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Opinion

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

Ann M. Gronowski[1*]

Recently, the American Thyroid Association (ATA)[2] issued new guidelines for the diagnosis and management of thyroid diseases during pregnancy and the postpartum period *(1)*. The document is an excellent review of current literature relating to the assessment of thyroid status during pregnancy. While universal screening for thyroid disease before or during pregnancy remains controversial, thyroid status can be accurately screened with thyroid-stimulating hormone (TSH), and additional testing such as free thyroxine (FT4) is required only when TSH is abnormal. However, one of the recommendations of the ATA document stood out: Recommendation 3 reads, "Accurate estimation of the FT4 concentrations can also be done by calculating a FT4 index." The FT4 index is a virtually obsolete estimation of FT4 that has been replaced by newer and more accurate FT4 immunoassays and LC-MS/MS. This recommendation is based on the panel's observation that "Current uncertainty around FT4 estimates in pregnancy has led some to question the wisdom of relying on any FT4 immunoassays during pregnancy." Here I would like to review the source of this uncertainty and propose an alternative interpretation of the literature.

SOURCES OF UNCERTAINTY

In 1991, Roti et al. compared 10 different radioimmunoassay methods for free triiodothyronine (FT3) and FT4 *(2)*. They observed that whereas FT4 concentrations were often lower in pregnant (third trimester) women than nonpregnant women, the TSH concentrations remained within the reference interval. These findings suggested that many of the assays available at that time for the measurement of serum free thyroid hormone concentrations did not seem adequate to evaluate the real thyroid status of pregnant women. Indeed, since then numerous studies have demonstrated that FT4 measured by various commercial immunoassays decreases with gestational age *(3–6)*.

In 2009, Lee et al. built on Roti's observation *(7)*. Their group demonstrated that FT4 concentrations decreased during the second and third trimesters when measured using 2 commercial immunoassay methods, whereas the FT4 index did not decrease. They concluded that, because the FT4 index retained an appropriate relationship with TSH throughout pregnancy, FT4 measurement by immunoassay methods was unreliable, or "flawed" as the title of their publication stated. As a result of this single study, both the Endocrine Society *(8)* and the ATA *(1)* recommend the use of the FT4 index to estimate FT4 concentrations during pregnancy.

There are reasons that immunoassays could potentially be inaccurate during pregnancy, including the fact that pregnant women have higher concentrations of thyroxine-binding globulin and nonesterified fatty acids that could, in theory, alter the properties of immunoassays developed and validated with use of nonpregnant serum. There is no doubt that trimester-specific reference intervals should be established for each commercial immunoassay.

ALTERNATIVE INTERPRETATION

However, in my opinion, the logic that Lee et al. applied to conclude that the FT4 index is "more accurate" than immunoassays is flawed. The authors came to this conclusion because both TSH and the FT4 index remained within the reference interval during late pregnancy; therefore, the FT4 index must be correct and the immunoassay results must be incorrect. However, the authors did not measure FT4 with use of a gold-standard method such as dialysis or ultrafiltrate LC-MS/MS. Studies have shown that FT4 concentrations, measured by direct equilibrium dialysis or ultrafiltration and LC-MS/MS, also decrease with gestational age *(9, 10)*.

Therefore, there is good evidence that FT4, measured by either immunoassay or dialysis/ultrafiltrate LC-MS/MS, decreases with gestational age. Yet, it seems physiologically illogical that TSH should remain within the reference interval, while the FT4 is below the reference interval. However, there are other conditions in which TSH remains normal and FT4 is low, namely, sick euthyroid syndrome *(11)*. Similar conditions are seen with starvation, chronic renal failure, and cardiopulmo-

[1] Department of Pathology and Immunology, Washington University School of Medicine, St. Louis, MO.
* Address correspondence to the author at: Department of Pathology and Immunology, Washington University School of Medicine, Box 8118, 660 S. Euclid, St. Louis, MO 63110. Fax 314-362-1461; e-mail gronowski@wustl.edu.
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[2] Nonstandard abbreviations: ATA, American Thyroid Association; TSH, thyroid-stimulating hormone; FT4, free thyroxine; FT3, free triiodothyronine.

nary bypass. The changes observed during late pregnancy resemble those of sick euthyroid syndrome with decreasing FT4 (even outside the normal nonpregnant reference interval) and TSH primarily within the reference interval. The changes in thyroid status in these conditions make sense as they are periods that require conservation of energy.

Like sick euthyroid syndrome, late pregnancy is also associated with increased reverse T3 concentrations *(12, 13)*. The increase in reverse T3 concentrations in sick euthyroid syndrome has been attributed to changes in deiodinase activity associated with an increase in serum glucocorticoid concentrations, which is also observed during pregnancy *(14)*. Another similarity with sick euthyroid syndrome is that while TSH in most patients remains normal, TSH in some patients can fall below the lower reference interval limit with advancing illness or pregnancy despite the low FT4 concentrations *(7, 11)*. Unlike sick euthyroid syndrome, TT3 and TT4 concentrations increase during pregnancy. However, this is accounted for by the dramatically increased thyroxine-binding globulin concentrations found during pregnancy. This pattern of increased thyroxine-binding globulin (and hence TT3 and TT4) is also observed in some forms of nonthyroidal illness such as acute hepatitis B *(11)*. There are only a few studies measuring FT3 through the third trimester of pregnancy by use of equilibrium dialysis, ultrafiltration, or LC-MS/MS. However, in the studies that have been published, FT3 parallels FT4 in late pregnancy, just as it does in sick euthyroid syndrome *(12, 13)*. The similarity between pregnancy and nonthyroidal illness has been proposed previously by Berghout et al. *(13)*, who point out that the decrease in serum FT4 in pregnancy cannot be accounted for by changes in plasma volume, albumin, thyroxine-binding globulin, free fatty acids, or iodine. Furthermore, energy intake during late pregnancy has been shown to be lower than the calculated need for energy. This energy deficit is concordant with decreased FT3 and FT4 concentrations and together may contribute to energy savings, similar to sick euthyroid syndrome.

FT4 immunoassay methods may not be inaccurate or "flawed" in the euthyroid pregnant population. The altered reference intervals of FT4 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.

The FT4 index is a calculated value based on the total T4 measurement and thyroid-binding capacity (which provides a measure of the available thyroxine-binding sites). The FT4 index is not really an estimation of FT4; rather, it uses a formula to assess whether the amount of total T4 present in serum can be accounted for by the amount of binding protein present. If the total amount cannot be accounted for by binding proteins, it is assumed to be due to increased FT4. This calculation was valuable in the era when reliable commercial FT4 assays were not readily available.

Caution is advised when suggesting the use of an outdated assay such as the FT4 index in a complicated setting such as pregnancy. Lee et al. did not evaluate the use of the FT4 index in comparison with other methods to identify hyper- and hypothyroid pregnant patients. More importantly, the FT4 index has been reported to correlate poorly with FT4 measured by commercial immunoassays and equilibrium dialysis in patients with nonthyroidal illness *(15)*. Today, use of gold-standard methods such as equilibrium dialysis LC-MS/MS should be the only methods recommended in professional guidelines; the ATA and Endocrine Society *(1, 8)* do endorse the use of these methods. An antiquated test such as the FT4 index should not be used as a substitute for much-needed trimester-specific reference intervals.

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