies will shed further light on this controversial topic.

Recently since associations between thyroid dysfunction in terms of hypo- and hyperthyroidism, thyroid autoimmunity and adverse pregnancy outcomes (maternal, fetal and neonatal) have become more evident, this has led to increased scientific debate on the advisability of universal thyroid screening.

This review aims to discuss updates on the important issue of thyroid screening during pregnancy and to highlight the gap in evidence that has led to the controversies on this topic.

Methods

The terms "screening" AND "thyroid" AND "pregnancy" were used to search Medline for English-language papers published from 1990 to the end of January 2018; a combination of more general search term usage with additional filtering of articles was applied to include all relevant articles. We limited our search results considering observational studies, clinical trials, review articles, meta-analyses and guidelines of major international organizations. After reviewing of titles of 482 articles by two endocrinologists, the articles were divided into 4 broad categories: (I) those that covered screening of thyroid disorders during pregnancy, (II) observational studies that addressed consequences of untreated thyroid disorders and/or thyroid autoimmunity during pregnancy in terms of pregnancy, fetal, neonatal and offspring outcomes, (III) articles the main focus of which were the effects of treatment of subclinical hypothyroidism on pregnancy outcomes, and (IV) the ones that discussed effects of treatment of subclinical hypothyroidism on fetal and offspring outcomes. Finally, we focused on high quality and important studies. As a shortcoming of each narrative review, selection bias cannot be excluded.

Results

Thyroid dysfunction will be missed when the case-finding screening approach is implemented

Thyroid dysfunction is a common occurrence in pregnancy and affects both maternal and fetal outcomes. It seems that targeted thyroid screening is not efficient in identifying women at risk of thyroid dysfunction; here we do not discuss subclinical or overt hyperthyroidism as the former usually has no adverse clinical consequences during pregnancy and the latter usually occurs with obvious signs and symptoms that would not be missed in clinical practice.

In a recent study by Hosseini *et al.*, incidence of subclinical hypothyroidism was reported to be similar among women with risk factors for hypothyroidism and those without these risk factors and targeted screening were shown to miss 10% of women with hypothyroidism (7). A cross-sectional prospective study conducted on 1,600 Iranian pregnant women in their first trimester of pregnancy found that the targeted high-risk case finding approach overlooked about one-third of pregnant women with thyroid dysfunction (8). Vaidya *et al.* (9) reported that by using the targeted high-risk case finding approach, about 30% of women with hypothyroidism went undetected. A study of pregnant women in Boston metropolitan area found that 80.4% of pregnant women with TSH elevation would have been missed based on current high-risk screening guidelines (10).

Overall, 1% of pregnant women suffer from overt hypothyroidism that had been present before conception; in such cases, adverse pregnancy outcomes are almost inevitable and treatment of overt thyroid disease decreases maternal and fetal morbidity and mortality (11) and is cost effective (12,13). Even women planning a pregnancy within 6 months should be regarded as having a 'pregnant

status' and need to be followed more closely, because preconception TSH elevation is reported to be associated with increased risk of adverse pregnancy outcomes, even if the values are within the normal non-pregnant range (14).

Consequences of missing overt thyroid dysfunction during pregnancy

It is established that both overt hypothyroidism and overt hyperthyroidism lead to adverse pregnancy outcomes and must be treated (15-17). Many observational studies showed that maternal hypothyroidism, both overt and subclinical, are strongly associated with preterm birth, low birth weight, reduced head circumference growth in infants, placental abruption, gestational hypertension, gestational diabetes, cognitive delay and many other abnormal neurobehavioral problems of exposed offspring (16,18-20). No prospective, randomized clinical trial of levothyroxine on preventing adverse pregnancy outcomes has been designed, because it is considered unethical to design such study in overt hypothyroid mothers. Therefore, the current consensus is that all overt thyroid disorders must be treated during pregnancy.

Consequences of missing subclinical thyroid dysfunction during pregnancy

The question that remains unanswered is: "*What are the benefits*, *if any*, *of treating subclinical hypothyroidism during pregnancy*". There are relatively few well-designed randomized clinical trials available aimed at answering this question.

