# Thyroid screening in pregnancy

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For more than a decade, endocrinologists and obstetricians have been debating whether screening for thyroid disorders during pregnancy should be routine or should continue to be based on symptoms and risk factors. The primary impetus behind this debate was the publication of 2 observational studies in 1999.[1,2] Both demonstrated that offspring of women with asymptomatic thyroid dysfunction were at increased risk for impaired neurodevelopment. Subsequent reports also indicate that pregnant women with subclinical thyroid disease, particularly those identified with an elevated thyroid-stimulating hormone (TSH), may be at increased risk for pregnancy complications such as fetal death, preterm birth, or placental abruption.[3,4] These data have prompted both obstetric and endocrinologic professional societies to draft statements or recommendations regarding screening for thyroid disease during pregnancy, which are not entirely consistent.[5-7]

This topic was debated recently at the 33rd annual meeting of the SMFM.

## For universal thyroid screening

The list of patient profiles that were recommended for targeted thyroid screening in the Endocrine Society Practice Guidelines is very comprehensive and includes all women >30 years old, patients with clinical symptoms suggestive of thyroid hypofunction, patients with a family history of thyroid disease or autoimmune disorders, personal history of infertility, previous miscarriage, preterm delivery, type 1 diabetes mellitus, an autoimmune disorder, goiter, or thyroid nodule. Any woman with known antithyroid peroxidase antibodies, previous thyroid surgery, or a history of radiation to her head and neck region should also be screened.[7] In many clinical practices, few patients would escape screening if the aforementioned criteria for screening during pregnancy were followed.

An aggressive case-finding approach is known to miss a considerable proportion of patients with hypothyroidism. If we screen only women with symptoms of hypothyroidism during pregnancy, it is important to acknowledge that such symptoms may mimic pregnancy (eg, weight gain, exhaustion, forgetfulness, dry skin, coarse hair, constipation). This makes this approach to screening less than ideal. Moreover, it has been estimated that only 30-80% of women with hypothyroidism would be identified through screening based on symptoms/risk factors.[8-11] Thus, it appears that case-finding guidelines are inadequate for the identification of all women with thyroid dysfunction.

If a disease is frequent enough and interventions can improve perinatal outcome, then screening usually is justified and will likely be cost-effective. Thyroid dysfunction is the second most common endocrine disorder to affect women of reproductive age.[3,5] A recent national study of more than one-half million serum samples from pregnant women that were included in the Quest Diagnostic Informatics Data Warehouse revealed that, of 23% of women who underwent TSH analysis, 15.5% had an elevated TSH level. The authors concluded that gestational hypothyroidism is more common than generally acknowledged.[12]

Because there are no large randomized trials that have demonstrated a benefit to routine screening during pregnancy, published cost-effectiveness studies include theoretic models based on the observational study by Haddow et al[1] in 1999. For example, Thung et al[13] published a decision analysis that compared the cost-effectiveness of routine screening vs a case-finding approach. Assuming a two-thirds reduction in offspring with an IQ <85 through identification and treatment, this model predicted routine screening would result in fewer children born with low IQ and save 8.3 million dollars per 100,000 women screened. Similar findings were noted in a Markov model constructed by Dosiou et al.[14]

The million dollar question is whether treatment of patients, particularly those identified with subclinical hypothyroidism, makes a difference in perinatal outcome for Mom and baby? The association between adverse pregnancy and possible subsequent childhood neuropsychologic and cognitive impairment in mothers' known to have overt hypothyroidism is not questioned. Thyroxine replacement with careful monitoring of thyroid function in these women clearly is indicated.[15,16] The problem is that we have conflicting data that thyroid replacement benefits pregnant women who are identified with milder thyroid dysfunction and their offspring. Several observational studies have suggested a benefit to screening and treatment.[17-19] Conversely, the larger Controlled Antenatal Thyroid Screening trial revealed that thyroxine replacement in women with isolated high TSH or isolated low free T4 (fT4) levels had no impact on cognitive function in children evaluated at 3 years old.[20] Although these data appear to be a compelling argument against the screening and treatment of pregnant patients with subclinical hypothyroidism, it is important to note that patients in this

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study did not initiate thyroid replacement therapy until almost 14 weeks of gestation, which is beyond the critical period in fetal brain development.

