Int J Clin Exp Med 2016;9(10):20080-20084
www.ijcem.com /ISSN:1940-5901/IJCEM0016420

Original Article

The reference range of gestational thyroid function and the prevalence of thyroid dysfunction in Jinan district of China

Jun Lv[1*], Rui-Hua Han[1*], Ming-Yuan Liu[1], Jing-Feng Fu[1], Ming-Ying Duan[1], Yan Cai[2], Shan Yu[1]

Departments of [1]Obstetrics, [2]Antenatal Diagnosis, The Jinan Maternity and Child Care Centers, The No. 2 of Jianguo Xiaojing Three Road, Jinan 250001, China. [*]Equal contributors.

Received September 15, 2015; Accepted February 22, 2016; Epub October 15, 2016; Published October 30, 2016

Abstract: Objective: To explore the prevalence of thyroid dysfunction during pregnancy, we analyzed the indexes of gestational thyroid function in Jinan Maternity and Child Care Centers of China's Shandong province, and set up the reference range of pregnant thyroid function. Methods: 2669 cases of pregnant women were collect between January 2013 and December 2013 in obstetrics outpatient clinic of Jinan maternity and child care. The levels of serum thyroid-stimulating hormone (TSH), free thyroxine (FT4) and thyroid peroxidase antibody (TPOAb) of each pregnant women were detected by using chemiluminescence methods. The results were analyzed and compared with the normal reference range of international guidelines. Results: The median and reference range of TSH were 1.27 mIU/L (0.12-3.82) in early pregnancy, 1.33 mIU/L (0.17-4.14) in middle pregnancy, and 1.50 mIU/L (0.39-4.76) in late pregnancy, respectively. The FT4 median and reference range in early pregnancy, middle pregnancy and late pregnancy were 14.90 pmol/L (11.1-21.8), 14.01 pmol/L (8.87-19.65) and 14.21 pmol/L (8.92-18.83), respectively. The incidence of hypothyroidism, subclinical hypothyroidism, hyperthyroidism, low T4 concentration and positive TPOAb among 2669 cases of pregnant women without history of thyroid risk factors were 0.19%, 2.85%, 0.60%, 4.46% and 7.79%, respectively. Conclusions: Gestational thyroid function was presented in a varied condition, TSH was lowest in early pregnancy and gradually increased in later phase. The level of pregnancy serum TSH in Jinan district of Shandong was significantly increased than the reference range of international guidelines. The no high risk factors of normal pregnant women have still probably occurred thyroid dysfunction. Therefore, early screening for thyroid function was essential during pregnancy.

Keywords: Pregnancy, thyroid-stimulating hormone, reference range, thyroid function, incidence

Introduction

Thyroid disease is common endocrine disease of women in childbearing age, especially for changing of thyroid function during pregnancy [1]. Thyroid binding globulin (TBG) increases during pregnancy, which leads to increase total thyroxine (TT4) in serum. The hypothalamus-pituitary-thyroid axis of women is in a special kind of stress state during pregnancy. In the early stage of pregnancy, the thyroid-stimulating hormone (TSH) of human chorionic gonadotropin (HCG) can restrain the secretion of TSH [2]. In the middle stage of pregnancy, the basal metabolic rate of pregnant women is increased and the consumption of thyroid hormones is also added.

With increasing glomerular excretion rate and demand for iodine in fetal growth, the thyroid hormone synthesis is relatively insufficient during pregnancy. Pregnant women characterized by reduced serum free thyroid hormones in that stage, while negative feedback causes pituitary thyroid gland to secrete TSH increased until late pregnancy. The thyroid function indexes are different from the normal reference range during pregnancy, which were influenced by different region and detection kits [3, 4]. Only by establishing specific region or local hospital of pregnant thyroid function normal reference range, we can correctly evaluate gestational thyroid function variation and understand the effectiveness of screening thyroid function during pregnancy.

Table 1. The median and different percentile values of TSH and FT4 in 2461 cases of pregnant women

Groups	Cases	2.5th	5th	50th	95th	97.5th
TSH (mIU/L)						
T1	1755	0.12	0.22	1.27	3.07	3.82
T2	459	0.17	0.32	1.33	3.41	4.14
T3	247	0.39	0.48	1.50	3.87	4.76
FT4 (pmol/L)						
T1	1755	11.10	11.60	14.90	20.30	21.81
T2	459	8.87	10.02	14.01	18.50	19.65
T3	247	8.92	10.24	14.21	18.35	18.83

T1: 8-12 weeks of pregnancy; T2: 13-27 weeks of pregnancy; T3: 28 to 40 weeks of pregnancy.

Materials and methods

Patients

2669 cases of pregnant women were collected between January 2013 and December 2013. All pregnant women were examined for the first time in obstetrics outpatient clinic of Jinan maternity and child care, and the health care manual of each people was established. Including 1915 cases of early pregnancy (8-12 weeks of gestation), 495 cases of middle pregnancy (gestational age 13-27 weeks) and 259 cases of late pregnancy (28 to 40 weeks of gestation). The pregnant women average age, numbers of gravidity and urine iodine median were 27.91 ± 2.9 years, 1.78 ± 0.7 and 179.4 μg/L, respectively. The specific inclusion criteria: (1) single pregnancy; (2) no previous history of thyroid diseases and family history; (3) no history of medicine affect thyroid function; (4) no endemic goiter life history; (5) no previous history of abnormal gestation and birth; (6) no goiter at the palpation and ultrasound examination; (7) more than two years of Jinan local residence.

