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Gestational Age-specific Cut-off Values Are Needed for Diagnosis of Subclinical Hypothyroidism in Early Pregnancy

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During the first trimester of pregnancy, thyroid-stimulating hormone (TSH) > 2.5 mIU/L has been suggested as the universal criterion for subclinical hypothyroidism. However, TSH levels change continuously during pregnancy, even in the first trimester. Therefore the use of a fixed cut-off value for TSH may result in a different diagnosis rate of subclinical hypothyroidism according to gestational age. The objective of this study was to obtain the normal reference range of TSH during the first trimester in Korean gravida and to determine the diagnosis rate of subclinical hypothyroidism using the fixed cut-off value (TSH > 2.5 mIU/L). The study population consisted of pregnant women who were measured for TSH during the first trimester of pregnancy (n = 492) and nonpregnant women (n = 984). Median concentration of TSH in pregnant women was lower than in non-pregnant women. There was a continuous decrease of median TSH concentration during the first trimester of pregnancy (median TSH concentration: 1.82 mIU/L for 3+0 to 6+6 weeks; 1.53 mIU/L for 7+0 to 7+6 weeks; and 1.05 mIU/L for 8+0 to 13+6 weeks). Using the fixed cut-off value of TSH > 2.5 mIU/L, the diagnosis rate of subclinical hypothyroidism decreased significantly according to the gestational age (GA) at TSH (25% in 3+0 to 6+6 weeks, 13% in 7+0 to 7+6 weeks, and 9% for 8+0 to 13+6 weeks, $P < 0.001$), whereas the diagnosis rate was 5% in all GA with the use of a GA-specific cut-off value ($P = 0.995$). Therefore, GA-specific criteria might be more appropriate for the diagnosis of subclinical hypothyroidism.

Keywords: Hypothyroidism; Pregnancy Trimester, First; Thyrotropin; Reference Values

INTRODUCTION

Subclinical hypothyroidism is an abnormally high thyroid-stimulating hormone (TSH) level with normal free thyroxine level without symptoms of hypothyroidism (1). Subclinical hypothyroidism during pregnancy has been reported to be associated with adverse pregnancy outcomes and impaired fetal neurodevelopment, such as gestational diabetes, preeclampsia, preterm labor, placental abruption (2-4), increased cesarean section rates for fetal distress (5), spontaneous abortion (6), and low intelligence quotient (IQ) score of the offspring (7). In addition, Negro et al. (4) showed that the supplementation of thyroid hormone in pregnant women with subclinical hypothyroidism improved pregnancy outcomes. Following these results, Thung et al. (8), The Spanish Society of Endocrinology and Nutrition (9), and Dosiou et al. (10) recommended maternal serum screening of thyroid-stimulating hormone in early pregnancy. In addition, the Endocrine Society recommended replacement of levothyroxine in pregnant women with subclinical hypothyroidism (11).

Because of dynamic changes of human chorionic gonadotropin (hCG) and thyroxine-binding globulin, which affects hypothalamic-pituitary-thyroid axis, the concentrations of TSH and free thyroxine (fT4) change during pregnancy (12-17). Based on these reports, the American Thyroid Association (ATA) guideline recommended the trimester-specific criteria of TSH concentration for the diagnosis of subclinical hypothyroidism (the reference ranges: first trimester, 0.1-2.5 mIU/L; second trimester, 0.2-3.0 mIU/L; third trimester, 0.3-3.0 mIU/L) (10, 18).

However, the concentration of TSH also changes even in the first trimester of pregnancy due to abrupt changes in hCG and thyroxine-binding globulin concentrations during this period. The recent report of Li et al. (19) showed that the median TSH concentration at 4 to 6 weeks was higher than that observed at 7 to 12 weeks of gestation. Considering the physiological decrease of TSH concentrations during the first trimester of pregnancy, it may be postulated that the use of a fixed cut-off value for TSH in the first trimester (> 2.5 mIU/L) may result in different diagnosis rates of subclinical hypothyroidism across gestational ages.

To address this issue, we obtained the normal reference range of TSH during the first trimester in pregnant Korean women and determined the diagnosis rate of subclinical hypothyroidism using the fixed cut-off value (TSH > 2.5 mIU/L).

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MATERIALS AND METHODS

Study design

In this cross-sectional study, singleton pregnant women who were tested for serum TSH during the first trimester of pregnancy and delivered at Seoul Metropolitan Government Seoul National University Boramae Medical Center between July 2008 and December 2013 were enrolled. Additionally, healthy non-pregnant women who were tested for TSH as part of a routine checkup in Boramae healthcare center were age-matched (one pregnant woman: two non-pregnant women) and enrolled. Women with known thyroid disease were excluded. Pregnant women with multiple pregnancies, miscarriage, stillborn, or those with underlying medical diseases, such as pregestational diabetes or chronic hypertension, were also excluded.

