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Evaluation of Thyroid Function during Pregnancy: Have We Taken a Wrong Turn?

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Guest: Dr. Ann M. Gronowski is Professor of Pathology and Immunology at Washington University in St. Louis, Missouri.

Bob Barrett: This is a podcast from *Clinical Chemistry,* sponsored by the Department of Laboratory Medicine at Boston Children's Hospital. I am Bob Barrett.

Normal pregnancy is associated with profound hormonal and metabolic changes in the mother, including changes in thyroid hormones. These normal changes include increased thyroid binding globulin, increased total T3 and total T4, transient decrease in TSH, and in some patients, a transient increase in serum FT4 during the first trimester.

In 2017, the American Thyroid Association issued new guidelines for the diagnosis and management of thyroid diseases during pregnancy, which can be difficult due to the numerous normal physiological changes. Most would agree that the document is an excellent review of current literature relating to the assessment of thyroid status during pregnancy. However, one researcher wonders if a particular recommendation of the document is misguided.

Today, we have with us Dr. Ann Gronowski, Professor of Pathology and Immunology at Washington University, who published a paper in the March 2018 issue of *Clinical Chemistry* entitled "Evaluation of Thyroid Function during Pregnancy: Have We Taken a Wrong Turn?"

Dr. Gronowski, great to have you back! Can you explain which of the American Thyroid Association's recommendations that you disagree with and why?

Dr. Gronowski: First, let me say that I believe that the American Thyroid Association's new guidelines provide excellent guidance on how to diagnose and manage thyroid disease during pregnancy and the postpartum period. It's a valuable and well-written document. However, recommendation three states that, and I quote, "accurate estimation of the free T4 concentrations can also be done by calculating a free T4 index."

Now, most experts in the laboratory community today would say that the free T4 index is an obsolete estimation of free

T4 that's been replaced by newer and more accurate free T4 immunoassays and LC-MS/MS. In my opinion, the American Thyroid Association should not recommend the use of this outdated biochemical marker.

Bob Barrett: Okay. Well, let's back up for just a second and what is the free T4 index?

Dr. Gronowski: Well, that's a good question because a lot of people today have probably never heard of the free T4 index. So, this test was developed many years ago before we had reliable free T4 immunoassays. It's actually a calculation based on the total T4 concentrations and the thyroid binding capacity, also called T uptake, which provides a measure of the available thyroxine binding sites. It's not really an estimate of free T4 concentrations but rather it's an estimation of whether the amount of circulating total T4 can be accounted for by the amount of thyroid-binding globulin. If the total amount cannot be accounted for by binding proteins, it's assumed to be due to increased free T4. It has many limitations. And today, direct measurement of free thyroxine has replaced the free T4 index.

Bob Barrett: So what do you think led to the American Thyroid Association recommending free T4 index as a biomarker to measure in pregnancy?

Dr. Gronowski: Well, I believe that the recommendation for free T4 index arose out of a single published paper. So, backing up, numerous studies have demonstrated that in some women, free T4 measured by various commercial immunoassays decreases with gestational age, while TSH remains within the normal reference interval. But people find this perplexing because TSH and free T4 have a very sensitive inverse relationship with each other.

Why would TSH remain in the reference interval while free T4 decreases in what appears to be a euthyroid person? Well, in 2009, a paper by Lee et al., demonstrated that free T4 concentrations decreased during the second and third trimesters when measured using two commercial immunoassay methods, whereas free T4 index did not decrease. So, they concluded that because free T4 index retains the appropriate relationship with TSH throughout pregnancy, free T4 measurement by immunoassay methods were "flawed."

It's really as a result of this single paper, as best that I can tell, that both the Endocrine Society and the American Thyroid Association recommend the use of free T4 index to estimate free T4 concentrations during pregnancy.

Bob Barrett: Their conclusions sound reasonable. In what ways do you disagree with the Lee paper?

Dr. Gronowski: Well, first I should say that there are reasons in theory that immunoassays could potentially be inaccurate during pregnancy. Pregnant women have higher concentrations of thyroxine-binding globulin and non-esterified fatty acids that could potentially alter the properties of immunoassays that were developed and validated using non-pregnant serum.

I think that there is no doubt that trimester-specific reference intervals should be established for each commercial immunoassay. But the authors of the Lee paper did not measure free T4 using dialysis or ultrafiltrate LC-MS/MS which are considered to be the gold standard for measuring free T4. Studies have shown that free T4 concentrations measured by direct equilibrium dialysis or ultrafiltration and LC-MS/MS also decrease with advancing gestational age.

