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

Bob Barrett: This is the podcast from *Clinical Chemistry*. I am Bob Barrett. 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 by Dr. James Haddow's group, 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?

The October issue of the journal *Clinical Chemistry* published a Question & Answer piece entitled, "Thyroid Function during Pregnancy: Who and How Should we Screen?" The paper summarized the opinions of four experts representing different views on the subject of thyroid function during pregnancy.

On our podcast today, we have the lead author, Dr. Ann Gronowski, who is the Professor in the Departments of Pathology & Immunology & Obstetrics & Gynecology at Washington University School of Medicine, and James Haddow, Professor of Pathology & Laboratory Medicine at Brown University, and the lead author of the 1999 study on the association of maternal thyroid status and neurodevelopment of children.

First, Dr. Gronowski, why is the function of the maternal thyroid important during pregnancy?

Dr. Ann Gronowski: Well, we know that hyper or overactive, and hypo, underactive, thyroidism can have adverse effects on the mother and her unborn baby. For instance, poorly controlled hyperthyroidism during pregnancy can lead to conditions such as congestive heart failure, thyroid storm, infections, spontaneous abortions, and increased rate of stillbirth, low birth weights, preterm delivery, fetal or neonatal hyperthyroidism, and intrauterine growth retardation.

Likewise, in overt hypothyroidism, obstetrical complications such as spontaneous miscarriage, stillbirth, perinatal death, and preterm occur with increased frequency. In addition, the fetus could be affected by low birth weight and in very severe cases, cretinism, which is marked by growth failure and mental retardation.

Hypothyroidism can be caused by iodine deficiency, which is still a problem in certain parts of the world. So there is no doubt that these conditions of overt hyper and hypothyroidism should be treated. What has become a question is whether milder forms of hypothyroidism, referred to a subclinical hypothyroidism, should be screened for and treated. Subclinical hypothyroidism is defined as

patients who have normal free T4 but slightly elevated TSH, between 2.5 and 10 mIU/liter.

Bob Barrett: Why do you think that this topic has gained such interest recently?

Dr. Ann Gronowski: Part of it stems from Dr. Haddow's 1999 study showing an association between an underactive thyroid gland during pregnancy and delayed neurodevelopment in the offspring that you mentioned earlier. Since that time, several medical associations have created guidelines on screening and treating hypothyroidism during pregnancy, but they have differing opinions.

The American Association of Clinical Endocrinologists indicate that TSH screening should be routine before pregnancy or during the first trimester. If the TSH is greater than 10 mIU/liter, or if the TSH is between 5 and 10 mIU/liter, and the patient has goiter or positive anti-thyroid peroxidase antibodies, then thyroid hormone replacement therapy should be initiated.

On the other hand, the American Thyroid Association and The Endocrine Society agree that there is not enough evidence and not enough data for or against universal screening, but they also acknowledge that lack of evidence of benefit doesn't mean that there is no benefit. So they recommend only the screening of pregnant woman who are at a high risk of overt hypothyroidism; in other words, patients with a history of thyroid dysfunction, thyroid peroxidase antibody, or goiter. If the TSH in those patients is greater than 10, this indicates overt hypothyroidism and thyroid hormone replacement therapy should be initiated. But if the patient has subclinical hypothyroidism, The Endocrine Society feels the potential benefits outweigh the risks and women should be treated. The American Thyroid Association, however, says that women with subclinical hypothyroidism should be treated only if they are positive for thyroid peroxidase antibodies.

However, the American College of Obstetricians and Gynecologists has recommended against screening all pregnant women for hypothyroidism and against treating subclinical hypothyroidism. They argue that there is lack of clear evidence that the identification and treatment in women with subclinical hypothyroidism will improve maternal or infant outcome.

So despite the fact that three out of the four clinical guidelines recommend no screening or screening only high risk women, experts, including the four that we interviewed in our article, continue to debate who, if anyone, should be

screened for milder forms of thyroid disease and at what point treatment should be initiated.

So, clearly, more randomized controlled studies that document the safety and efficacy of intervention for both mother and infant are required before this debate is over. And in the meantime, testing and treatment remains at the discretion of the physician.

Bob Barrett: You mentioned a cause of hypothyroidism worldwide is iodine deficiency. Now, is this something we should be more concerned about?

Dr. Ann Gronowski: Well, there's been a major global effort to make iodized salts available to everyone, and currently two-thirds of the world is now covered by iodized salts. As a result, the global prevalence of children with insufficient iodine intake has fallen over the past decade. That's good.

However, there has been a slight increase in the prevalence of children with insufficient iodine intake in the Americas, and the UK actually remains one of the top ten iodine deficient countries, along with several African countries, the Russian Federation, and Afghanistan.

The reasons for the decreased iodine consumption in the United States is threefold. One, our overall desire to decrease salt consumption in the United States. Two, iodized salt is not actually used in many of the fast foods and processed foods that we eat here in the United States. And three, an increase in popular "designer salts" such as sea salts and kosher salts, which usually do not contain iodine.

Now, don't get me wrong, I am not suggesting that people in the United States should increase their salt consumption, but it is generally agreed that pregnant and lactating women should take supplements that contain 250 mg of iodine per day.