Methods

Physical check was performed for all pregnant women. 3 ml of venous blood was collected on an empty stomach and the serum was separated using suitable methods. The levels of serum TSH, free thyroxine (FT4) and thyroid peroxidase antibody (TPOAb) were detected by using chemiluminescence analysis. Morning urine iodine level was also tested by using arsenic-cerium catalytic spectrophotometry method at an empty stomach. All pregnant women were filled in questionnaires and fully informed and signed informed consent form permitting the collection and use of their samples in the study.

The diagnostic criteria: FT4 and TSH normal reference range between the 2.5th percentile and 97.5th percentile (the 2.5th and 97.5th percentile). If TSH < 2.5th percentile and FT4 > 97.5th percentile, the function of thyroid was diagnosed with clinical thyroid function increased (hyperthyroidism). If TSH > 97.5th percentile and FT4 < 2.5th percentile or TSH>10 mIU/L and no matter whether FT4 was decreased, the function of thyroid was diagnosed with clinical thyroid function decreased (hypothyroidism). If TSH > 97.5th percentile and FT4 at normal range, the function of thyroid was diagnosed with subclinical hypothyroidism. If TSH at normal range and FT4 < 5th percentile, the diagnosis of low T4 concentration. If TPOAb > 50 mUI, which was considered as positive state.

Statistical analysis

Statistical analysis was conducted by using SPSS 18.0 (SPSS, Inc., Chicago, IL, USA). $P < 0.05$ was considered to be significant.

Results

The median and normal reference range of gestational specific serum TSH

In 208 of 2669 cases of pregnant women blood TPOAb values exceed 50 mUI, the remaining 2461 cases of pregnant women blood TPOAb values were conform to normal reference range established in gestational thyroid function laboratory. Among them, 1755 cases of early pregnancy, 459 cases of middle pregnancy, 247 cases of late pregnancy. The median of TSH was the lowest in early pregnancy, which was increased in middle and late pregnancy. As 2.5th percentile to 97.5th percentile reference ranges for the normal values of TSH, the median and reference range of TSH in our study was 1.27 mIU/L (0.12-3.82) in early pregnancy, 1.33 mIU/L (0.17-4.14) in middle pregnancy and 1.50 mIU/L (0.39-4.76), in late pregnancy, respectively. The median and percentile values of TSH in gestational was showed in **Table 1**.

Table 2. The incidence of thyroid dysfunction and positive TPO Ab in 2669 cases of pregnant women

Gestational weeks	Cases	I (%)	II (%)	III (%)	IV (%)	V (%)
T1	1915	4 (0.21)	57 (2.98)	13 (0.68)	85 (4.44)	160 (8.36)
T2	495	1 (0.20)	12 (2.42)	3 (0.61)	24 (4.85)	36 (7.27)
T3	259	0 (0)	7 (2.70)	0 (0)	10 (3.86)	12 (4.63)
Total	2669	5 (0.19)	76 (2.85)	16 (0.60)	119 (4.46)	208 (7.79)

T1: 8-12 weeks of pregnancy; T2: 13-27 weeks of pregnancy; T3: 28 to 40 weeks of pregnancy. I: Hypothyroidism; II: Subclinical hypothyroidism; III: Hyperthyroidism; IV: Low T4 concentration; V: Positive TPO Ab.

The median and normal reference range of gestational specific serum FT4

The FT4 median and reference range in early pregnancy, middle pregnancy and late pregnancy were 14.90 pmol/L (11.1-21.8), 14.01 pmol/L (8.87-19.65) and 14.21 pmol/L (8.92-18.83) pmol/L, respectively. The median and percentile values of FT4 in gestational was also presented in **Table 1**.

The incidence of thyroid diseases

According to the specific reference range of gestational thyroid function in our hospital, the incidence of hypothyroidism, subclinical hypothyroidism, hyperthyroidism, low T4 concentration and positive TPOAb among 2669 cases of pregnant women without history of thyroid risk factors were 0.19%, 2.85%, 0.60%, 4.46% and 7.79%, respectively. Thyroid dysfunction and condition of TPOAb positive in early, middle, and late pregnancy are showed in **Table 2**.

Discussion

The American Thyroid Association (American Thyroid Association, ATA) in the 2011 latest guidelines pointed out that we should establish the specific laboratory reference ranges of normal early, middle and late pregnancy, to evaluate thyroid function during pregnancy [5]. If there is no specific reference ranges, the recommend TSH reference range in early, middle and late pregnancy is 0.1-2.5 mIU/L, 0.2-3.0 mIU/L, 0.3-3.0 mIU/L, respectively. Our research formulated specific reference range of thyroid function during pregnancy according to the National Academy of Clinical Biochemistry (NACB) standards for screening normal pregnant women [6]. The so-called "normal pregnant women" refers to the enough iodine intakes, no previous history of abnormal gestation and birth, no history of thyroid diseases, no history of adverse pregnant outcomes and TPOAb negative.