Bob Barrett: Dr. Gronowski, it sounds like you believe that the decreasing free T4 concentrations during pregnancy are real and not due to flawed immunoassays, but you said that TSH and free T4 have a very sensitive inverse relationship with each other. Can you explain why you think free T4 does not correlate with the TSH concentrations during pregnancy?

Dr. Gronowski: Yeah. Well, there are conditions where TSH remains normal and free T4 is low. For instance, this happens in people who are very ill. We call this sick euthyroid syndrome or non-thyroidal illness syndrome. In essence their body decreases the amount of free T3 and free T4 in order to slow down their metabolism but their TSH remains normal indicating that their body is okay with this decrease. The body is attempting to conserve energy. This kind of pattern is also seen in conditions of starvation, chronic renal failure, and cardiopulmonary bypass surgery. The changes observed during late pregnancy resemble those of sick euthyroid syndrome, with a decreasing free T4 even outside the normal non-pregnant reference interval, and TSH within the reference interval. So the changes in thyroid status in these conditions make sense as they are periods which require a conservation of energy.

Bob Barrett: So you're saying that during late pregnancy, the body may be attempting to save energy and that's why free T4 can be low but TSH remain normal. Are there other ways that pregnancy is like sick euthyroid syndrome which would support this idea of yours?

Dr. Gronowski: So first of all, I should point out that I'm not the first person to have this idea. In 1998, Berghout et al. introduced this concept and pointed out that the decrease in serum free T4

in pregnancy cannot be accounted for by changes in plasma volume or albumin or TBG or free fatty acids or iodine, suggesting that it's a real decrease. But there are other ways that late pregnancy is similar to sick euthyroid syndrome. So, like sick euthyroid syndrome, late pregnancy is also associated with increased concentrations of reverse T3. The increase in reverse T3 in sick euthyroid syndrome has been attributed to changes in deiodinase activity that's associated with an increase in serum glucocorticoid concentrations that is also observed during pregnancy. Pregnancy is different than sick euthyroid syndrome in that total T3 and total T4 concentrations increase during pregnancy, but decrease in sick euthyroid syndrome. However, this is accounted for by the dramatically increased TBG concentrations that are found during pregnancy.

In addition, this pattern of increased TBG, and hence total T3 and total T4, is also observed in some forms of non-thyroidal illness such as acute hepatitis B. There are only a few studies that have measured free T3 throughout the third trimester of pregnancy using equilibrium dialysis, ultrafiltration, or LC-MS/MS. However, in the studies that have been published, free T3 parallels free T4 in late pregnancy just as it does in sick euthyroid syndrome.

Finally, we know that energy intake during late pregnancy is lower than the need for energy creating an energy deficit. The deficit is concordant with the decreased free T3 and free T4 concentrations and together may contribute to energy savings similar to sick euthyroid syndrome. So the altered concentrations of free T4 may reflect an altered set point for the hypothalamic–pituitary–thyroid axis during pregnancy. Further studies are needed to compare the clinical and biochemical conditions of pregnancy with sick euthyroid syndrome.

Bob Barrett: Okay, doctor, you've made a very convincing case that free T4 immunoassays may reflect a real decrease in free T4 concentrations during pregnancy. But is measuring free T4 index wrong in your opinion?

Dr. Gronowski: In my opinion, caution should be used when suggesting the use of an outdated assay such as free T4 index in a complicated setting such as pregnancy. The authors of the Lee paper did not evaluate the use of free T4 index in comparison with other methods to identify disease state such as hyper- and hypothyroidism in pregnant patients.

More importantly, free T4 index has been reported to correlate poorly with free T4 measured by commercial immunoassays and equilibrium dialysis in patients with non-thyroidal illness. Therefore, if pregnancy really is a

condition like nonthyroidal illness, then free T4 index may perform really poorly in this population.

So, in my opinion, the use of gold standard methods such as equilibrium dialysis, LC-MS/MS should be the only method recommended in professional guidelines. My take home message is that an antiquated test such as free T4 index should not be used as a substitute for much needed trimester specific reference intervals.

Bob Barrett: Dr. Ann Gronowski is Professor of Pathology and Immunology at Washington University in St. Louis, Missouri. She's been our guest in this podcast from *Clinical Chemistry*. I'm Bob Barrett. Thanks for listening!