Subclinical hypothyroidism and pregnancy 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 (21,22), others reported no significant associations (23).

Thyroid autoimmunity and pregnancy outcomes

Laboratory tests of thyroid autoantibodies are now available worldwide. Thyroid antibody_positivity is relatively common in women, with a prevalence of over 18% (24,25). There is controversy regarding the role of thyroid autoimmunity in causing adverse pregnancy outcomes; it is not clear whether autoimmunity causes adverse outcomes through activating autoimmune processes or by decreasing the reserve of the thyroid gland and causing a relatively mild form of thyroid dysfunction. Even the role of LT4 in preventing adverse pregnancy outcomes in euthyroid pregnant women is controversial, with some observational studies demonstrating an association between the presence of thyroid antibodies in euthyroid women in their first trimester with increased rates of spontaneous miscarriage and preterm delivery (26-29).

Effects of levothyroxine treatment of subclinical hypothyroidism on pregnancy outcomes

Results of studies that focused on treatment with regard to thyroid autoimmunity were not encouraging. A prospective randomized trial assessing the impact of LT4 in euthyroid pregnant women with TSH levels between 0.5 and 2.5 mIU/L and autoimmune thyroid disease showed no impact of therapy on the rate of miscarriage and preterm delivery (30). Other studies showed that euthyroid, TPOAb positive women treated with LT4 and euthyroid TPOAb negative women displayed a lower rate of preterm deliveries compared with euthyroid, TPOAb positive women who were not treated with levothyroxine (31,32).

Negro *et al.* demonstrated that the treatment of thyroid dysfunction detected by universal screening prevented adverse outcomes in pregnant women (33); they also showed that euthyroid TPOAb positive women who received levothyroxine (LT4) had a significant reduction in preterm deliveries (from 22% to 7%) and miscarriage rates (from 14% to 3.5%) (31). In a recent study, it was shown that LT4 could decrease preterm delivery in TPOAb negative women with TSH values ≥4.0 mIU/L (34). Findings of the Thyroid AntiBodies and LEvoThyroxine (TABLET) study, aimed to investigate whether taking a small (50 μg) dose of LT4 by TPOAb positive euthyroid women before and during pregnancy will decrease the rate of miscarriage and preterm delivery (ISRCTN15948785, https://doi.org/10.1186/ISRCTN15948785), have not yet been published.

Fetal and offspring outcomes in subclinical hypothyroidism

The effect of subclinical hypothyroidism on cognitive function and neurodevelopmental aspects of fetus and offspring remains controversial.

A prospective observational study from Netherlands reported that the mean mental developmental index score at the age of 6 and 12 months was 16 points lower for infants

who were born to mother with subclinical hypothyroidism compared to those born to euthyroid pregnant women (35). Findings of the Li *et al.* study showed children aged 25–30 months of women with subclinical hypothyroidism at 16–20 weeks of gestation, had mean intelligence scores (8.88 points) and mean motor scores (9.98 points) lower than those of the control group; increased maternal serum TSH, decreased maternal serum FT4, and elevated maternal TPOAb titers were associated with lower intelligence scores (ORs 15.63, 12.98, and 6.69, respectively) and poorer motor scores (ORs 9.23, 5.52, and 8.25, respectively) (36). In a recent prospective cohort study from Netherlands, maternal TSH concentrations in 9–18 weeks of pregnancy were not associated with child IQ evaluated at a median of 6 years of age (37).

Effects of levothyroxine treatment of subclinical hypothyroidism on the fetus and offspring

The Stagnaro-Green *et al.* study consisting 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 (38).

