Research Article

Establishment of Reference Interval for TSH in Pregnant Georgian Women

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Abstract

Introduction: Maternal thyroid dysfunction has been associated with variety of adverse maternal and fetal outcomes. Due to many physiological changes during pregnancy, interpretation of thyroid function tests needs trimester-specific reference intervals for a specific population. Aim of this study was to determine the second trimester-specific reference interval for thyroid-stimulating hormone (TSH) in healthy pregnant Georgian women. **Methods:** 2876 pregnant women were admitted to Batumi Maternity House (BMH) from January 2009 to December 2011 for second trimester routine prenatal examination, including TSH screening. Standardized information regarding thyroidal, obstetric and general medical status of women was collected. The reference interval for TSH, based on 2.5th and 97.5th percentiles, was calculated from thyroid dysfunction risk free pregnant women. **Results:** Derived reference interval for TSH in the second trimester of pregnancy was 0.21–4.1 mIU/L and it was significantly different from the reference intervals recommended by American Thyroid Association (ATA) and the reference interval provided by manufacturer for non-pregnant adults. **Conclusion:** We calculated clinically relevant trimester-specific reference interval for TSH in order to facilitate detection and improve management of thyroid dysfunction in Georgian pregnant women.

Keywords: Pregnancy, Reference interval, Second trimester, TSH

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Introduction

Over the last twenty years a major expansion of our knowledge regarding the role of thyroid function during pregnancy has taken place. Thyroid hormones are crucial in fetal development [1]. Maternal thyroid disorders, particularly hypothyroidism, can lead to obstetric complications and cause adverse effects on cognitive and neurological development of the fetus [2, 3, 4]. Appropriate detection of thyroid dysfunction and prompt interventions improve maternal-fetal prognosis [5]. Hormonal changes and increased metabolic demand occurring during pregnancy result in profound and complex effects on thyroid function, and therefore significantly affect the interpretation of thyroid function tests [6, 7]. For this reason, formation and application of reliable gestational specific reference interval from the pregnant population with minimal risk for thyroid dysfunction is of utmost necessity [8]. Although several studies are available from different regions of the world [9-18], results are inconsistent, due to differences in ethnicity, iodine status, laboratory assay method and rigor for selection of the reference population. Considering the lack of data regarding thyroid hormones specific reference intervals in pregnant Georgian women, we carried out this study to determine laboratory and geography-specific reference interval for TSH in healthy Georgian pregnant women.

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Material and Methods

This retrospective cross-sectional study was conducted by the National Institute of Endocrinology (Tbilisi, Georgia) in collaboration with Obstetrics and Gynecology outpatient department of BMH, which is a primary care provider for pregnant women from different parts of Autonomous Republic of Adjara (Western Georgia).

We used data from medical records during pregnancy and birth of 2876 pregnant women who had undergone

routine prenatal examination and TSH screening in the second trimester of pregnancy (between 16-20 weeks of gestation) in BMH from January 2009 to December 2011. Standardized information including demographic data, thyroidal, obstetric-gynecological and general medical status was collected and the database was created. From this entire population 1351 women were available with complete information (study population).

Reference population was selected in accordance with the recommendations of National Academy of Clinical Biochemistry (NACB) [8], excluding women with a family or personal history of thyroid dysfunction, visible or palpable goiter, any kind of thyroid operations, use of thyroid medications, evidence for autoimmune thyroid disease. In addition, women with multiple or complicated pregnancies and deliveries, with a past history of spontaneous abortions were also removed from the study population. The values of TSH from established reference population were used to derive reference interval. The study protocol was approved by the ethical committee of the National Institute of Endocrinology according to the Declaration of Helsinki.

The TSH test was performed by Enzyme-Linked Immunosorbent Assay (ELISA) technique, using a Humareader single machine and reagent kits from Human diagnostics (Wiesbaden, Germany). Laboratory procedures, including calibration and internal quality control were as per instructions from the manufacturer. The proposed reference intervals of the standard kit for the ELISA method for TSH in this study was 0.4–5.0 mIU/L.

