Thyroid Function during Pregnancy: Who and How Should we Screen?

Moderator: Ann M. Gronowski1*
Experts: James Haddow,2 Sarah Kilpatrick,3 John H. Lazarus,4 and Roberto Negro5

In the past several years there has been considerable discussion in both the scientific and lay literature about the merits of prenatal screening for thyroid disorders. Much of this debate was initiated by a 1999 study showing an association between an underactive thyroid gland during pregnancy and delayed neurodevelopment in the offspring. That study begs the question: “Should all pregnant women be screened for hypothyroidism?” (1). (Suggested references on this topic are also included in the Data Supplement that accompanies the online version of this Q&A at http://www.clinchem.org/content/vol58/issue10.)

Several medical associations have weighed in on this subject. Guidelines from the American Association of Clinical Endocrinologists indicate that thyroid-stimulating hormone (TSH)6 screening should be routine before pregnancy or during the first trimester. If the TSH is >10 mIU/L or if the TSH is 5–10 mIU/L and the patient has goiter or positive anti–thyroid peroxidase (TPO) antibodies, then thyroid hormone replacement therapy should be initiated. The American Thyroid Association and the Endocrine Society agree that there are not enough data for or against universal screening but also acknowledge that lack of evidence of benefit doesn’t mean that there is no benefit. They recommend only the screening of pregnant women who are at high risk of overt hypothyroidism [e.g., history of thyroid dysfunction, TPO-antibodies positive, goiter]. If the TSH is >10 mIU/L, this indicates overt hypothyroidism, and thyroid hormone replacement therapy should be initiated. However, the American College of Obstetricians and Gynecologists has recommended against screening all pregnant women for hypothyroidism. This group argues that there is lack of clear evidence that the identification and treatment of women with subclinical hypothyroidism will improve maternal or infant outcomes.

Here we ask 4 experts in the area of thyroid disease during pregnancy for their opinions on the effects of thyroid deficiency during pregnancy and the need for maternal screening.

**Would you agree that evidence supports the idea that overt hypothyroidism in a pregnant mother has negative effects on her fetus?**

James Haddow: The most dramatic example of negative fetal effects is found in regions of extreme iodine deficiency, where both a woman and her fetus can be severely hypothyroid. Under those conditions, fetal mortality is increased, and surviving newborns suffer from impaired neurocognitive development and a variety of neurological problems (gait problems, microcephaly, deafness, strabismus). In iodine-sufficient regions, the consequences of isolated maternal hypothyroidism (with normal fetal thyroid function) appear to be less serious. An observational study by our group in 1999 found a 7-point lower mean IQ at age 8 years among offspring of women with autoimmune thyroiditis and undiagnosed overt hypothyroidism during pregnancy; the rate of offspring IQ scores <85 was also increased 4-fold (1). In a second observational study, we identified a higher rate of fetal death between the second trimester and term in the presence of undiagnosed hypothyroidism.
Sarah Kilpatrick: Inadequately treated overt hypothyroid disease in pregnancy is associated with preterm delivery, preeclampsia, miscarriage, and maybe stillbirth. It is clear that in areas of iodine deficiency there is a high rate of severe hypothyroidism in pregnant women and that these women have a high rate of cretinism in their offspring. Whether the cretinism is due to iodine deficiency (iodine crosses the placenta and is necessary for normal fetal thyroid development) or due to the overt hypothyroidism in the mother is not entirely clear. Most experts would agree that the iodine deficiency itself is the larger contributor. In non–iodine-deficient hypothyroid women, it is difficult to discern how large the effect of low maternal thyroid hormone is on fetal neurologic or cognitive development. Small amounts of the mother’s thyroid hormone do cross the placenta and severe uncontrolled maternal hypothyroidism probably deleteriously affects her children. But consistent convincing data that milder forms of non–iodine-deficient maternal hypothyroid disease causes deleterious neurologic or cognitive outcomes in children are lacking. Nonetheless, controlling overt hypothyroid disease before pregnancy and during pregnancy to maximize both the health of the mother and perinatal outcomes is paramount.

What about subclinical hypothyroidism? Do you feel that subclinical hypothyroidism can have negative effects on the infant?

