Thyroid function reference ranges during pregnancy in a large Chinese population and comparison with current guidelines

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Abstract

Background: A correct thyroid function reference range is important for the accurate diagnosis of thyroid disease during pregnancy. However, there is no consensus on whether thyroid function reference ranges in Chinese population should follow the America Thyroid Association (ATA) guidelines. This study aimed to establish a thyroid function reference range more suited to the Chinese population by evaluating the current thyroid function reference range in pregnant Chinese women and comparing it to the ATA guidelines.

Methods: A total of 52,027 pregnant women were enrolled from January 2013 to December 2016. Thyroid stimulating hormone (TSH), free thyroxine (FT4), and thyroid peroxidase antibody (TPOAb) levels were tested during the first and third trimesters of pregnancy. Reference ranges of TSH and FT4 were established from the 2.5th and 97.5th percentiles of the TPOAb-negative population of women. The Mann-Whitney *U* test was used to compare thyroid hormones between the TPOAb-positive and TPOAb-negative groups.

Results: We obtained that the TSH reference ranges were 0.03 to 3.52 mU/L and 0.39 to 3.67 mU/L, and the FT4 reference ranges were 11.7 to 19.7 pmol/L and 9.1 to 14.4 pmol/L, in the first and third trimester, respectively. If we used the 2011 ATA criteria about 7.0% and 4.0% pregnant women would be over diagnosed in first and third trimester, respectively, compared with local population thyroid hormone reference. When we compared our local criteria with the new 2017 ATA criteria, about 1.2% and 0.8% pregnant women would have a missed diagnosis in first and third trimester, respectively.

Conclusions: Based on our data, which is in line with the current ATA guidelines, a population-based thyroid function reference range would be the first choice for diagnosis of thyroid disease during pregnancy in China. In case such population-based thyroid function reference ranges are unavailable in the east of China, our reference ranges can be adopted, if the same assay is used.

Trial Registration: www.chictr.org.cn (No. ChiCTR1800014394).

Keywords: Thyroid hormones; Reference values; Pregnant women; Guideline

Introduction

Adequate thyroid hormone is essential for an uncomplicated pregnancy and normal growth and development of the fetus. Studies have shown that abnormal thyroid function is associated with a wide range of adverse obstetric and child development outcomes, such as miscarriage, premature birth, and stunted fetal neurodevelopment.[1-4] In addition, an increasing number of studies indicate that milder forms of thyroid function disorder are also associated with these adverse outcomes.[5] Thus, establishing the optimal thyroid function reference range in pregnancy is very important. In particular, the lower and upper cut-off value of thyroid stimulating hormone (TSH) and free thyroxine (FT4) are commonly used as criteria to diagnose hypothyroidism, hyperthyroidism, subclinical hypothyroidism, and subclinical hyperthyroidism. Therefore, establishing the correct reference range of thyroid function can help clinicians better identify pregnant women with abnormal thyroid function, and further carry out clinical intervention as needed. Thyroid hormones are affected by gestational age, iodine intake, ethnicity, and test methods.[6-8] It has been widely accepted now to establish the trimester-specific, region-specific, and method-specific thyroid function references. However, these reference ranges are not always available, and we also found that upper limit for TSH was fixed based on available data. In 2011, the American Thyroid Association (ATA) recommended a TSH upper limit reference of 2.5 mU/L in first trimester and 3.0 mU/L in second and third trimesters. However, based on new data from the 2017 ATA, this upper limit was changed to

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4.0 mU/L in first, second and third trimesters. Which TSH upper limit is the most optimal choice for diagnosis of thyroid dysfunction in pregnancy remains controversial. In the last 10 years, various studies have shown that the upper TSH limit was higher in Chinese population than that in European or American ones during early pregnancy.[9-11] In this study, we try to explore whether the 4.0 mU/L cut-off level from the 2017 ATA guideline is a rational cut-off level for TSH in the first and third trimesters in Chinese population. To our knowledge, only few studies have explored thyroid function reference ranges during late trimester pregnancy in China. Moreover, the existing studies were based on limited sample sizes with <4000 patients.[8,9,12] There is a lack of studies that compare the different local criteria to the 2011 and 2017 ATA criteria within the local population, which is essential because it relates to the prevalence of overdiagnosis and missed diagnosis of thyroid dysfunction. That is why in this study we have used evidence from a convincingly large sample size to explore the normal reference ranges in both first and third trimesters of pregnancy in Chinese population.

