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Development of gestation-specific reference intervals for thyroid hormones in normal pregnant Northeast Chinese women: What is the rational division of gestation stages for establishing reference intervals for pregnancy women?

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ABSTRACT

Background: A laboratory- and region-specific trimester-related reference interval for thyroid hormone assessment of pregnant women was recommended. Whether the division by trimester is suitable requires verification. Here, we tried to establish appropriate reference intervals of thyroid-related hormones and antibodies for normal pregnant women in Northeast China.

Methods: A total of 947 pregnant women who underwent routine prenatal care were grouped via two methods. The first method entailed division by trimester: stages T1, T2, and T3. The second method entailed dividing T1, T2, and T3 stages into two stages each: T1-1, T1-2, T2-1, T2-2, T3-1, and T3-2. Serum levels of TSH, FT3, FT4, Anti-TPO, and Anti-TG were measured by three detection systems.

Results: No significant differences were found in TSH values between T1-1 group and the non-pregnant women group. However, the TSH value of the T1-1 group was significantly higher than that of T1-2 group ($P < 0.05$). The TSH values in stage T3-2 increased significantly compared to those in stage T3-1 measured by three different assays ($P < 0.05$). FT4 and FT3 values decreased significantly in the T2-1 and T2-2 stages compared to the previous stage ($P < 0.05$). The serum levels of Anti-TPO and Anti-TG were not having significant differences between the six stages.

Conclusion: The diagnosis and treatment of thyroid dysfunction during pregnancy should base on pregnancy- and method-specific reference intervals. More detailed staging is required to assess the thyroid function of pregnant women before 20 gestational weeks.

1. Introduction

In recent years, thyroid disease during pregnancy has become one of the major focuses of endocrinology and perinatology. Research continues to accumulate that asserts that maternal thyroid hormone levels play a vital role in the first phase of the fetal brain development (1–20 weeks of gestation). Fetal thyroid function does not occur before 12 weeks of gestation. Although fetal thyroid function gradually develops from 12 to 20 weeks, thyroid hormones are still primarily derived from maternal thyroid hormone. A significant negative impact on both fetus and mother occurs in pregnant women with hypothyroidism, especially during early pregnancy [1–3]. A study showed that the risk of miscarriage increased 60% in patients with clinical hypothyroidism during pregnancy [4]. Leung et al. [5]reported that the rate of gestational hypertension was significantly higher in pregnant woman with hypothyroidism (22%) compared to that of the general population (7.6%). And the risk of stillbirth increased in pregnant women with hypothyroidism [6]. Therefore, early diagnosis and prevention of clinical and subclinical hypothyroidism (SCH) during pregnancy requires serious consideration.

Abbreviations: SCH, subclinical hypothyroidism; ATA, American Thyroid Association; CSE, Chinese Society of Endocrinology; CSPM, Chinese Society of Perinatal Medicine; FT3, free triiodothyronine; FT4, free thyroxine; TSH, thyroid stimulating hormone; Anti-TPO, anti-thyroid peroxidase; Anti-TG, anti-thyroid globulin; CLSI, Clinical and Laboratory Standards Institute; NACB, National Academy of Clinical Biochemistry; QC, quality control; CV, coefficient of variation.

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Thyroid hormone levels are one of the most important parameters for diagnosis of thyroid disease in pregnancy. While due to the use of different detection systems, reference intervals of thyroid hormone proposed by reagent manufacturers are quite different. Therefore, the thyroid hormone reference range differs between hospitals and regions. As a unique physiological process, pregnancy produces major changes in thyroid function; thus, thyroid function of pregnant women should not be evaluated by reference levels for the general adult population. To standardize the diagnosis and treatment of thyroid disease in pregnancy, the American Thyroid Association (ATA), the Chinese Society of Endocrinology (CSE), and the Chinese Society of Perinatal Medicine (CSPM) published guidelines for the diagnosis and management of thyroid disease during pregnancy and postpartum for American women in 2011 and Chinese women in 2012 [7,8]. These guidelines recommended that in order to accurately diagnose thyroid dysfunction in pregnant women, a series of laboratory- and region-specific reference intervals during the three-trimesters should be established.

The purpose of this study was to verify the specific reference intervals for thyroid-related hormones and antibodies of normal pregnant women suggested by ATA, CSE and to establish pregnancy- and manufacture-specific reference intervals for Northeast China. We further evaluated the application of the specific reference intervals. These thyroid function tests include free triiodothyronine (FT3), free thyroxine (FT4), thyroid stimulating hormone (TSH), anti-thyroid peroxidase (Anti-TPO), and anti-thyroid globulin (Anti-TG). We followed the methods released by the Clinical and Laboratory Standards Institute (CLSI) [9].