Roberto Negro: The recently published study by John Lazarus and colleagues (3) shows that maternal subclinical hypothyroidism is not associated with reduced IQ in children. The study compared 2 groups of women with free thyroxine (FT4) <2.5th percentile and/or TSH >97.5th percentile, 1 of whom was treated with levothyroxine. The neurocognitive performance in the 2 groups of children at 3 years was not different. In this multicenter study, the median TSH was 3.8 mIU/L in the UK and 3.1 mIU/L in Italy. The degree of hypothyroidism that the authors found is probably too mild to find a significant difference between treated and untreated patients. In this view, it is a reassuring result. Unfortunately, the study did not clarify at which concentration of TSH the mother has to be treated and whether we have to treat the condition of isolated hypothyroxinemia to prevent reduction of the child’s IQ.

John H. Lazarus: Subclinical hypothyroidism in pregnancy may have adverse obstetric effects at delivery. In addition, there are prospective and retrospective data showing reduction in IQ in infants and delayed motor and mental development. There are also indications of an increased frequency of other behavioral disorders such as expressive language delay.

Sarah Kilpatrick: The diagnosis of subclinical hypothyroidism is made when the patient is asymptomatic but has an increased TSH and FT4 within reference intervals. Over the last 10 years, there have been several reports and retrospective and prospective series that have compared perinatal outcomes and offspring childhood cognitive outcomes from women with TSH within reference intervals to those with increased TSH during pregnancy. These results have been conflicting, with several suggesting worse cognitive outcomes in young children of mothers with increased TSH in pregnancy. However, other reported studies have found no difference in perinatal outcomes, including preterm delivery. These data are provocative and have stimulated intense discussion of this topic between endocrinologists and obstetrician-gynecologists. I am not convinced that subclinical hypothyroidism is truly associated with poor cognitive childhood outcomes or other poor perinatal outcomes. Further, even if new and better data supporting an association between maternal increased TSH and poor childhood cognitive outcomes become available, there continue to be no data to indicate that treatment with thyroid hormone changes that association. The answer to this important question will come from randomized trials that, fortunately, are now in progress. In fact, one was just published in 2012 that compared pregnancy outcomes between women randomized to either screening for and treating increased TSH with thyroid hormone, or screening for but not treating. The primary outcome of IQ score at age 3 years in the children of these mothers was not significantly different between these 2 groups (3).
There is recent evidence that iodine deficiency is a bigger problem than we expected, even in developed countries. Are you worried about this and do you feel pregnant women should be screened for iodine deficiency?

John H. Lazarus: While correction of iodine deficiency by universal salt iodization followed by an increased household consumption of iodized salt has made notable strides in developing countries during the past 20 years, this has not occurred to the same extent in developed countries. Recently, the UK has been shown to be iodine deficient and there is very little iodized salt available for consumption. Clearly, the iodine status in every country should be established. In iodine-deficient areas pregnant women should be advised to take iodine supplements, ideally starting before conception. It is more difficult to screen an individual for iodine deficiency because of the variation in urinary iodine from day to day. However, populations can be readily screened.

Roberto Negro: Iodine deficiency still represents a health problem, especially in Europe. Iodine deficiency, inducing low maternal FT₄ and eventually increased TSH concentrations, may have a negative impact on children's neurocognitive performance. The study by Henrichs and colleagues (4), for example, demonstrated that mothers with mild or severe hypothyroxinemia have children with expressive language and nonverbal cognitive delay at 18 and 30 months of life. Notably, 2 studies of intervention from Spain (5,6) showed that iodine supplementation (200–300 μg/day) was able to prevent impaired psychomotor performance and motor and social development. It should be noted that while the importance of gestational iodine supplementation is undisputed, it is also important that women considering conception should be advised to take iodine supplementation for several months before pregnancy.

James Haddow: There is no reliable screening test for iodine deficiency on an individual basis (urine iodine measurements reflect iodine intake over only a short period). Urine iodine measurements, however, are useful in assessing iodine status at the population level. In a recent NHANES (National Health and Nutrition Examination Survey) conducted by the CDC, the distribution of urine iodine concentrations among pregnant women in the US was consistent with mild iodine deficiency. During pregnancy, iodine requirements increase (to 200–250 μg/day), and iodine-containing vitamins (usually containing 150 μg per tablet) are recommended by the Institute of Medicine. Not all vitamin preparations for pregnant women contain iodine. The most effective approach to dealing with concerns about iodine deficiency is to assure adequate intake.