The median TSH values in each gestational age were obtained in pregnant women and were compared to that of non-pregnant women. Gestational age (GA)-specific 5th to 95th percentile values were obtained from the study population. The prevalence of subclinical hypothyroidism in each GA at measurement using the fixed cut-off value (TSH > 2.5 mIU/L) and using the GA-specific cut-off value of TSH (defined as > GA-specific 95th percentile value) were obtained. It is a routine practice to confirm gestational age (GA) by ultrasound during the first trimester of pregnancy in our institution.

Measurement of TSH

Serum TSH was measured by Centaur XP (Siemens, Erlangen, Germany). Functional sensitivity of TSH was 0.008 mIU/L, and the laboratory reference range for adult is 0.55-4.78 mIU/L for our laboratory.

Statistical analysis

Statistical analysis was performed by SPSS software (version 20.0, Chicago, IL, USA), using the Mann-Whitney U-test, Fisher's exact test, or chi-square test for trends, as indicated. The result was considered statistically significant when the *P* value was less than 0.05. Percentiles were calculated from the empirical distribution of the observed data. Plot of TSH against GA was delineated with a nonparametric regression such as locally weighted scatterplot smoothing (LOWESS).

Ethics statement

This retrospective study was approved by the institutional review board of Seoul Metropolitan Government Seoul National University Boramae Medical Center (IRB No. 16-2012-11). The board waived submission of informed consent.

RESULTS

During the study period, a total of 492 pregnant women met the inclusion criteria and 984 non-pregnant age-matched women were also enrolled. Median age was 33 yr in both groups (*P* = 0.163).

Fig. 1 shows the median and the 5th and 95th percentile of TSH in pregnant women of each gestational age. Table 1 compares the median TSH values of each gestational age in pregnant women and non-pregnant women. The median TSH con-

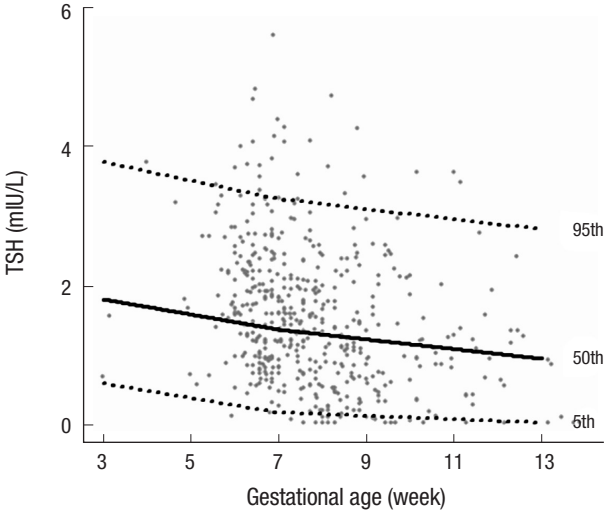

Fig. 1. 5th, 50th, and 95th percentile of thyroid-stimulating hormone of pregnant women in each gestational age.

Table 1. Median concentrations of TSH of non-pregnant women and pregnant women in each gestational age

Gestational age (week)	No	TSH concentrations (mIU/L) median (range)	*P* value*	*P* value†
Non-pregnant women	984	2.32 (0.05-8.52)		
Pregnant women (GA, weeks)	Total 492	Total 1.45 (0.05-7.90)		< 0.001
3+0 - 5+6	28	1.85 (0.15-3.77)	0.067	0.067
6+0 - 6+6	149	1.81 (0.19-7.80)	0.456	< 0.001
7+0 - 7+6	134	1.53 (0.05-4.28)	0.008	< 0.001
8+0 - 8+6	85	1.12 (0.05-7.90)	0.010	< 0.001
9+0 - 9+6	43	0.97 (0.05-2.97)	0.582	< 0.001
10+0 - 13+6	53	0.96 (0.05-3.64)	0.601	< 0.001

**P* value, median level of TSH comparing with the upper group; †*P* value, median level of TSH comparing with the non-pregnant group. GA, gestational age; TSH, Thyroid-stimulating hormone.

Table 2. 5 to 95 percentile values of TSH of non-pregnant and each gestational age pregnant women

GA	No	TSH (mIU/L)							*P* value*	*P* value†
		5th	10th	25th	50th	75th	90th	95th		
Non-pregnant	984	0.94	1.17	1.63	2.32	3.15	4.30	5.24		
Pregnant women (GA, weeks)										
3+0 - 6+6	177	0.61	0.74	1.04	1.82	2.52	3.27	3.78	< 0.001	< 0.001
7+0 - 7+6	134	0.23	0.48	0.92	1.53	1.97	2.69	3.20	0.003	< 0.001
8+0 - 13+6	181	0.05	0.13	0.50	1.05	1.71	2.46	2.97	< 0.001	< 0.001

*P value, median level of TSH comparing with the upper group; †P value, median level of TSH comparing with the non-pregnant group. GA, gestational age; TSH, Thyroid-stimulating hormone.