Finally, although the proponent for screening concedes that current evidence does not necessarily justify the screening of all pregnant women for subclinical hypothyroidism, the benefits of the identification and treatment of women with overt hypothyroidism are less controversial. Best estimates of the incidence of overt hypothyroidism in the United States are on the order of 2 in 1000.[21] A substantial proportion of these women will not exhibit symptoms of hypothyroidism in the early stages of disease. If we were to assume that 50% of these patients might be identified through a case-finding approach, then 1 in 1000 pregnant women would remain undiagnosed. Said another way, there are roughly 4000 pregnant women with overt hypothyroidism who are undiagnosed in the United States each year.[22] We currently screen pregnant women and neonates for conditions with lower incidence rates. Even if screening for hypothyroidism does not strictly fulfill all criteria for an ideal screening test, it is difficult to justify missing this important diagnosis, given the beneficial effects treatment may have on both maternal and neonatal outcome.

## Against universal thyroid screening

The US Preventative Services Task Force has suggested criteria that should be met before the adoption of a new population screening test. These criteria include: (1) the diagnosis for which you are screening should be prevalent or important enough to warrant population screening; (2) clear evidence of bad outcomes associated with the diagnosis; (3) an intervention that shows improvements in the outcome; and (4) the screen should be cost-effective.[23]

The prevalence of overt thyroid disease is estimated to be 1-3 per 1000 pregnancies and historically has not been considered high enough to justify routine screening. More recently, however, lower TSH thresholds (>2.5 mU/L) for the diagnosis of hypothyroidism have been promoted, and women with subclinical thyroid dysfunction commonly are included in estimates of thyroid disease during pregnancy. Additionally, based largely on the findings from 1 study of euthyroid pregnant women with thyroid peroxidase antibodies, routine assessment of thyroid autoimmunity has also been suggested.[19] If these subgroups of women were included to define hypothyroidism during pregnancy more broadly, then the prevalence of disease in the United States might exceed 5%. Although this exaggerated prevalence rate alone would seem to justify screening, it includes a majority of women without clear evidence of associated poor outcomes.

Impaired neurodevelopment in offspring is commonly linked to pregnant women with subclinical thyroid disease. Assessment of this evidence is hampered by the fact that 2 distinct laboratory entities (isolated elevated TSH and isolated low fT4) are often erroneously considered together as subclinical hypothyroidism. In 1999, Haddow et al[1] reported that offspring of women with TSH levels >98th percentile were more likely to have lower IQ scores at 7-9 years old. Even though at least two-thirds of these women had what would be considered overt hypothyroidism, this study is often used to link subclinical hypothyroidism with low IQ in offspring. Also, in 1999, Pop et al[24] reported a link between isolated maternal hypothyroxinemia and lower Bayley scores in children up to 3 years old.[2] Importantly though, identification of such women would be unlikely because most thyroid screening regimens start with an evaluation of TSH, which would be normal.

The most compelling current evidence on this issue is the recently completed Controlled Antenatal Thyroid Screening Trial.[20] After screening almost 22,000 pregnant women for either isolated high TSH or isolated low fT4, 390 children of treated women with either diagnosis were compared with 404 children of similar women who were not treated during pregnancy. Treatment had no effect on mean offspring IQ at age 3 years or the number of children with an IQ <85. The authors of this definitive study concluded that antenatal screening and maternal treatment for women with subclinical thyroid dysfunction did not result in improved cognitive function in children at 3 years old.

The impact of these diagnoses on pregnancy outcomes represents another motivating factor behind recommendations for routine screening. However, data that link subclinical thyroid dysfunction to poor pregnancy outcomes are also not consistent. Women with an isolated elevated TSH level or subclinical hypothyroidism that was identified in the first one-half of pregnancy have been shown to have an increased risk for preterm birth and placental abruption in 1 study of >17,000 women.[3] However, these findings were not replicated in another large study of >10,000 women who were screened in the first or second trimester.[25] Conflicting findings have also been reported in pregnancies that have been complicated by isolated maternal hypothyroxinemia. In an analysis of sera from the FaSTER study, there was a weak association between low fT4 level during the first or second trimester and the diagnosis of gestational diabetes mellitus and birthweight >4000 g.[25] Conversely, Casey et al[26] were unable to detect any pregnancy outcomes that were associated with isolated hypothyroxinemia in their larger cohort study. There are currently no intervention trials that demonstrate improved outcomes in women with either subclinical hypothyroidism or isolated maternal hypothyroxinemia.

In summary, without the inclusion of women with subclinical thyroid dysfunction, the prevalence of women with undetected overt hypothyroidism does not justify routine screening. There is an ongoing treatment trial by the *Eunice Kennedy-Shriver* National Institute of Child Health and Human Development's Maternal-Fetal Medicine Units Network that will provide further clarity to this important subject. ■

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