2. Material and methods

2.1. Subjects

A total of 947 women who underwent routine prenatal care from May 2014 to March 2015 at the Shengjing Hospital of China Medical University were enrolled in the study. Recruitment criteria were in accordance with the recommendation of the National Academy of Clinical Biochemistry (NACB) [10]: (1) No family or personal history of thyroid disease, or personal history of other autoimmune diseases; (2) no medical history affecting thyroid function (except estrogen); (3) no goiter; (4) natural singleton pregnancy and no history of abortion. Exclusion criteria were: liver, kidney, or other system disease; hypertension, or diabetes in pregnancy, and positive Anti-TPO or Anti-TG antibodies. Another 150 age-matched healthy non-pregnant women were recruited as the control group. All 947 pregnant women in this study were selected to be no repeated enrollment during different pregnant period, the populations completely independent for each of the groups.

2.2. Sample collection and conservation

Fasting blood samples were collected into BD Vacutainers (contains clot activator) (Franklin Lakes, New Jersey, USA) from subjects in a resting state in the morning. Serum samples were separated and stored at −70 °C until analysis. Lipemic (triglycerides > 20.52 mmol/L), icteric (bilirubin level ≥ 171 μmol/L), and hemolyzed (hemoglobin level ≥ 5 g/L) samples were excluded.

2.3. Laboratory analysis

Serum levels of TSH, FT3, FT4, Anti-TPO, and Anti-TG were measured by the ARCHITECT i2000 analyzer (Abbott Laboratories, Abbott Park, Illinois, USA), Modular Analytics E 170 (Roche Diagnostics, Mannheim, Germany), and UniCel DxI 800 Immunoassay System (Beckman Coulter Inc., Brea, CA, USA) with their respective system accessory kits. All the instruments were calibrated before analyzing the samples. Two levels of quality control (QC) samples were included in each batch testing. The tests results were deemed valid when the concentrations of the QC samples were in the range of expected concentrations. The inter-day imprecision of three laboratory methods were evaluated by measuring 2 levels of QC samples over 20 days.

2.4. Statistical analysis

The data were analyzed by EP evaluator software release 9 (Data Innovations, South Burlington, VT, USA). The reference intervals of thyroid related hormone were expressed using median (P_{50}), 2.5th, and 97.5th percentiles ($P_{2.5}$ and $P_{97.5}$). The reference intervals of thyroid-related antibodies were expressed as 95% confidence intervals of unilateral reference range limit using median (P_{50}) and 95th percentiles(P_{95}). Data of non-normal distribution were normalized using log transformation. The reference ranges of different parameters were expressed by anti-log transformed 95th or 2.5th and 97.5th percentiles. Comparisons of data during different stages of pregnancy were finished using Kruskal–Wallis H Test, and multiple comparisons were tested by Bonferroni correction. The consistency of assessment of thyroid function in pregnant women using different reference intervals were assessed by Kappa consistency. These comparisons were performed using SPSS 18.0 version (SPSS Inc., Chicago, IL, USA).

The experimental procedure was approved by the Ethics Committee of Shengjing Hospital.

3. Results

3.1. Age and gestational age of pregnant population

The subjects in this study ranged in age from 20 to 40 years. We grouped the pregnant women via two methods and analyzed the data. The first method (hereafter referred to as three stages) entailed division by trimester according to ATA guidelines: stage T1 (1–12 weeks), stage T2 (13–27 weeks), and stage T3 (28–40 weeks). The second method (hereafter referred to as six stages) entailed dividing T1, T2, and T3 stages into two stages each: T1-1, T1-2, T2-1, T2-2, T3-1, and T3-2. Data regarding women at these stages is presented in Table 1.

3.2. The imprecision and coefficient of variation (CV) of QC samples

The values of precision and CV for five thyroid function parameters using three different measurement systems are presented in Table 2. Imprecision of the three system accessory kits all met the requirements of instructions supplied by the manufacturers.

3.3. Reference intervals of thyroid functional parameters for the three trimesters

The upper limits of TSH in T1 stage detected by the Abbott, Roche, and Beckman system were 4.46 mIU/L, 4.92 mIU/L, and 3.98 mIU/L, respectively. Although the lowest values of the upper limit for TSH were all found at the T2 stage, no significant differences of median values or the overall distribution were found between stages T1 and T2. The level of FT4 in the second trimester was significantly lower than that

Table 1
Demographic data for pregnant women in study population.

	No.	Median age: years(range)	Median gestational age: weeks(range)
T1	312	27.0(20.0–39.0)	8.00(4.57–12.00)
T1-1	168	27.0(20.0–39.0)	6.57(4.57–8.00)
T1-2	144	27.5(20.0–39.0)	9.86(8.14–12.00)
T2	304	28.5(20.0–40.0)	22.00(12.14–27.00)
T2-1	132	28.5(20.0–39.0)	16.29(12.14–20.00)
T2-2	172	28.0(21.0–40.0)	24.29(20.14–27.00)
T3	331	29.5(20.0–40.0)	36.00(27.14–40.00)
T3-1	135	29.0(21.0–40.0)	30.71(27.14–33.00)
T3-2	196	29.5(21.0–40.0)	38.00(33.14–40.00)

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