FIRST-TRIMESTER THYROID HORMONE REFERENCE DATA IN A TURKISH PREGNANT WOMEN POPULATION LIVING IN MIDDLE BLACKSEA REGION

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ABSTRACT

Objective: No reference values for thyroid hormones have been established for Turkish pregnant women yet in the first trimester of pregnancy. The aim of the present study was to determine first trimester reference values for thyroid hormones in pregnant women living in middle Black Sea region of Turkey and getting service from our institution’s laboratory.

Material and Method: 1144 pregnant women admitted to Gaziosmanpaşa University Faculty of Medicine hospital between January 2005 and January 2009 for first trimester visit were enrolled retrospectively. Maternal thyroid hormones measured as a part of laboratory examination were analyzed.

Results: Anti-TPO and anti-TG antibodies were measured in 250 of the total 1144 women. 166 of these had antibody levels within the normal ranges. The 2.5th and 97.5th percentiles of these 166 antibody negative women were as follows: for TSH (µIU/mL): 0.043-3.968, for fT4 (ng/dL): 0.840-1.638 and for fT3 (pg/mL): 2.059-4.386. The 2.5th and 97.5th percentiles of the remaining 894 antibody status unknown women were as follows: for TSH (µIU/mL): 0.059-4.196, for fT4 (ng/dL): 0.634-1.527 and for fT3 (pg/mL): 2.340-4.143.

Conclusion: For diagnosis of thyroid abnormalities; population, laboratory and even method based reference values should be established. This is a preliminary data from Turkish pregnant women.

INTRODUCTION

Thyroid physiology changes significantly during gestation. Thyroid binding globulin and the synthesis of thyroid hormones increase, serum iodine decreases, the deiodinase activity changes and there is an expansion of plasma volume. Also human chorionic gonadotropin has a thyroid-stimulating effect that is prominent toward the end of the first trimester. As a result thyroid hormone levels change.

It is well known that maternal thyroid dysfunction has adverse effects on both mother and child during pregnancy if not corrected. Therefore interpretation of thyroid function tests in pregnancy gains critical importance. In many studies it has been reported that gestational normative reference ranges for thyroid function tests are required because the results of these tests especially during the first trimester of pregnancy are often outside non-pregnant reference ranges and normal reference ranges from a non-pregnant population are not to be considered “normal” in pregnancy.

No reference values for thyroid hormones have been established for Turkish pregnant women yet in the first trimester of pregnancy yet. Studies from other countries provided trimester-specific thyroid function test results. It has been reported that the interpretation of screening thyroid function tests from obstetric patients is quite variable from practice to practice. Based on this data it has been recommended that any laboratory providing services to pregnant women should establish and monitor TSH reference ranges to assure reliability. The aim of the present study was to calculate first trimester reference values for thyroid hormones in pregnant women living in middle black sea region of Turkey and were provided with service from our institution’s laboratory.

MATERIAL and METHOD

A total of 1144 pregnant women admitted to Obstetrics Department of Gaziosmanpaşa University Faculty of Medicine hospital between January 2005 and January 2009 for first trimester (gestational weeks of ≤13 weeks established by last menstrual period and ultrasound) visit were retrospectively enrolled. Patients with multiple gestations, gestations of ≥14 weeks, had known thyroid diseases, underwent any kind of thyroid operations, had high anti-thyroid antibody levels and with fetal anomalies that were detected with sonography were excluded. All participants provided informed consent and institutional approval was obtained for the study. All the data from the eligible patients were obtained from patient files.

Maternal thyroid hormones that were measured as a part of laboratory examination were analyzed. These hormones included thyroid stimulating hormone (TSH) (reference range: 0.27-4.2 µIU/mL), total thyroxine (T4) (4.5-14 µg/dL), total triiodothyronine (T3) (70-180 ng/dL), free T4 (FT4) (0.85-1.78 ng/dL), free T3 (FT3) (1.57-4.71 pg/mL), anti-thyroglobulin (anti-TG) antibodies (1-50 IU/mL) and anti-thyroid peroxidase (anti-TPO) antibodies (1-35 IU/mL). Women were
considered antibody positive if the anti-TPO antibodies were >35 IU/mL or if anti-TG antibodies were >50 IU/mL. It was seen that not all these hormones had been measured in all patients and for analysis only the measured hormone levels were used.

Thyroid hormones were measured by immunoassay method (Access® Immunoassay kits, Beckman Coulter UniCel DXI 800). The intra-assay coefficients of variations for tT3, fT4, anti-TG and anti-TPO antibodies were 4%, for total T3 and total T4 it was 5% and for TSH it was <16%.

Statistical analysis was accomplished on a personal computer by using statistical program for social sciences version 11.5 (SPSS 11.5, demo, SPSS Inc. Chicago, Illinois). Mean, median, 2.5th and 97.5th percentiles were calculated. Kolmogorov-Smirnov test with Lilliefors’s correction was used to test whether the variables used in the study were normally distributed. Mann-Whitney U test was used to compare thyroid hormones, maternal ages, gestational weeks, gravidity and parity. A p value of <0.05 was assumed to be significant.

RESULTS

Anti-TPO and anti-TG antibodies were measured in 250 of the total 1144 women (21.9%). 166 of these 250 women (66.4%) had antibody levels within the normal ranges and 84 women who had high antibody levels were excluded. The mean, median, 2.5th and 97.5th percentiles of these 166 antibody negative women are depicted in Table 1. In 894 women (78.1%) thyroid antibodies had not been measured. In these patients mainly TSH, fT3 and fT4 were measured and the mean, median, 2.5th and 97.5th percentiles are shown in Table 1. The characteristics of the antibody negative and antibody status unknown patients are shown in Table 2.