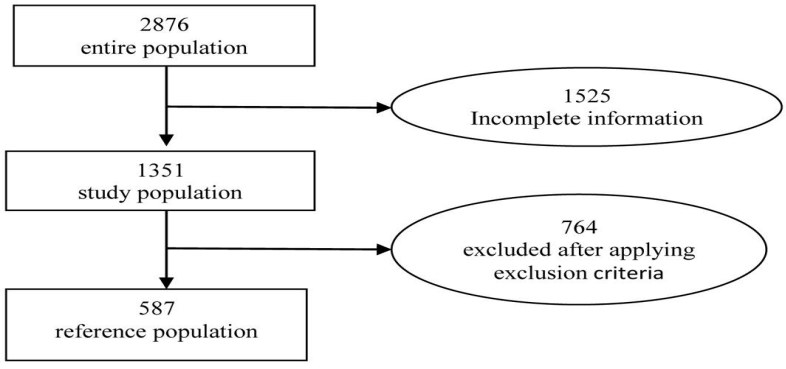
The reference intervals of TSH from reference population were calculated according to the recommendation of NACB (8): in view of the non-normal distribution of TSH results, the TSH measurements were first transformed to log TSH and 2.5−97.5 percentiles of the inverse log TSH were determined as the reference interval of second trimester of pregnancy. Categorical variables were expressed as frequency and percentage. Chi-square analyses were used to examine associations between categorical variables. All P values below 0.05 were considered statistically significant. Data were analyzed by SPSS 18 (SPSS Inc., Chicago, IL, USA).

Results

The age of the 1351 women (study population) ranged from 15 to 45 years (mean 24.8 ± 5.26), of which 294 (21.8 %) were under 20 years, 856 (63.4%) between 20 and 30 years and 201 (14.8%) over 30 years. The pregnancy order ranged from 1 to 7, with a median of 2, and for 839 women (62.1%) this was their first pregnancy. History of spontaneous abortions and thyroid illness in the family were present in 166 (12.3%) and 89 (6.5%) women, respectively. Clinical examination showed goiter in 243 (17.9%). At the time of TSH analysis, the gestational age determined by last menstrual period and ultrasound ranged from 16-20 weeks.

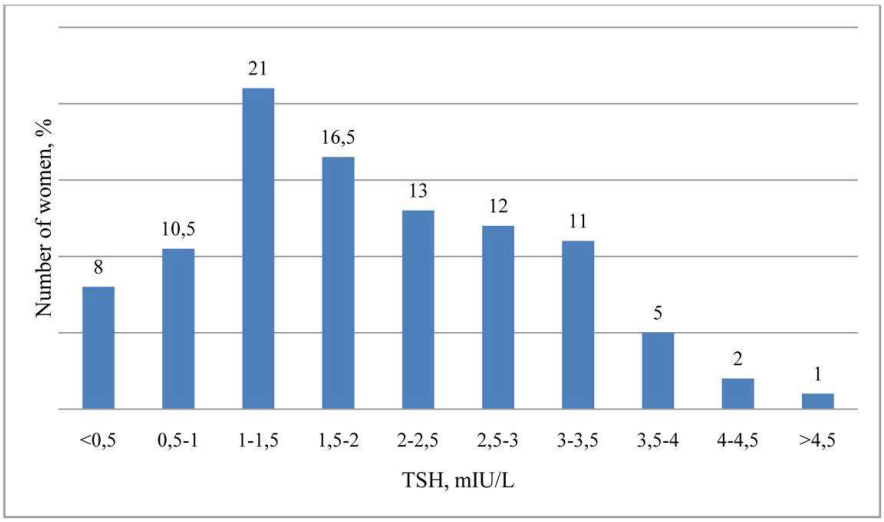
After applying aforementioned exclusion criteria, 764 women were excluded from the study population, resulting to a final population of 587 women used to determine reference intervals for TSH for the second trimester of pregnancy (Figure 1). Selected reference population was adequate for the statistical study according to the NACB criteria [8]. Mean age of women was 24.7±4.9 years. The majority of mothers were of Georgian origin (92.3%) residing in the region for more than 10 years.