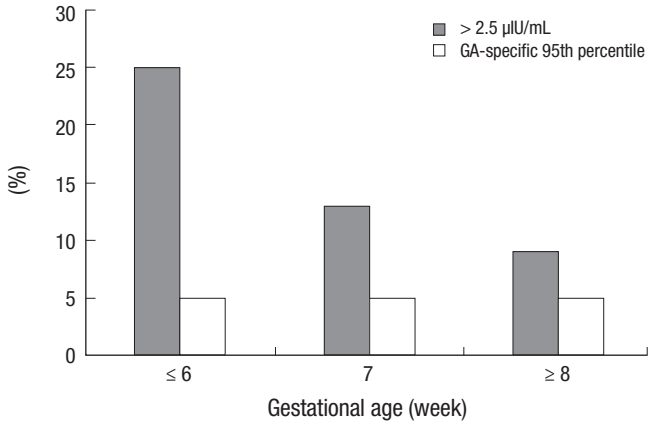

Fig. 2. The prevalence of subclinical hypothyroidism in each gestational age at measurement according to the fixed cut-off value or gestational age specific cut-off value of thyroid-stimulating hormone: The prevalence of subclinical hypothyroidism significantly decreases along with increasing gestational age when using the fixed cut-off value of TSH > 2.5 mIU/L ($P < 0.001$, chi-square test for trend). However, the prevalence of subclinical hypothyroidism was 5% in all gestational age with the use of GA-specific cut-off value ($P = 0.995$, chi-square test for trend).

centrations of pregnant women were lower than that of non-pregnant women with marginal significance in 3+0 to 5+6 weeks of gestation and with statistical significance in 6+0 to 6+6, 7+0 to 7+6, 8+0 to 8+6, 9+0 to 9+6, 10+0 to 13+6 weeks of gestation. Compared with the median TSH value of that of the earlier gestational age group, the median TSH value decreased significantly from the 6th to 7th week ($P = 0.008$) and from the 7th to 8th week ($P = 0.010$) of gestation (median TSH concentration: 1.81 mIU/L for 6+0 to 6+6 weeks; 1.53 mIU/L for 7+0 to 7+6 weeks; and 1.12 mIU/L for 8+0 to 8+6 weeks). According to this significant decrease in TSH concentration, we re-classified gestational age into 3 categories: 3+0 to 6+6 weeks, 7+0 to 7+6 weeks, 8+0 to 13+6 weeks of gestation (177 gravida in 3+0 to 6+6 weeks, 134 gravida in 7+0 to 7+6 weeks, and 181 gravida in 8+0 to 13+6 weeks of gestation). The 5th to 95th percentile values of TSH in each of these groups are summarized in Table 2 (5th to 95th percentile values: 0.61-3.78 mIU/L for 3+0 to 6+6 weeks; 0.23-3.20 mIU/L for 7+0 to 7+6 weeks; 0.05-2.97 mIU/L for 8+0 to 13+6 weeks).

Using the fixed cut-off value of TSH > 2.5 mIU/L, the diagnosis rate of subclinical hypothyroidism significantly decreased with increasing gestational age (25% [45/177] in 3+0 to 6+6 weeks, 13% [18/134] in 7+0 to 7+6 weeks, and 9% [17/181] for 8+0 to 13+6 weeks, $P < 0.001$, chi-square test for trend, Fig. 2). However, the diagnosis rate of subclinical hypothyroidism was 5% in all gestational age with the use of GA-specific cut-off value (5% [9/177] in 3+0 to 6+6 weeks, 5% [7/134] in 7+0 to 7+6 weeks, and 5% [9/181] for 8+0 to 13+6 weeks of gestation, $P = 0.995$, chi-square test for trend).

DISCUSSION

The principal findings of the current study were the following: 1) median concentration of TSH in pregnant women was lower than that in age-matched non-pregnant women; 2) there was a continuous decrease of median TSH concentrations during the first trimester of pregnancy; 3) using the fixed cut-off value of TSH > 2.5 mIU/L, the diagnosis rate of subclinical hypothyroidism decreased significantly according to the gestational age at TSH measurement. However the diagnosis rate was 5% in all gestational age with the use of GA-specific cut-off value.