Previous studies have shown that thyroid peroxidase antibody positive (TPOAb-positive) pregnant women have a higher TSH level and lower FT4 level in the first trimester.[13,14] While there is no study that details the exact physiologic changes that occur in pregnancy due to thyroid hormone changes in TPOAb-positive pregnant women, especially in the third trimester; it is crucial to figure out these physiologic changes to help clinicians guide the clinical treatment and ensure the safety of the mother and baby. It has been reported that Asian people have the highest prevalence of TPOAb positivity among all ethnic races.[7] For these reasons, we have also tried to investigate the physiologic changes with different TPOAb status and tried to establish the TPOAb-specific thyroid hormone reference intervals.

Methods

Ethical approval

This study was performed in accordance with principles of the *Declaration of Helsinki*. The study was approved by the Ethics Committee of the International Peace Maternity and Child Health Hospital (IPMCH), School of Medicine, Shanghai Jiaotong University (No. GKLW 2012-49). Written informed consent was obtained from all adult participants.

Population for analysis

The study group consisted of pregnant women who had their trimester prenatal care done at the IPMCH. According to ATA recommendations, the inclusion criteria for establishing the thyroid reference range in Chinese population are: single birth, Chinese women, no history of thyropathy or autoimmune disease, no goiters, no use of medicines affecting the thyroid hormone levels. The exclusion criteria are: twin pregnancies, women who became pregnant after *in vitro* fertilization, women who used thyroid interfering medication before pregnancy or during pregnancy, women who had pre-existing thyroid disease.

From January 2013 to December 2016, a total of 52,027 pregnant women were enrolled in the study. We collected the subjects' age, body mass index (BMI), and TSH and FT4 levels during the 9th to 13th weeks of pregnancy and 32nd to 36th weeks of pregnancy. Blood samples were collected from eligible pregnant women upon their visits to the antenatal clinic.

Fasting blood samples were drawn from the median cubital vein, and the serum was separated by centrifugation within 6 h. TSH, FT4, triiodothyronine (T3), thyroxine (T4), and TPOAb levels were measured with Abbott (ARCHITECT i2000; Abbott, Chicago, IL, USA) kits according to the manufacturer's protocol. The inter- and intra-assay variations of TSH were 3.59% and 1.60%, respectively. The inter- and intra-assay variations of FT4 were 4.01% and 1.90%, respectively. TPOAb above 5.6 U/mL is defined as positivity.

Statistical analyses

Reference ranges of TSH and FT4 were defined by the 2.5th and 97.5th percentiles of the entire population of women who presented to the hospital from January 2013 to December 2016. Data were presented as median and 95% range (2.5th–97.5th) for continuous variables with non-normal distribution, and as frequency and percentage for categorical variables. The distribution normality was checked through the shape of histograms and with Kolmogorov-Smirnov test. The Chi-squared test was used for categorical variables. The Mann-Whitney *U* test was used to compare thyroid hormones between TPO-positive and TPO-negative groups. All statistical analyses were performed using R statistical software v3.03 (Statistical Computing, Vienna, Austria) or Statistical Package of Social Sciences for Windows (SPSS 22.0; IBM Corp, Armonk, NY, USA). Statistical significance was defined when *P*-value was <0.05.

Results

Characteristics of study participants

After excluding ineligible participants, the final study population comprised of 46,262 women [Figure 1], descriptive characteristics of whom are shown in Table 1. In the study population, the median maternal age was 30.0 years old, the median BMI was 20.8 kg/m^2 and the median gestational age at delivery was 39.1 weeks. The median TSH concentration in the first and third trimester was 1.17 and 1.47 mU/L, respectively; the median FT4 concentration in the first and third trimester was 14.8 and 11.5 pmol/L, respectively; 10.0% of the study population was TPOAb positive.

The relationship between TSH and FT4

In the 46,262 pregnant women, we analyzed the relationship between TSH and FT4. FT4 was relatively constant with the median at 14.0 to 15.0 pmol/L, when TSH level was 0.5 to 4.0 mU/L. When serum TSH levels were above 4.0 mU/L, FT4 began to change greatly [Figure 2].