Sarah Kilpatrick: Although there are some data indicating that more women in the US may have lower iodine concentrations, I am not aware that iodine deficiency is a significant problem in the United States and I do not recommend screening pregnant women for iodine deficiency. I do recommend that pregnant women take a prenatal vitamin with at least 150 μg/day of iodine in it and that potassium iodide be the preferred source of iodide in the vitamin.

Do you feel that women should have thyroid function testing performed during pregnancy? If so, who should be tested, and what should be measured (i.e., TSH, TPO, iodine) and what cutoffs do you recommend?

John H. Lazarus: Because thyroid dysfunction is common in pregnancy I do think that thyroid function testing in early pregnancy is justified in all women. I am aware that current guidelines suggest a range of criteria (e.g., history of autoimmune disease, past history of neck irradiation) for those who should be tested but there are data to indicate that if these criteria are followed, up to 65% of women with abnormal test results will be missed. However, there is only one randomized study examining the effects of T₄ administration on childhood IQ and that did not show any benefit (7). At present, I think TSH should be measured in all pregnant women in the first trimester; if it is >2.5 mIU/L, a T₄ assay should be performed. If the TSH is >5 mIU/L, a TPO antibody test should be performed. Alternatively, if a gestational reference range for TSH has been established in the laboratory, the TSH should be regarded as abnormal if it is above the 97.5th percentile. The cutoff for T₄ should be the lowest 2.5th centile and for TPO antibodies should be determined according to the specific assay used.

Sarah Kilpatrick: For any screening test the following criteria should be met: a high enough disease incidence to warrant screening and a known effective treatment to reduce the deleterious effect of the disease screened for. The incidence of hyperthyroid disease in pregnancy is <0.5% so does not warrant screening. The incidence of hypothyroid disease (clinical and subclinical) in studies of routine screening is approximately 3%, which is high enough to consider screening. Importantly, the majority of these women have only subclinical hypothyroid disease. However, as I noted above, there are no data indicating that treatment ameliorates any po-
potential adverse perinatal or childhood outcomes associated with maternal subclinical hypothyroid disease. These facts are why routine screening is not indicated. However, it is very important to test women at high risk for thyroid disease because treatment for both maternal and fetal benefit is warranted for women with overt thyroid disease. The women who should be tested include those with a history of thyroid disease, strong family history of thyroid disease, history of neck irradiation, presence of a goiter, known antithyroid antibodies, or presence of other autoimmune disorders or type 1 diabetes. These women should have a TSH measured at their first prenatal visit. If the TSH is increased then free T₄ or free thyroxine index and TPO antibodies should be measured. Overt hypothyroid disease should be treated with thyroid hormone to maintain a TSH within reference intervals. I would consider treating subclinical hypothyroid disease if TPO antibodies are present. If the TSH is suppressed the patient should be evaluated for any signs of hyperthyroid disease and if these are not present and the patient was in her first trimester when the TSH was measured, then a repeat TSH with an FT₄ should be performed in the mid-second trimester and I would consider treating her only if these are consistent with hyperthyroid disease. It is well known that women may have a transient subclinical or clinical hyperthyroidism from the first through the middle second trimester in pregnancy due to transient TSH suppression by human chorionic gonadotropin. There is no morbidity to this condition and it resolves spontaneously so it is not necessary to treat.

Roberto Negro: Personally, I stand in favor of universal screening for thyroid disease at the beginning of pregnancy. We have to consider that in Western countries the mean age of first pregnancy is 25–30 years, and a recent report showed that in women older than 25 years more than 15% have thyroid abnormalities. Furthermore, everyone agrees that it is necessary to treat overt thyroid dysfunction, and in particular overt hypothyroidism. A recent paper published by Dosiou and coworkers (7) clearly shows that universal screening is cost-effective not only compared with no screening, but also compared with screening only women at high risk for thyroid dysfunction. Notably, in this analysis the authors assumed that women with any degree of hypothyroidism receive treatment, but only women with overt hypothyroidism benefit from treatment. My personal opinion is that, above all in countries with high-quality healthcare systems, a 25–30-year-old woman at her first pregnancy has the right to know if she is hypothyroid, at risk of developing hypothyroidism, or at risk of developing a postpartum hypothyroiditis. TSH and TPO antibodies should be the first test used to screen a woman for thyroid dysfunction. A TSH concentration >2.5 mIU/L in the first trimester, and >3.0 mIU/L in the second and third trimester, should be considered as pathologic.