Pregnancy brings many physiological changes that affect the thyroid environment, including increased plasma volume and increased renal clearance (20). The cross-reactivity of hCG to the TSH receptor and the increase of thyroid hormone carrier (thyroxine-binding globulin) also affect the levels of TSH and free T4 in normal pregnancy. Considering the dynamic change of hCG concentrations and physiological events affecting thyroid hormone during the course of entire pregnancy, it is not surprising that the normal range of thyroid hormones changes during pregnancy. Moreover, the most dynamic decrease of TSH concentrations is observed during the first trimester (18). Our study also showed the normal reference value of TSH concentrations changes even within the first trimester of pregnancy, with especially abrupt changes observed during the gestational ages of 7 to 9 weeks. This may have potential clinical implication because the current guideline from ATA provides only trimester-specific references for TSH, and there may be a rationale for subdividing the first trimester when providing reference ranges for TSH. Indeed, the diagnosis rate of subclinical hypothyroidism changed according the gestational ages at TSH measurement when using fixed cut-off value (TSH > 2.5 mIU/L), despite the consistent prevalence of subclinical hypothyroid-

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ism with the use of GA-specific 95th percentile TSH value in the current study. This issue is clinically important, and which cut-off is more useful to improve the pregnancy and fetal outcome warrants further study.

We obtained normal reference values of TSH concentrations of each gestational age in the first trimester of pregnant Korean women. To our knowledge, this is the first study which reported the normal reference values of TSH concentrations of each gestational age in Korea. The cut-off value from ATA guideline is derived from populations with optimal iodine intake (18). Iodine status can affect TSH concentrations, and the Korean diet is known to be rich in iodine because of seaweed and salt-water fish (21-23). In addition, it is well known that there is a slight but significant difference in TSH concentration among ethnic groups (18), and Asians along with black women were observed to have approximately 0.4 mIU/L lower TSH values in comparison with white women (24, 25). By using fixed cut-off value (TSH > 2.5 mIU/L) of ATA guidelines, the prevalence of subclinical hypothyroidism in the current study was 9% to 25%, much higher than previously reported (26).

In addition we compared the reference values in pregnant women to those in non-pregnant women after controlling for maternal age. In the study Li et al. (19), the reference range of pregnant women at 4-6 weeks of gestation was comparable to that of non-pregnant women and suggested that non-pregnant TSH value may be used as the reference value in early pregnancy (less than 6 weeks of gestation). However, in the current study the median concentration of TSH in 3+0 – 5+6 weeks was lower with marginal significance (P = 0.067) and the median concentration of TSH in 6+0 – 6+6 weeks was significantly lower (P < 0.001) than that in non-pregnant women (Table 1). This different result between the study of Li et al. (19) and the current study might result from the accuracy of our data which compared the median TSH between pregnant and age-matched non-pregnant women as the thyroid hormone is known to be affected by age (27).

The optimal timing for TSH screening and intervention for subclinical hypothyroidism is not well established. The recommended normal reference range of TSH concentrations by ATA guidelines was derived from the cohorts at 9 to 12 weeks of gestation (18). It is well known that the fetus depends on maternal thyroid hormone through the first trimester, and appropriate hormone concentrations are needed for fetal development (28). Establishing the reference value of TSH in earlier gestational age may be needed because many experts agree on the effect of early screening and treatment (4), and previous studies have reported improved pregnancy outcomes with thyroid hormone replacement before 12 weeks of pregnancy, until which time the fetus is entirely dependent on maternal thyroid hormones (29).

Subclinical hypothyroidism has been reported to be associated with adverse outcomes, and the supplementation of levothyroxine in women with subclinical hypothyroidism improved pregnancy outcomes (4). However, the data on the benefit of TSH universal screening and the fetal benefit of levothyroxine supplementation are not sufficient, and there is controversy on universal screening and treatment strategy in pregnancy (18, 30). Further studies are needed for these issues, and the cut-off value for the diagnosis and treatment of subclinical hypothyroidism may require re-evaluation because most previous studies adopted fixed cut-off values [TSH > 2.5 mIU/L in the study of Negro et al. (4), and TSH > 4.5 mIU/L in the Study of Dhanwal et al. (31)].

In conclusion, the diagnosis rate of subclinical hypothyroidism decreases significantly with gestational age at TSH measurement when fixed cut-off values of TSH are adopted. These data suggest that further studies are warranted to determine the optimal cut-off values of TSH for the diagnosis of subclinical hypothyroidism, especially in terms of pregnancy and fetal outcomes.

DISCLOSURE

The authors have no conflicts of interest to disclose.

AUTHOR CONTRIBUTION

Conception and coordination of the study: Lee SM, Kim HS, Kim BJ. Acquisition of data: Kim BJ, Hwang KR, Jeon HW, Lee SM. Data review: Kim HS, Lee DY. Statistical analysis: Kim HS, Oh S, Lee SM. Manuscript preparation: Kim HS, Lee SM. Manuscript approval: all authors.

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