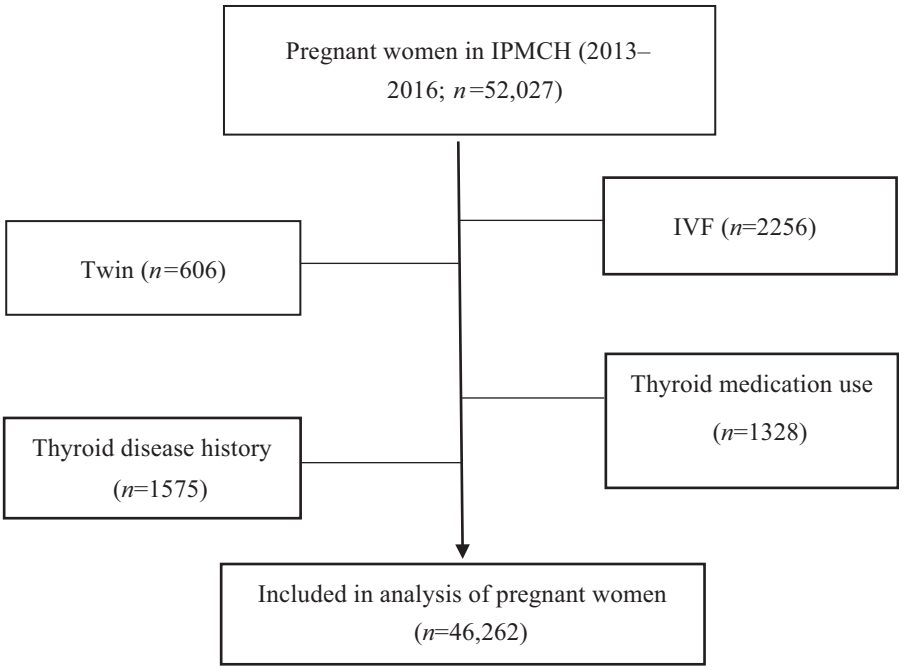

Figure 1: Flowchart exhibiting the selection of the study population. After excluding the twin pregnancy, IVF, thyroid disease, and thyroid medication usage, the final study population comprised 46,262 women. IPMCH: International Peace Maternity and Child Heath Hospital; IVF: *In vitro* fertilization.

Comparison of local thyroid reference to ATA guidelines

Figure 3 shows the distribution of TSH measurements within the reference range in the first and third trimesters. Comparing 2011 ATA TSH criteria of 2.5 mU/L with 2017 ATA criteria of 4.0 mU/L, about 8.2% and 4.8% pregnant women were overdiagnosed as subclinical hypothyroidism in first and third trimesters in the Chinese population, respectively [Figure 3A and 3B]. Comparing our region-specific reference with 2011 ATA criteria, about 7.0% and 4.0% pregnant women were overdiagnosed as subclinical hypothyroidism in first and third trimesters, respectively [Figure 3C and 3D]. While, comparing our region-specific reference with 2017 new ATA criteria, there are about 1.2% and 0.8% pregnant women with missed diagnosis in the first and third trimesters, respectively [Figure 3E and 3F].

The comparison of thyroid hormone in pregnant women with different TPOAb status

In the present study, we also investigated the association between maternal TSH, FT4, T4, T3 levels, and TPOAb status from early to late stage of pregnancy. As shown in Table 2, TSH level was significantly higher in pregnant women who were TPOAb positive than that in pregnant women who were TPOAb negative during the first trimester (1.53 *vs.* 1.14 mU/L, $Z=-25.63$, $P<0.001$); on the contrary, there was no significant difference of TSH level between TPOAb positive and negative pregnant women in the third trimester. FT4 level was significantly lower in pregnant women who were TPOAb positive than that in pregnant women who were TPOAb negative during the first trimester (14.7 pmol/L *vs.* 14.8 pmol/L, $Z=-5.43$, $P<0.001$), while FT4 level was significantly higher in pregnant women who were TPOAb positive than that in pregnant women who were TPOAb negative during the third trimester (11.7 *vs.* 11.5 pmol/L, $Z=-8.46$, $P<0.001$). There was no significant difference in T3 level between TPOAb positive or negative pregnant women, either during the first or third trimester. T4 levels in the third trimester significantly differed between TPOAb positive and negative pregnant women (111.1 *vs.* 108.0 nmol/L, $Z=-4.90$, $P<0.001$), while there was no significant difference in T4 levels during the first trimester between TPOAb positive and negative pregnant women [Table 2].