Figure 1: Flow diagram of the study process for the determination of the reference population



The distribution of TSH values in reference population is shown in figure 2.

Figure 2: TSH distribution in reference population (n=587)



Additionally, medians, the 2.5th and 97.5th percentiles for serum TSH by gestational weeks (16-20 weeks) and for whole second trimester is shown in Table 1.

Table 1: Median, 2.5th and 97.5th percentiles for TSH by gestational weeks and for the whole second trimester

Gestational week	**N**	**TSH mIU/L**		
		Median	**2.5th %ile**	**97.5th %ile**
16 -17	146	1.83	0.19	4.13
17-18	135	1.8	0.21	4.07
18-19	157	1.84	0.2	4.15
19-20	149	1.89	0.24	4.22
Whole 2nd trimester	587	1.8	0.21	4.1

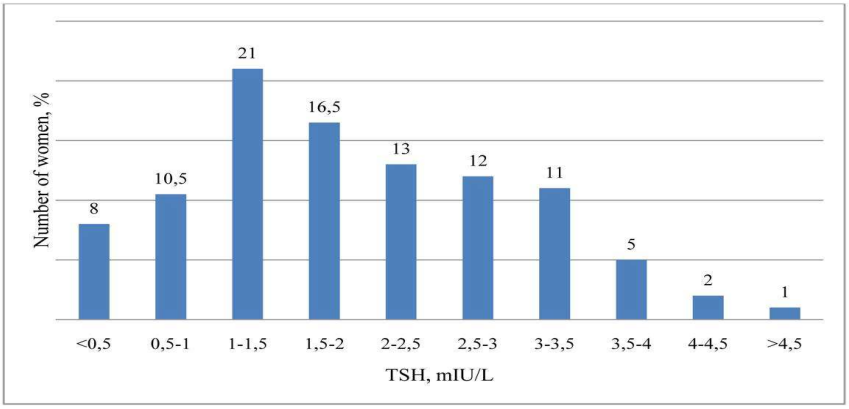
According to our results, the second trimester specific reference interval of serum TSH for the whole reference group was 0.21-4.1 mIU/L. Derived reference interval was used to interpret TSH results (e.g. 'high'=above 97.5th percentile, 'normal'=within 2.5th to 97.5th percentile, and 'low'=below 2.5th percentile) and then was compared with the ATA recommended standards and the reference intervals for non-pregnant women provided by the manufacturer kit. As a result, Table 2 which is given below reflects the percentage of potentially misclassified women in that case if non-pregnant reference intervals and ATA recommended standards are used.

Table 2: The percentage of potentially misclassified women if the manufacturer's, ATA recommended and the derived reference intervals were used

Reference interval	**Low TSH,n (%)**	**Normal TSH,n (%)**	**High TSH,n (%)**
Manufacturer (0.4-5.0 mIU/L)	62 (4.6)	1210 (89.6)	79 (5.8) *
ATA (0.2-3.0 mIU/L)	16 (1.2)	1021 (75.6)	314 (23.2) †
Derived (0.21-4.1 mIU/L)	18 (1.3)	1186 (87.8)	147 (10.9)

*p < 0,0001 in comparison to derived
†p< 0,0001 in comparison to derived

Figure 2: TSH distribution in reference population (n=587)



Additionally, the comparison of derived reference interval with the second trimester-specific reference intervals for TSH reported worldwide [13-16] is presented in Table 3.

Table 3: Summary of worldwide studies reporting second trimester specific reference intervals for TSH during pregnancy

Study	Country	Sample size	Percentiles used	TSH reference intervals
Soldin et al.	USA	83	2.5^{th} – 97.5^{th}	0.46 –2.95
Stricker et al.	Switzerland	528	2.5^{th} – 97.5^{th}	0.31 – 2.9
Marwaha et al.	India	137	5^{th} - 95^{th}	0.43 – 5.78
Bocos-Terraz et al.	Spain	243	2.5^{th} – 97.5^{th}	0.12 -2.64
Yan et al.	China	168	2.5^{th} – 97.5^{th}	0.47 – 4.54
Current study	Georgia	587	2.5^{th} – 97.5^{th}	0.21-4.1

Discussion

Thyroid dysfunction is one of the most common disorders in pregnant women. It harmfully affects the health of pregnant women and their fetuses [19]. Since the fetus does not completely establish its own thyroid functions until 20 weeks of pregnancy, fetal thyroid hormones are derived mainly from the mother in early pregnancy and their deficiency may impair future neuropsychological development of the fetus [4, 20]. Thus, the identification of thyroid disorders during pregnancy has attracted increased interest from researchers in recent years [21].

