To the Editor:

We read with interest the case conference by Fantz et al. (1) on thyroid function during pregnancy. The presented case is typical of gestational thyrotoxicosis (2), and the authors reviewed beautifully the related problems of interpretation of thyroid function tests in pregnancy.

We had proposed a new clinical entity, “gestational thyrotoxicosis”, defined by clinical features as follows (3): (a) thyrotoxic symptoms, such as palpitation, increased sweating, and weight loss in early pregnancy; (b) marked increase in free thyroxine (T₄; more than twice the upper limit of the reference range) and free triiodothyronine (T₃); (c) complication with hyperemesis gravidarum; (d) spontaneous recovery in the later half of pregnancy; (e) negative for antithyroid microsomal or thyroid peroxidase antibodies; (f) negative for anti-thyroid-stimulating hormone (TSH) receptor antibodies; (g) no goiter; and (h) circulating human chorionic gonadotropin (hCG) with high biological activity.

We examined the case of Fantz et al. (1) in light of our experience. They did not examine the anti-thyroid antibodies in their case, although the importance of antibody measurement was described in the discussion.

Their laboratory data on thyroid function are curious. The free T₄ index was more than fourfold higher than the upper reference value of nonpregnant healthy subjects, but the TSH was 0.8 mIU/L (1). The negative feedback regulation in the pituitary-thyroid axis is well preserved even during pregnancy (4); thus, TSH should completely be suppressed. The TSH value of 0.8 mIU/L might be obtained if high hCG α-subunit interfered in the assay or if the sample was obtained at a different date than the free T₄ sample.

The increase of serum thyroglobulin concentration during pregnancy decreases, rather than increases, thyroglobulin (5). Decreased serum thyroglobulin in pregnancy is compatible with a previous report from Japan where iodine intake is sufficient (6). A recent study in the United States also clarified that there was no significant change in thyroglobulin concentration during and after normal pregnancy (7). Gestational thyrotoxicosis is induced mainly by the overstimulation of asialo-hCG, which has strong thyroid stimulation bioactivity (2). The conventional immunoassay for hCG cannot specifically detect asialo-hCG, and thus, the serum concentrations of hCG in gestational thyrotoxicosis did not differ significantly from those in euthyroid normal pregnant subjects (2).

In the cases of Graves thyrotoxicosis, measurement of anti-TSH receptor antibodies (TRAbs) is important for diagnosis, as the authors discussed. The radioreceptor assay for TRAbs was developed first by Smith et al. (8) in the United Kingdom, and they used the term “TSH”. Therefore, TSI indicates TRAbs measured by radioreceptor assay and does not express biological activity. At present, the term TSH receptor-binding inhibitory immunoglobulin (TBI) is widely used (9). Instead of TSI, thyroid-stimulating antibody (TSAb) is commonly used for the expression of biological stimulating activity.

Thyroid growth-stimulating immunoglobulin (TGI) is somewhat difficult to assay for a routine test, and there is still debate whether TGI is the same as TSAb.

Fantz et al. (1) are thoughtful to discuss postpartum thyroid dysfunction because this problem is far more common than gestational thyrotoxicosis. Our recent review provides further discussion of the clinical importance of postpartum thyroid dysfunction (10).
To the Editor:
Fantz et al (1) describe a case of hyperthyroidism of hyperemesis gravidarum. They discuss the changes in thyroid function during pregnancy and the causes and investigations of hyper- and hypothyroidism during pregnancy. One of the important differential diagnoses is to determine whether the hyperthyroidism is likely to be transient (as in hyperemesis gravidarum) or related to underlying thyroid disease such as Graves disease.

Red cell zinc or red cell carbonic anhydrase (CA1) is useful in this differentiation. The zinc-containing CA1 is inhibited by thyroid hormones, and in hyperthyroidism red cell zinc and CA1 are low (2, 3). Because the inhibition of this enzyme takes place in developing red cells, changes in red cell zinc or CA1 require several weeks. Thus, it is a useful test to differentiate between transient hyperthyroidism and Graves disease (4, 5).

With regard to the etiology of the hyperthyroidism in hyperemesis, not all studies show a difference in serum human chorionic gonadotropin (hCG) concentration between those hyperemetic subjects with hyperthyroidism and those without (6). Several studies have suggested that there may be subtle differences in the hCG molecule, such as acidic isoforms with increased thyrotropic activity (7, 8).

Frantz et al (1) also fail to mention that hyperemesis is more common in certain racial/ethnic groups (9, 10).

The authors of the Case Conference cited in the previous two letters respond:

To the Editor:
We thank Drs. Amino and Swaminathan for their comments on our review of thyroid function during pregnancy (1). In response to Dr. Amino, the low but measurable serum thyroid-stimulating hormone (TSH) concentration observed in our patient is atypical. The TSH and thyroxine (T4) were obtained on the same date, and it is unlikely that the TSH represents cross-reactivity with human chorionic gonadotropin (hCG) in the patient’s serum because the assay used (IMX; Abbott Laboratories, Abbott Park, IL) shows no detectable interference up to 200,000 IU/L hCG. It would have been informative to follow this patient over time because these values may reflect changing titers, but this was not possible in this patient.

The information on serum thyroglobulin concentrations in pregnancy is appreciated.

The comments regarding various terminologies for TSH receptor antibodies are noteworthy from a historical perspective. However, we feel that the terminology as used in our review is commonly accepted (2–5).

In response to Dr. Swaminathan, we agree, and in fact discuss in our review, that the etiology of hyperthyroidism in hyperemesis is unclear.

The information on hyperemesis in different racial groups is very useful. Although red cell zinc and red cell carbonic anhydrase have been proposed as markers of long-standing thyroid disease, they are not widely used, nor are they readily available.

References

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