Discussion

Based on the ATA criteria, 41,634 pregnant women in IPMCH were included to establish the normal reference range of thyroid hormone during pregnancy for Chinese women. Comparing the upper cut-off value of TSH between ATA 2017 criteria and 2011 criteria, 8.2% and 4.8% of pregnant women could be reclassified as normal thyroid function group during first and third trimester in China, respectively. In the present study, the upper limit reference of TSH during the first trimester is 3.52 mU/L, if using the 2011 ATA criteria of 2.5 mU/L as the upper limit reference of TSH, about 7.0% of pregnant women would be overdiagnosed as subclinical hypothyroidism during the first trimester. While using the upper limit reference of TSH from the new ATA 2017 criteria which was 4 mU/L, about 1.2% of pregnant women would be misdiagnosed during the first trimester. It seems that the new ATA 2017 recommended TSH upper limit value of 4 mU/L is closer to the one found in the present study of 3.52 mU/L, in comparison to the previous ATA 2011 recommended TSH

Table 1: Descriptive characteristics of the study population.

Parameters	Value
Age (years)	30.0 (24.0–38.0)
BMI (kg/m^2)	20.8 (17.1–26.9)
Gestational age at delivery (weeks)	39.1 (35.6–41.1)
Nullipara	37,564 (81.2)
Educational levels	
No education or primary education	11,057 (23.9)
Bachelor	26,793 (57.9)
Master	7744 (16.7)
Doctor	668 (14.5)
Diabetes	
Pregnancy induced	4248 (9.2)
Preexistent	58 (0.12)
Hypertension	
Pregnancy induced	1316 (2.8)
Preexistent	1000 (2.2)
Maternal thyroid function	
TSH (mU/L)	
First trimester	1.17 (0.03–3.64)
Third trimester	1.47 (0.38–3.67)
FT4 (pmol/L)	
First trimester	14.8 (11.7–19.7)
Third trimester	11.5 (9.1–14.4)
T3 (nmol/L)	
First trimester	2.2 (1.6–3.1)
Third trimester	2.0 (1.4–2.8)
T4 (nmol/L)	
First trimester	122.0 (82.8–177.0)
Third trimester	108.0 (73.1–150.0)
TPOAb positivity	4628 (10.0)

After excluding the twin pregnancy, *in vitro* fertilization, thyroid disease, and thyroid medication usage, the final study population comprised 46,262 women. Values are presented by median (P2.5, P97.5), or *n* (%). BMI: Body mass index; FT4: Free thyroxine; T3: Triiodothyronine; T4: Thyroxine; TPOAb: Thyroid peroxidase antibody; TSH: Thyroid stimulating hormone.

upper limit value of 2.5 mU/L, and 1.2% is much <7.0%. There were about 200,000 newborns in Shanghai last year. If we use the 2017 ATA criteria, there would be about 2400 pregnant women with missed diagnosis, which is a large number of people. In our population study, the upper cut-off level of TSH in third trimester is 3.67 mU/L. If using the 2011 ATA criteria of 3.0 mU/L, about 4.0% pregnant women would be overdiagnosed in the third trimester. If using the ATA 2017 criteria of 4.0 mU/L, about 0.8% pregnant women would have a missed diagnosis in third trimester. Since neither overdiagnosis nor missed diagnosis is acceptable, we propose that the local-specific reference is the best choice. If such reference is unavailable, then reference ranges from similar population using similar TSH assays will be the second best choice.

