FIRST TRIMESTER OF PREGNANCY REFERENCE RANGES FOR SERUM TSH AND THYROID TUMOR RECLASSIFIED AS BENIGN

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Abstract

The 2011 American Thyroid Association (ATA) guidelines recommended that the interpretation of thyroid function in pregnancy be based on trimester specific reference ranges: TSH values should be 0.1-2.5 mIU/L (first trimester), 0.2-3.0 mIU/L (second trimester), and 0.3-3.5 mIU/L (third trimester)(1). Recently, a study performed on a nationwide cohort of 6671 Danish healthy pregnant women and published in June 2016 in Journal of Clinical Endocrinology and Metabolism (4) showed first trimester values of TSH varied according to gestational week. Up to sixth week of pregnancy, TSH levels had nonpregnant reference ranges. During weeks 9- 12, TSH serum level were 0.4 mIU/L lower than non-pregnancy upper limits, with lower range of 0.1 mIU/L. So, the use of uniform limits of TSH normality for the entire first trimester may lead to frequent misclassification and unnecessary treatment given.

Although with indolent behavior, patients with encapsulated follicular variant of papillary thyroid carcinoma (EFVPTC) are often treated as classical papillary thyroid carcinoma. In a retrospective study recently published in the Journal of the American Medical Association Oncology(5), authors reevaluated 268 EFVPTC. In group 1(noninvasive EFVPT), patients observed for 10 -26 years and all were alive with no evidence of disease. Based on this low risk of adverse outcomes of patients from group 1, authors suggested a new nomenclature for this thyroid tumor: “noninvasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTP)”.

Key words: pregnancy, TSH, thyroid cancer, follicular variant.

It is generally known that maternal hypothyroidism is associated with complications in pregnancy and may have adverse effects on foetal neurological development. We also know that pregnancy leads to changes of thyroid function tests. According with these statements, the 2011 American Thyroid Association (ATA) guidelines recommended that the

interpretation of thyroid function in pregnancy be based on trimester specific reference ranges as defined in populations with optimal iodine intake: TSH values should be 0.1-2.5 mIU/L (first trimester), 0.2-3.0 mIU/L (second trimester), and 0.3-3.5 mIU/L (third trimester) (1). Also, Endocrine Society and European Thyroid Association guidelines for treatment of hypothyroidism in pregnancy suggests maintaining serum TSH level under 2.5 mIU/L for first trimester and under 3 mIU/L for second and third trimester of pregnancy (2, 3). Recently, a study performed on a nationwide cohort of 6671 Danish healthy pregnant women and published in June 2016 in Journal of Clinical Endocrinology and Metabolism (4) showed first trimester values of TSH varied according to gestational week. Up to sixth week of pregnancy, TSH levels had nonpregnant reference ranges. During weeks 9- 12, TSH serum levels were 0.4 mIU/L lower than non-pregnancy upper limits, with lower range of 0.1 mIU/L and even lower during week 11. So, the use of uniform limits of TSH normality for the entire first trimester may lead to frequent misclassification and unnecessary treatment given. TSH upper reference limit was lower in multiparous women and women with lower iodine intake but higher in obese women. Obstetric and neonatal outcomes were aimed in a prospective Brazilian study on 660 first trimester pregnant women (median gestation age of 9 weeks). In this study, 2.5th and 97.5th percentiles of TSH were 0.04 and 2.68 mIU/L, respectively. There were no differences between obstetrical and neonatal outcome of pregnant women with TSH ≤ 0.1, between 0.1 and 2.5, and between 2.5 and 4 mIU/L.

Differentiated thyroid cancer is the most frequent type of thyroid cancer, 85 of this being papillary carcinoma, 12 % follicular carcinoma and up to 3% are poorly differentiated thyroid cancer (5). Encapsulated follicular variant of PTC without invasion (EFVPTC), minimally invasive follicular thyroid carcinoma are forms with more favorable outcome and

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should be noted during histopathologic examination report, according to new ATA guidelines published in January 2016 (6). EVVPTC is encountered in half to two thirds of patients with FVPTC and frequently has RAS mutations, whereas nonencapsulated follicular variants usually have BRAFV600E mutations, similar to classic papillary carcinomas (7). Due to its indolent behavior, patients with encapsulated follicular variant of papillary thyroid carcinoma are classified in the new 2016 ATA guidelines in the category of patients with low 10 years risk of structural disease recurrence (1-2%).

In a retrospective study recently published in the Journal of the American Medical Association Oncology(8), authors reevaluated 268 EFVPTC divided into 2 groups: one with noninvasive EFVPTC, without radioiodine treatment and at least 10 years of follow up and one with EFVTP and vascular and/or tumor capsule invasion and at least 1 year of follow-up. In group 1, patients were observed for 10 to 26 years and all were alive with no evidence of disease at the end of the study. Sixty-seven of these patients were treated with lobectomy only. In group 2, among 101 patients (85 treated with radioiodine), 12 (12%) had complications: 5 patients developed distant metastases (lung and/or bone), 2 of whom died of disease, 1 patient had a lymph node recurrence, 1 had persistent disease, and 5 had detectable serum thyroglobulin. A simplified diagnostic nuclear scoring scheme was developed and validated. Based on this low risk of adverse outcomes of patients from group 1, authors suggested a new nomenclature for this thyroid tumor: “noninvasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTP)” and thought that this reclassification will affect psychologically and in clinical management a large population of patients previously diagnosed with thyroid cancer.

Management of patients with EFVTP is frequently similar with all patients with thyroid carcinoma, with radioiodine treatment and long-term suppressed TSH levels with levothyroxine. According to new ATA guidelines, “Radioiodine remnant ablation is not routinely recommended after thyroidectomy for ATA low-risk differentiated thyroid carcinoma patients”, although with weak evidence. During initial follow-up, serum thyroglobulin (Tg) on thyroxine therapy should be measured every 6–12 months, with periodic cervical ultrasound examination. Initial TSH goal should be 0.5-2 mUI/mL if non-stimulated Tg is <0.2 ng/mL (excellent response to previous therapy: no clinical, structural or biochemical evidence of disease) and should be maintained between 0.1-0.5 mUI/mL if nonstimulated Tg is >0.2 ng/mL (indeterminate or

incomplete response). In patients treated with lobectomy or subtotal thyroidectomy, “TSH may be maintained in the mid to lower reference range (0.5–2 mU/L) while surveillance for recurrence is continued. Levothyroxine therapy may not be needed if patients can maintain their serum TSH in this target range”. Periodic Tg level should be measured and monitored; although there are no specific cutoff levels that distinguish normal thyroid tissue from persistent thyroid cancer. Rising Tg values over time are suspicious for recurrence of disease(6).

Conflict of interest

The author declares that he has no conflict of interest concerning this article.

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