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 (39). Results of "the second wave of the Controlled Antenatal Thyroid Screening (CATS II) study" (40) have recently been released (41); IQ at age of 9.5 years of children of 119 LT4-treated and 98 untreated mothers with subclinical thyroid dysfunction during their pregnancy was compared to that of children of 232 mothers with normal gestational thyroid function. Maternal LT4 treatment was not associated with neurocognitive improvement of offspring at age of 9.5. Another RCT by Casey *et al.* was conducted on 677 women with subclinical hypothyroidism and 526 ones with hypothyroxinemia who underwent randomization at a mean of 16.7 and 17.8 weeks of gestation, respectively; in this study, treatment for subclinical hypothyroidism or hypothyroxinemia, initiated in 8–20 weeks of gestation did not result in significantly better cognitive outcomes in children through 5 years of age, compared to outcomes in those who had received no treatment for the conditions (42).

The main shortcoming of above-mentioned trials is that LT4 treatment has been initiated late at the second trimester of pregnancy when fetal thyroid development and thyroid hormone synthesis and secretion have nearly been completed (43).

Cost-effectiveness of universal versus case-finding screening methods

A decision-analytic model that compared the incremental cost per quality-adjusted life-year (QALY) gained among those who underwent universal screening or categorized to high-risk screening group versus the no screening one documented that risk-based screening and universal screening were both cost-effective relative to no screening, with incremental cost-effectiveness ratios (ICERs) of $6,753/QALY and $7,138/QALY, respectively. Also universal screening was cost-effective, compared to the case finding strategy (12); results of other cost-effectiveness studies were concordant with this finding (13,44). Overall, it appears that studies tend to support universal screening in terms of cost-effectiveness.

The reasons behind controversies in screening strategies

The Wilson criteria for disease screening emphasize the important features of any screening program, as shown in *Table 1*. There is a dilemma between universal screening and selective screening of women at high risk of thyroid dysfunction during pregnancy that has remained unresolved. One of the criteria is that treatment should be more effective if initiated early.

Since a higher percentage of thyroid dysfunction in pregnant women is in the form of subclinical hypothyroidism, and given the lack of clear data for efficacy of treatment, there is ongoing controversy/debate regarding the need for universal screening for thyroid dysfunction during pregnancy versus a case-finding approach (1,45). This could be due to flaws in study design regarding the study

Table 1 The Wilson and Jungner criteria for screening of diseases

The condition should be an important health problem
The natural history of the condition should be understood
There should be a recognizable latent or early symptomatic stage
There should be a test that is easy to perform and interpret acceptable, accurate, reliable, sensitive and specific
There should be an accepted treatment identified for the disease
Treatment should be more effective if started early
There should be a policy on who should be treated upon diagnosis and treatment should be cost-effective
Case-finding should be a continuous process

Adopted from the World Health Organization, Geneva, 1968 (3).

population, definition of subclinical hypothyroidism- with different biochemical cut-offs, thyroid autoimmunity, time of recruitment of pregnant women and the time of follow-up. Additionally, it seems that cost-effectiveness of screening programs is still under question that should be taken into account for each country individually. Health policy makers should choose the most cost-effective screening method for public health programs for each specific population based on their guaranteed maximum price. In many countries in the world, where their gross national product (GNP) and health budgets are low, screening of diseases such as thyroid diseases in pregnancy may not be a priority in health matters.

Areas of uncertainty

Studies have been hindered by the limited data available regarding assessment of thyroid function during early pregnancy. More studies are needed to evaluate the benefits of thyroid screening and treatment before and/or in early pregnancy. So far studies conducted for evaluation of levothyroxine effects in pregnancy have used protocols where levothyroxine treatment is initiated only at the end of the first trimester or later (39,42). Further studies should consider this issue at the design stage and evaluate the effect of treatment as early as possible. In addition, limited studies have evaluated the relationship between preconception thyroid hormone levels and pregnancy outcomes; a secondary analysis of a prospective cohort of 18–40-year-old women with 1–2 previous pregnancy losses, showed that subclinical hypothyroidism and thyroid autoimmunity were not associated with an increased risk of preterm delivery, gestational diabetes mellitus, or preeclampsia (46).

Conclusions

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 (false-positive test). The number of individuals with positive results who actually proceed to follow-up and receive treatment is a critical issue to consider for pregnant mothers. Finally, screening strategies need to be individualized for each country according to disease burden, case finding costs and available health services.

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