Bob Barrett: Okay, thank you Dr. Now, we turn to Dr. James Haddow. Dr. Haddow, can you tell us about your 1999 study that led to much of the excitement in this area of study?

Dr. James Haddow: Yes, our group started doing prenatal screening, although this prenatal screening was not related to thyroid testing at the time, and we provided these services to women all over the State of Maine, and this began in 1979.

As part of the routine of our laboratory, we saved all of the leftover serum samples in the freezer and we had them available for studies that might occur to us in the future.

And so these samples actually served for the basis for the study that we are talking about today.

In the mid-1990s, we took out 25,000 samples from pregnancies that had delivered about six years earlier and we measured TSH in all 25,000 of these pregnancies. It was then possible to select the highest 3 out of every 1,000 TSH measurements.

And then we contacted the women who had been identified through this process and we asked permission to perform IQ testing on their children. Their children would be about the age of eight years at the time, and this was a particularly good time for testing them, because it's considered that IQ testing is highly reliable at that age.

Most of the TSH measurements on the women from the time of the pregnancy were above 10 International Units/Liter. And this is considered by current day definition to be in the overt hypothyroidism range.

We then matched the 62 women who had agreed to have their children tested, each of them was matched with two controlled mothers whose TSH measurements were normal during the same time period and we sought their permission to have their children tested, and ultimately we tested 124 of these controlled children.

The major finding of the study was that the full scale IQ averaged 7 points lower among the 48 children of women with undiagnosed hypothyroidism than among the controls. And I think of equal importance was the fact that 19% of these children had IQs below 85, as opposed to 5% of the controlled children. This was felt by the consultant to our project, who was a neuropsychologist, to be of particular importance, because she said that children with IQs below 85 have struggles both in school and in life in general, so we really paid a lot of attention to that.

A second, I would have to say unanticipated, finding in our study was that, when we went back at ten years to follow up the women who were undiagnosed as having hypothyroidism, 32 of the 48 of those women had gone on to become permanently hypothyroid. And this we felt really told us a great deal about what course of action might be taken to try to prevent this. One of the problems that we uncovered in addition to the actual number of 32 of 48, which was actually two-thirds of all those women, we discovered that it took an average of five years before a clinical diagnosis could be made, and 4 of those 32 women were only identified by us when we offered follow-up TSH testing ten years later, and 3 of these 4 women were clearly

seriously hypothyroid; a couple of them having TSH measurements in the mid-200 range.

Bob Barrett: Doctor, is there any other evidence that subclinical hypothyroidism can have negative effects on the fetus?

Dr. James Haddow: I would like to just make a point in response to that question to point out that the study that I just described has often been misinterpreted as focusing on children of women with subclinical hypothyroidism, and I think that there was a confusion there between undiagnosed thyroid deficiency and subclinical hypothyroidism. In fact, our study actually dealt with children of women with undiagnosed overt hypothyroidism. This is an important point because there is still a great deal of unanswered information about women and children in the subclinical range, but certainly I think there is much less disagreement about women and children with TSHs above 10.

The problem with the undiagnosed aspect of our population was that we now understand that the symptoms of women who are hypothyroid are quite nonspecific, and it's not easy to distinguish these women from women who have similar complaints from other causes. Examples, easy fatigability and constipation are common complaints during pregnancy, but in fact also occur as a direct result of hypothyroidism.

There was a recent randomized trial in the United Kingdom, which I think many people are familiar with, it was published in *The New England Journal [of Medicine]*, and it reported there was no impact of elevated maternal TSH on offspring IQ. This is an important study, and it certainly is reassuring about preservation of IQ, but the women who were recruited to that study were mostly women with TSH measurements in the subclinical range. Studies that have examined pregnancy outcomes involving women with TSH in the 4-10 IU/liter range have been conflicting in other areas, for instance, that have to do with complications of pregnancy itself. And I would have to say that at this point a definitive answer is not possible.

The one point that is worth coming back to however is that when it comes to the mother's health, it is well documented that about 1 in 5 pregnant women with TSH in the subclinical hypothyroid range will become permanently hypothyroid at some point in their lives.

Bob Barrett: Well, Dr., do you feel that women should have thyroid function testing performed during pregnancy, and if so, well then, there is all the other questions; who should be tested; what should be measured; what are the cutoffs that should be recommended?

Dr. James Haddow: My view is that all women should have a TSH measurement performed during pregnancy. We have a good model to follow with some of the other prenatal screening that's done to assure that there is a proper system in place, both for interpreting the tests and for providing guidance for follow up when women have elevated TSH.

The TSH is clearly the most reliable indicator of existing thyroid dysfunction. If I were to design a cutoff, if I were to choose one, I would say that it would be reasonable to start somewhere at the 97.5th-98th percentile of reference range that had been set for the population that's under study. Clearly, it's necessary to have specific cutoff ranges based on gestational age during pregnancy, because they do change from trimester to trimester.

In recent years, discussions pro and con screening have focused exclusively on fetal well-being. My feeling is that we should now consider the mother's health as a priority even prior to definitive proof of fetal morbidity that might be associated with subclinical hypothyroidism.