The upper limit for TSH in the present study was 3.52 mU/L during the first trimester, which is similar to the ones reported in Europe and the United States.[15-18] The values reported there are actually lower than the values reported in India 5.78 mU/L,[19] higher than the values reported in Australia 2.15 mU/L and Spain 2.65 mU/L.[20,21] In other Chinese studies, the upper-limit reference of TSH in the first trimester varies from 3.31 to 4.51 mU/L.[6,8-10,22,23] The different assays might be the main cause for the various results among different studies. In this study, TSH upper cut-off value is 3.52 mU/L, which is slightly lower than 3.78 mU/L, the value reported in another Chinese study using the same assay method with 1514 participants.[22] The difference may also mainly be due to the limited sample size. At present, only few studies focus on the thyroid hormone in late stages of pregnancy.[22,23] It is important to note that even though the fetuses can synthesize the thyroid hormone after 16 to 18 weeks independently, they still need the maternal thyroid hormone supplement.[24] The maternal thyroid hormone level is still crucial for fetal development. However, the thyroid hormone reference ranges in Chinese population are not well established, especially in late

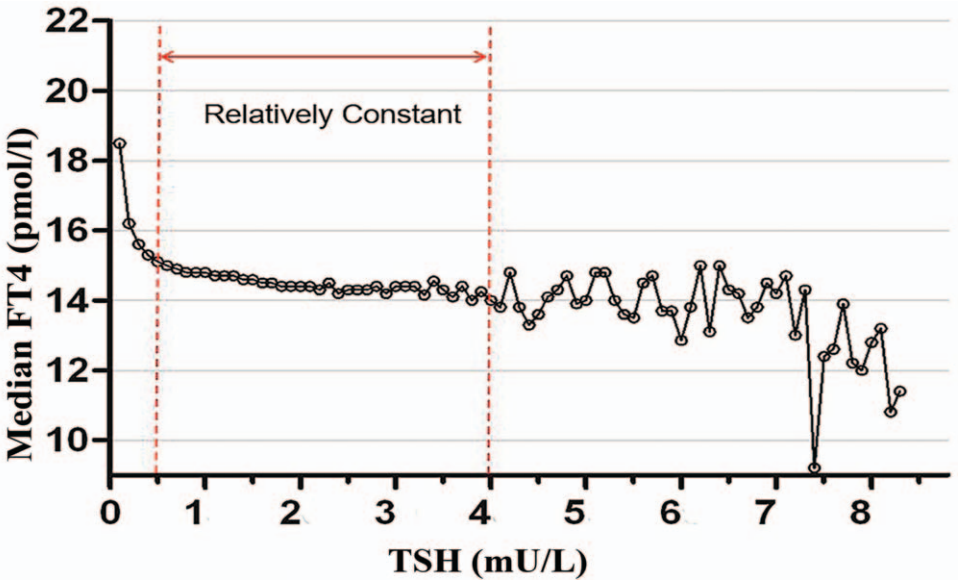

Figure 2: Relationship between TSH and FT4. When TSH levels were 0.5 to 4.0 mU/L, FT4 was relatively constant and the median was 14 to 15 pmol/L. When serum TSH levels were above 4.0 mU/L, FT4 began to change significantly. FT4: Free thyroxine; TSH: Thyroid stimulating hormone.