James Haddow: My view is that all women should have a TSH measurement performed during pregnancy and that this service should be delivered within a programmatic framework, using existing prenatal screening models for guidance. TSH is the most reliable indicator of existing thyroid dysfunction. A reasonable TSH cutoff might be the 97.5th or 98th centile of the appropriate reference range for gestational age. In recent years, discussions pro and con screening have focused exclusively on fetal wellbeing. It is now time for the mother’s health to be taken into account, even before definitive proof of fetal morbidity that might be associated with subclinical hypothyroidism. In addition to cases of subclinical hypothyroidism, our observational study found that about 3 pregnant women per thousand had undiagnosed overt hypothyroidism. There is general agreement that treatment is indicated in such cases. Two-thirds of these women subsequently became permanently hypothyroid. A mean period of 5 years elapsed before a diagnosis was made clinically, and 4 of the 32 hypothyroid women in our study were not diagnosed until we performed follow-up TSH measurements 10 years later.

What is your opinion about treating pregnant women with subclinical hypothyroidism before or during pregnancy?

Sarah Kilpatrick: There is no evidence that treating pregnant women with subclinical hypothyroid disease affects any outcome. Further, there are no compelling data that subclinical hypothyroid disease has significant morbidity in nonpregnant individuals, and multiple professional associations have differing opinions on screening nonpregnant individuals for thyroid disease and whether treatment is warranted in the nonpregnant individual with subclinical hypothyroid disease. If there is no consensus on morbidity then certainly there is no reason to treat. The issue of TPO-antibodies–positive women is a bit more complex because there does seem to be an increased risk for miscarriage in TPO-antibodies–positive women. However, whether the mechanism for miscarriage is related to autoimmunity or true thyroid dysfunction is not clear and treatment trials with thyroid hormone have not consistently shown reduced risk of miscarriage. So I defer to my infertility colleagues regarding the management of women with infertility and...
whether to screen and treat subclinical hypothyroid disease before pregnancy.

James Haddow: About 1 in 5 women in this category will become permanently hypothyroid. There are 3 possible courses of action: (1) begin treatment with L-thyroxine and withdraw treatment after pregnancy to determine whether recovery has taken place (as measured by TSH); (2) repeat the TSH measurement at intervals and begin treatment if thyroid deficiency worsens; and (3) ignore the initial TSH result. Option 1 is my preference, recognizing that option 2 might also be reasonable. Option 3 is unacceptable. A randomized, double blind crossover trial in nonpregnant adults with subclinical hypothyroidism (mostly women) reported in 2010 documented symptomatic improvement on L-thyroxine treatment among study participants with 2 consecutive baseline TSH concentrations >4.5 mIU/L (most were in the subclinical hypothyroidism range) (8).

John H. Lazarus: I think women with subclinical hypothyroidism should be treated ideally before conception. If they are diagnosed in the first trimester they should also be treated. From our experience in the CATS (Controlled Antenatal Thyroid Screening) study most women can tolerate 150 µg of levothyroxine.

Roberto Negro: I strongly support levothyroxine treatment in women with subclinical hypothyroidism before and during pregnancy. The work of Ashoor and colleagues (9) showed that women with subclinical hypothyroidism are at increased risk of miscarriage. As a consequence, it is of pivotal importance that TPO-antibodies–positive women of childbearing age have prepregnancy TSH concentrations between 0.5 and 1.5 mIU/L. It is equally important to treat newly diagnosed subclinical hypothyroidism in early pregnancy. We published a randomized prospective study that demonstrated an increased rate of adverse events in women with subclinical hypothyroidism (TSH >2.5 mIU/L), and we also found that substi-tutive treatment, when started within the first trimester, is able to reduce the rate of complications (10).

Is there evidence to suggest that such a treatment can be detrimental to mother or infant?

James Haddow: The short answer is "No." Studies have demonstrated the absence of adverse effects. Given that L-thyroxine is simply replacing a hormone deficiency, there is no biologic plausibility for there to be detrimental effects.

John H. Lazarus: There are no data to suggest that such treatment may be harmful. Of course thyroid function must be monitored regularly and dose adjustments made as required.

Sarah Kilpatrick: Treatment of pregnant women with synthroid or levothyroxine for hypothyroid disease has not been shown to have risks for the mother or fetus. However, lack of risk, while reassuring, is not reason enough to use a treatment with unknown or unproven efficacy for its intended indication.

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