The study found that the upper normal limit of specific serum TSH of pregnancy in Jinan maternity and children's health care center was significantly increased than the recommend normal range from the ATA guidelines, which was consistent with the results from China's Shenyang and Iran's research, but lower as contrast to India's research [7-10].

The volume of obstetric delivery in Jinan maternity and child health care center accounting for one third of obstetric delivery in Jinan city. This research has common representative in Jinan district, which pregnant women come from eleven counties of Jinan and have a wide cases resource. Jinan is a mild iodine deficiency city. At present, the iodine nutrition in childbearing age women has reached or exceeded the moderate amount of iodine in Jinan, after reaching a common edible iodized salt from 1996 in China [11, 12]. In this study, the median urine iodine concentration in pregnant women was 179.4 μg/L, which was presented in the proper range.

The cause of pregnancy serum TSH normal reference value differences may be related to region, ethnic and different testing methods, in addition with iodine intake [13]. Research showed that the serum TSH was generally higher in our country (median: 2.4 mIU/L; TSH reference: 0.76-6.92 mIU/L), while the international median of TSH reported in literatures was largely below at 1.5 mIU/L [5, 14]. These hinted that the pregnancy serum reference value might be higher in our country. For the edible iodized salt country of Asian India and Iran, the TSH is closed to China or even higher, which suggested that consumption of iodized salt have effect on serum TSH.

According to the formulated normal reference range of our hospital, the prevalence of subclinical hypothyroidism in early pregnancy was 2.98%. While prevalence was increased to 11.13% after refer to international guidelines (TSH < 2.5 mU/L). Therefore, if hospital unable to set up their own laboratory diagnostic crite-

ria only by using international standards guides, the result would lead to excessive diagnosis of subclinical hypothyroidism. Therefore, it is important to establish country or region specific reference range of pregnant thyroid function.

Pregnancy has a great influence on thyroid function, whereas maternal thyroid dysfunction may cause adverse consequences for pregnancy and fetus. Pregnant women with hyperthyroidism increased adverse pregnancy outcomes, including, miscarriage, premature birth, stillborn foetus, stillbirth, gestational hypertension, hyperthyroidism heart disease, etc [15, 16]. Studies showed that the incidence of hyperthyroidism during pregnancy was 0.2%-2%. The incidence of pregnant hyperthyroidism was 0.6% in our research, which was consistent with previous studies.

Plenty of maternal thyroid hormone is very important to protect the mother and their offspring's health during pregnancy. Maternal clinical and subclinical hypothyroidism, low T4 levels and positive thyroid auto antibodies could bring adverse pregnancy outcomes to matrix, pregnancy process and fetal development [17, 18]. The fetal thyroid function has not yet been established during early pregnancy, the developing brain required thyroid hormone totally dependent on the mother, so this phase of maternal thyroid function is very important to the fetus [19].

Hollowell JG, etc [20]. Research showed that even slightly hypothyroidism (including subclinical Jiajian and low T4 levels) could also affect the development of the offspring's neural intelligence at the first half of pregnancy, resulted to bring down the scores of generations intelligence. By comparing TPOAb level with pregnancy outcomes, P Pradhan M, etc [21]. Found that pregnant women with TPOAb positive were positive correlative with threatened abortion, premature delivery, fetal abnormalities and intrauterine growth retardation. Poppe K, etc [22]. Compared 234 pregnant women for ART and found that the risk of miscarriage of TPOAb positive women is higher than TPOAb negative women in the first treatment.

This research showed that there was high prevalence of hypothyroidism with no thyroid risk factors of pregnant women. Among them, the prevalence of clinical hypothyroidism, subclinical hypothyroidism, low T4 and positive TPOAb was 0.19%, 2.85%, 4.46% and 7.79%, respectively. The incidence of positive TPOAb was lower compared to reported studies, perhaps because of this research focus on women at no high risks factors of thyroid [23, 24].

The Endocrine Society Clinical Practice Guidelines in 2007 recommended to screen TSH for pregnant women at high risk of thyroid diseases [25]. In view of the adverse pregnant outcomes and obvious benefits of thyroid diseases treatment during pregnancy, some experts suggested that screen thyroid diseases for all pregnant women [26, 27].

In conclusion, according to the results of this study, the prevalence of thyroid dysfunction was high in early pregnant women without history of thyroid diseases and family history. If we did not act routine screening, this part of pregnant women would be missed diagnosis. Therefore, this study supported early screening for thyroid function during pregnancy.

Disclosure of conflict of interest

None.

Address correspondence to: Shan Yu, Department of Obstetrics, The Jinan Maternity and Child Care Centers, The No. 2 of Jianguo Xiaojing Three Road, Jinan 250001, China. Tel: 086-0531-89029000; E-mail: 13012989395@163.com

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