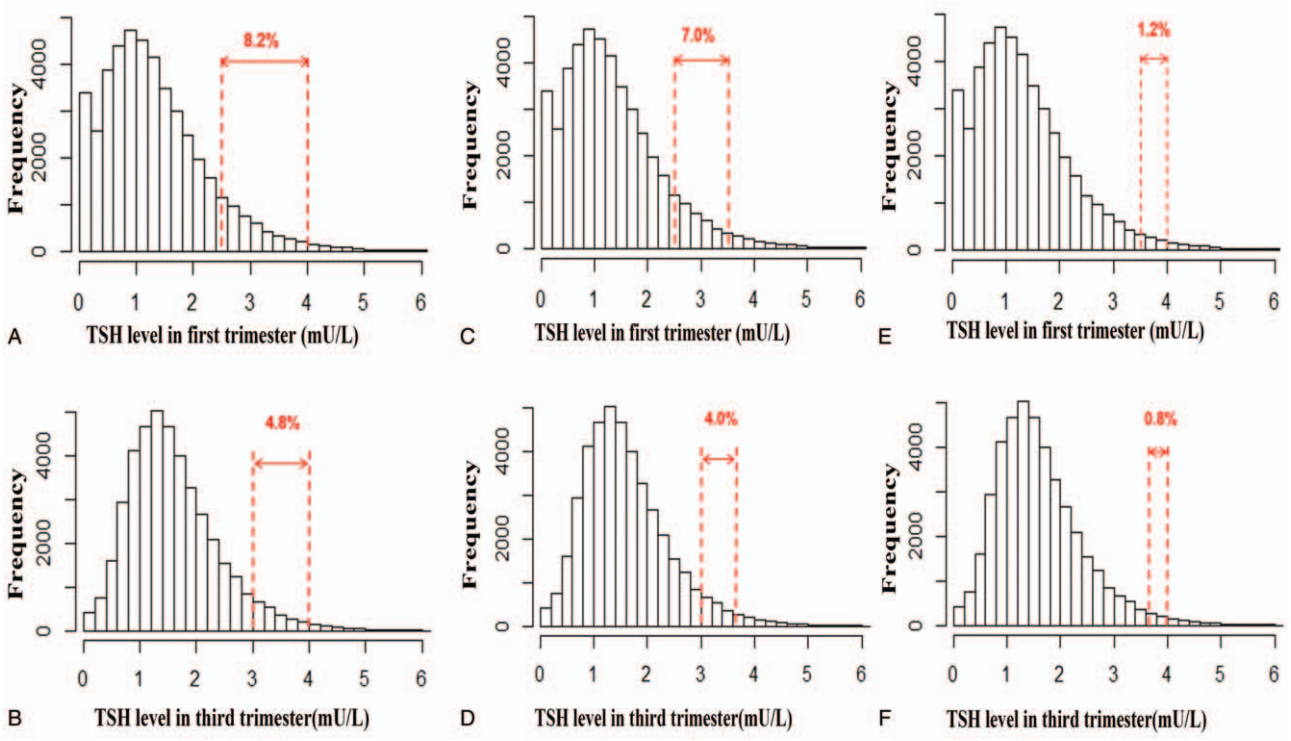

Figure 3: Distribution of normal range serum TSH levels in the first and third trimesters. Comparing 2017 ATA criteria with 2011 ATA criteria in first and third trimesters based on the Chinese population, respectively (A and B). Comparing our region-specific reference with 2011 ATA criteria in first and third trimesters, respectively (C and D). Comparing our region-specific reference with 2017 new ATA criteria in first and third trimesters, respectively (E and F). ATA: American Thyroid Association; TSH: Thyroid stimulating hormone.

pregnancy. To the best of our knowledge, this is the first study done in China which establishes the TSH reference range in both the first and third trimesters with a big sample size.

We also analyzed the relationship between TSH and FT4. We found that FT4 was relatively constant with the median at 14.0 to 15.0 pmol/L, when TSH level was 0.5 to 4.0 mU/L. The similar phenomenon was found in Li's study, which indicated that when the TSH levels were 0.8 to 4.8 mU/L, FT4 was relatively constant and the FT4 median was 15.0 to 16.0 pmol/L.[10] In addition, when serum TSH levels were above 4.8 mU/L, FT4 began to decline significantly studied by Li *et al*.[10] In this study, we also found a change in FT4 level when TSH was above 4.0 mU/L. However, we did not identify a significant downward shift. This may be due to the difference in population sizes. In addition, it is known that thyroid function is also affected by living habits, diet and geographical location. In our population, people were mainly from east part of China, while in Li's study, the population was mainly from the North-East of China.

Table 2: Maternal TSH, FT4, T4, and T3 levels from early to later pregnancy in TPOAb positive and negative group.

parameters	TPOAb (+) group (n=4628)	TPOAb (−) group (n=41634)	Statistics*	P
TSH (mU/L)				
First trimester	1.53 (0.05, 4.57)	1.14 (0.03, 3.52)	−25.63	<0.001
Third trimester	1.48 (0.31, 3.63)	1.47 (0.39, 3.67)	−0.06	0.949
FT4 (pmol/L)				
First trimester	14.7 (11.5, 19.3)	14.8 (11.7, 19.7)	−5.43	<0.001
Third trimester	11.7 (9.2, 14.8)	11.5 (9.1, 14.4)	−8.46	<0.001
T3 (nmol/L)				
First trimester	2.2 (1.6, 3.1)	2.2 (1.6, 3.1)	−0.28	0.782
Third trimester	2.0 (1.4, 2.7)	2.0 (1.4, 2.8)	−1.60	0.110
T4 (nmol/L)				
First trimester	121.5 (82.1, 174.7)	122.0 (82.8, 177.0)	−0.08	0.935
Third trimester	111.1 (76.3, 157.4)	108.0 (72.7, 149.0)	−4.90	<0.001