TSH is the most sensitive marker of thyroid dysfunction and is recommended as the first-line screening variable in determining thyroid dysfunction in pregnancy [8, 19]. In view of the alterations of TSH during pregnancy, establishing gestational-specific reference interval for this hormone is indispensable [7, 8]. Guidelines from the American Thyroid Association (ATA) suggest that trimester-specific reference intervals for TSH should be used in every population [7].

Several studies from different countries have attempted to create trimester-specific reference interval for TSH among pregnant women, with inconsistent results — perhaps reflecting differences in ethnic background, maternal iodine status, assessment of reference population, and method of analysis used among studies. Black and Asian women have TSH values that are on average 0.4 mIU/L lower than in white women [22, 23]. Accordingly, pregnant women whose origin is Turkish, Moroccan and Surinamese, have TSH values 0.2-0.3 mIU/L lower than Dutch women, though their country of residence is the Netherlands [24]. No relevant studies have been conducted with Georgian women. Our study represents the first study performed in Adjara - Western Georgia, an area of mild to moderate iodine deficiency, located on the eastern end of the Black Sea and extended to the mountains (2000-2500 m above sea level). Iodine deficiency disorders (IDD) were endemic for this region secondary to low iodine levels in water and soil. With the passage of the 2005 law banning the import and sale of non-iodized salt, Georgia met the primary World Health Organization for IDD elimination [25].

The present study provides reference interval for the TSH during the second trimester of pregnancy. From an epidemiological point of view, investigated population

was ethnically homogenous. In determining the TSH reference interval, it has been customary to log-transform the data because TSH values were not normally distributed. Reference interval based on 2.5th and 97.5th percentiles for TSH in pregnant Georgian women was 0.21–4.1 mIU/L. No definite trend was seen by analysis of the median serum TSH concentration across 16-20 weeks of gestation.

The major discrepancy in TSH reference values in our data compared with other reports mainly exists in the TSH upper reference limit, which in our study is relatively higher than that reported in other studies (Table 2) and ATA recommended standards (3.0 mIU/L for the second trimester), whereas it is significantly lower from those reported by the assay manufacturer for non-pregnant women.

The reference interval of TSH as supplied by the kit manufacturer for non-pregnant adult was 0.4–5.0 mIU/L. Before our study, these values were considered for the determination of thyroid disorders in pregnancy in our laboratory. When this non-pregnant reference interval was used to diagnose thyroid disorders an appreciable number of pregnant women escaped the diagnosis of hypothyroidism – 5.1 % pregnant women in their second trimester of pregnancy.

Data from our study showed an increase of subjects with increased TSH from 10.9% to 23.2% when the upper limit was changed from 4.1 to 3.0 mIU/L (ATA recommended). Consequently, use of an upper reference limit of 3.0 mIU/L instead of 4.1 mIU/L for TSH will result in an additional 12.3 % of women in the 2nd trimester being classified as abnormal. As it is our preliminary study, the next investigation will show the clinical significance of the above mentioned discrepancy.

Conclusion

We established gestational specific reference interval for TSH in pregnant Georgian women. Results of the present study suggest that the upper limit of normal TSH for the Georgian pregnant women would be 4.1 mIU/L for the second trimester, a limit higher than traditionally ATA recommended standards and lower then non-pregnant reference interval. Observed differences among the worldwide studies reported provide further evidence of importance of applying laboratory- and population-specific reference interval in order to avoid misclassification of pregnant women with thyroid dysfunction.

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