In addition to the cases of subclinical hypothyroidism, our observational study found that about 3 pregnant women per 1,000 had undiagnosed overt hypothyroidism, and I have mentioned that earlier in this discussion.

There is general agreement that treatment is indicated in such cases. That two-thirds of these women had subsequently became permanently hypothyroid are an important group to consider, and I think that it's really justification in itself to carry out screening.

The more recent cohort study of 10,000 pregnancies that were recruited from three major medical centers in the United States has documented a rate of undiagnosed hypothyroidism with TSH greater than 10 IU/liter in more than 2 women per 1,000. So the figure that we had from the 1999 study of 3 is borne out with this second study, which encompassed five different medical centers to supply the women who had consented.

So this is similar and it really reinforces the fact that there's a group of women who deserves immediate attention.

Bob Barrett: Well, Dr. Haddow, what's your opinion about treating women with subclinical hypothyroidism before or during pregnancy?

Dr. James Haddow: This is an area where I think you would have to consider that there is more flexibility in choice. As I mentioned earlier, about 1 in 5 women in this category will become

permanently hypothyroid. I view three possible options that might be considered.

The first would be, when you find that the TSH is elevated but it isn't as high as 10, you could begin treatment with L-thyroxine and then withdraw treatment after pregnancy to determine whether recovery has taken place. This can be done by just doing a repeat measurement of TSH.

The second option would be not to treat right away, but repeat the TSH measurement at intervals and begin treatment if thyroid deficiency worsens.

The third option would be simply ignore the initial TSH result.

I would have to say at the outset that option three is unacceptable to me. I simply don't see that that is a proper medicine.

I would choose personally the first option, which would be to start treatment right then and to withdraw treatment at the end of pregnancy to see if recovery had taken place.

I also really recognize that the second option of tracking the women and just making sure that the TSH does not go higher, that might also be reasonable.

There was one study which I thought might be of some interest. This was done, however, in women who were not pregnant. But what it did show was that this was a randomized double-blind crossover trial, a quite elegant study design, and it looked at subclinical hypothyroidism and it simply documented that there was symptomatic improvement on L-thyroxine treatment among study subjects who had two consecutive baseline TSH concentrations, above 4.5 mIU/liter. When I give that figure, I have to remind you that the double-blind crossover trial means that each woman served as her own control and this made the study highly efficient and also highly reliable, because it removed a lot of the background noise of symptomatology. And so I think that this study deserves a special attention and reinforces the value of treatment of women with subclinical hypothyroidism.

Bob Barrett: Is there any evidence to suggest that such a treatment can be detrimental to the mother or infant?

Dr. James Haddow: The immediate answer is no. There have been formal published studies that have demonstrated the absence of adverse effects, and this is during pregnancy. Given that L-thyroxine is simply replacing a hormone deficiency, there is no biologic plausibility for there to be detrimental effects.

The possibility of, say, giving too much treatment is always there, as with any medication, but when properly managed, there should be no adverse consequences.

The whole issue of treating women who are subclinically hypothyroid, once again, comes to the fore. And I would say that from what I have just described earlier when it comes to the mother's health, her own health, I would say that it's worthwhile starting the treatment right at the time when you identify the elevated TSH, and then just being assured after the pregnancy is over that the TSH either settles down within the normal range or indicates that continued treatment is necessary.

Bob Barrett: Well, finally Dr. Haddow, Dr. Gronowski mentioned that iodine deficiency is a bigger problem than we expected, even in developed countries. Are you worried about this? Do you feel pregnant women should be screened for iodine deficiency?

Dr. James Haddow: There really is not a reliable screening test for iodine deficiency. When it comes to the individual, the urine iodine measurements are commonly used at the level of population health, but really are not recommended for a woman's individual assessment. And this is because the iodine measurements reflect iodine intake over only a short period. So you have no really good measure available.

When you do use the urine iodine measurements on a population level, you can get a good idea of the distribution over say -- let's say you measure a 100 women or 1,000 women, you can get a very good idea how much iodine is available within the population at large.

There was a recent study surveyed by the CDC and urine iodine measurements were performed on a large sampling of pregnant women in the United States, and the determination was that in the population there was an indication of mild iodine deficiency.

I would recommend that rather than having to consider doing testing on these women, especially when the test is basically useless, that the most important step to be taken is to assure that every pregnant woman gets a vitamin supplement that contains iodine for the duration of the pregnancy, and usually this is about 150 micrograms of iodine per tablet. The caution here is that not all vitamin preparations for pregnant women contain iodine. So there has to be attention paid, not just to having a vitamin, but to having the vitamin with iodine.

Bob Barrett: Okay, Drs., thank you both so much for your time today. Dr. Ann Gronowski is a professor in the Departments of

Pathology & Immunology & Obstetrics & Gynecology at Washington University School of Medicine, and Dr. James Haddow is Professor of Pathology & Laboratory Medicine at Brown University. They have both been our guests in this podcast from *Clinical Chemistry*.

I am Bob Barrett. Thanks for listening!