Values are presented by median (P2.5, P97.5). *Mann-Whitney U test. FT4: Free thyroxine; T3: Triiodothyronine; T4: Thyroxine; TPOAb: Thyroid peroxidase antibody; TSH: Thyroid stimulating hormone.

The TPOAb status can reflect thyroid autoimmunity. TPOAb positivity relates to many adverse outcomes, such as miscarriage, premature delivery and low birth weight.[8,24-29] Thus, we have further explored the thyroid hormone changes in relation to the different TPOAb statuses. In this study, the prevalence of TPOAb positivity was 10%, a little bit lower than the 12.4% reported in an American study.[7] We separated pregnant women into 2 groups according to TPOAb status, and found that pregnant women with TPOAb positivity had a lower FT4 level in the first trimester but a higher level in the third trimester. Although the mean FT4 levels approached a very similar value between the 2 groups, the distribution of FT4 varied largely between TPOAb positive and negative women. The impaired thyroid response to human chorionic gonadotropin (hCG) in TPOAb-positive pregnant women may contribute to this phenomenon. In the first trimester, the FT4 level increases due to elevated levels of serum hCG directly stimulating the TSH receptor. In late pregnancy, FT4 level had a downtrend in normal pregnant women due to absence of the stimulation of hCG.[30] However, in pregnant women with TPOAb positivity, the thyroid function was impaired in its reaction to the stimulation of hCG. Thus, in these women, the increase of FT4 was not obvious in early pregnancy; meanwhile the decrease of FT4 in third trimester was also not obvious. Interestingly, we found that TPOAb-positive pregnant women had a higher TSH level in the first trimester, while this was not the case in the third trimester. The underlying mechanism may be explained by the impairment of thyroid function in pregnant women with TPOAb positivity. In TPOAb positive women, there is an impaired thyroidal response to hCG stimulation. Given that this results in a lack of increase in FT4, there also will be no decline in TSH, which normally occurs through the negative feedback system. This finding is in accordance with a study from the Netherlands that also found that TPOAb positivity was associated with higher maternal TSH levels and lower FT4 levels in the first trimester.[14,31] However, due to a lack of data in late stage pregnancy, they could not show that the physiology of thyroid hormone changes persisted into the later stages of pregnancy. This is a rare study that reveals the different thyroid hormone changes between the TPOAb-positive pregnant women and TPOAb-negative pregnant women throughout the whole pregnancy. Our findings might suggest that TPOAb-positive pregnant women require a different treatment approach than TPOAb negative women. In line with the new ATA 2017 guidelines, we recommend that in TPOAb negative women a TSH upper cut-off value of 4.0 mU/L can be used, if not hospital-specific reference ranges are available. Similarly, for TPOAb positive women, based on the same argumentations, we would recommend a TSH upper cut-off value of 2.5 mU/L.

The present study had some limitations. Firstly, we did not test thyroid function before pregnancy, so we could not compare thyroid function before and during pregnancy. Secondly, iodine insufficiency was not excluded from participants. In addition, the median urine iodine in pregnant women was 127 μg/L, which was classified as mild iodine deficiency. Thirdly, we lacked the data of thyroid hormone in the second trimester, as we could not measure thyroid hormone in the middle of the pregnancy. Fourthly, we lacked of the data of hCG to assess the association between TSH and FT4 during pregnancy.

In conclusion, we have established the trimester-specific and population-specific normal thyroid hormones reference ranges based on a large Chinese population. We recommend that population-based thyroid hormone reference range is the first choice for diagnosis. If it is unavailable, we suggest using the 2017 ATA criteria. In TPOAb negative women, we recommend the ATA 2017 TSH upper cut-off value to be 4.0 mU/L; however, in TPOAb positive women, we recommend the TSH cut-off value for treatment should be lower.

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Conflicts of interest

None.

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