In the antibody negative group 2 (1.2%), women with elevated TSH would not have been identified, and 11 (6.6%) women would have been incorrectly classified as having a low TSH if non-pregnant reference values were used. For fT4 2 (1.2%) women would have been classified as having normal values although they had high values. For fT3 2 (1.27%) women would have been misclassified (1 as normal although had low value and 1 as normal although had high value). For T4 7 (5.51%) and for T3 11 (8.94%) women would have been classified as having high values although they had normal values.

DISCUSSION

There are no available first trimester reference values of thyroid hormones in Turkish pregnant women.

The present study provides documentation for the first time about the first trimester thyroid hormone reference values in Turkish pregnant women living in a region of Turkey. It was found that TSH and fT4 levels were lower than average, tT4 and tT3 were higher than average in first trimester of pregnancy when compared with non-pregnant reference values. In pregnancy interpretation of the thyroid hormones may be difficult especially in the first trimester because of the change in thyroid physiology and serum thyroid hormone levels and there is a risk of false interpretation of thyroid function tests. It has been reported that population specific and laboratory dependent reference ranges are needed especially for the first trimester as identification and appropriate treatment of hypothyroidism is crucial for the optimum development of the fetus.2,11,12 If non-pregnant reference intervals are used some women would be misdiagnosed; 13/166 (7.8%) for TSH and 2/161 (1.2%) for fT4 in the present study for example.

In the present study reference values had been given for anti-thyroid antibody negative women and women with unknown antibody status. The antibody unknown women had higher 2.5th and 97.5th percentiles compared to antibody negative group. This may be because there may be women with positive anti-thyroid antibodies who did not know her illness in the former group. Pearce et al. stated that anti-TPO antibody →

### Table 1: Thyroid hormone reference data in thyroid antibody negative and thyroid antibody status unknown pregnant women

<table>
<thead>
<tr>
<th></th>
<th>Antibody negative (n:166)</th>
<th>Antibody status unknown (n:894)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean ± SD</td>
<td>Median (IQR)</td>
<td>2.5th %</td>
</tr>
<tr>
<td>TSH (µIU/mL)</td>
<td>1.71 ± 1.16</td>
<td>1.53 (1.62)</td>
</tr>
<tr>
<td>fT4 (ng/dL)</td>
<td>1.24 ± 0.29</td>
<td>1.20 (0.26)</td>
</tr>
<tr>
<td>tT3 (µg/mL)</td>
<td>3.04 ± 0.57</td>
<td>3.03 (0.59)</td>
</tr>
<tr>
<td>fT4 (ng/dL)</td>
<td>10.54 ± 2.24</td>
<td>10.31 (3.09)</td>
</tr>
<tr>
<td>tT3 (µg/mL)</td>
<td>141.31 ± 28.75</td>
<td>132.8 (37.0)</td>
</tr>
</tbody>
</table>

### Table 2: Characteristics and comparison of antibody negative and antibody status unknown pregnant women

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Antibody negative (n:166)</th>
<th>Antibody status unknown (n:894)</th>
<th>p*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maternal Age (years)</td>
<td>28.01 (5)</td>
<td>27.6 (6)</td>
<td>0.003</td>
</tr>
<tr>
<td>Gestational week</td>
<td>8.0 (3)</td>
<td>8.5 (5)</td>
<td>0.181</td>
</tr>
<tr>
<td>Gravidity</td>
<td>2 (2)</td>
<td>2 (2)</td>
<td>0.773</td>
</tr>
<tr>
<td>Parity</td>
<td>1 (1)</td>
<td>1 (1)</td>
<td>0.673</td>
</tr>
</tbody>
</table>
thyroid antibody negative women found in the present study is very close to values from some other studies. When measured with the same method, especially the lower threshold for TSH was found to be almost similar; with Beckman Coulter UniCel Dlx method Wyness et al.’s results and the results of the present study. However the upper limit of the TSH reference range varies and this uncertainty may result in misdiagnosis of mild hypothyroidism. As can be seen from Table 3, different groups reported different upper limits for TSH ranging between 2.65 and 3.968 µIU/mL. Because hypothyroidism has catastrophic effects on growing embryo/fetus, it has been recommended to consider 2.5 µIU/mL, which is the lowest 97.5th percentile reported to date in a US series, as the upper limit in order not to miss any hypothyroid pregnant women. For this reason there may also be need for method-specific reference intervals for all thyroid analytes. In conclusion, thyroid physiology changes during pregnancy and reference ranges for non-pregnant women should not be taken into account for pregnant women especially in the first trimester. Thyroid hormones are very important for the developing fetus and any abnormality should be treated appropriately.

For diagnosis of thyroid abnormalities, population, laboratory and even method based reference values should be established. This study aimed to establish reference values for a Turkish pregnant women population living in middle black sea region of Turkey and for the laboratory of our institute providing service to these women. This is a preliminary data from Turkish pregnant women. A nation wide population based study for establishment of reference values for each trimester or even week-specific cut off levels should be conducted.

* Authors declare no conflict of interest and there is no support for the present study.

**REFERENCES**


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### Table 3: First trimester thyroid hormone reference values from different countries measured with different methods.

<table>
<thead>
<tr>
<th>G.A.</th>
<th>Country</th>
<th>Method</th>
<th>TSH Free T4</th>
<th>Free T3</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;8-12 wk</td>
<td>Switzerland</td>
<td>Abbott Architect</td>
<td>0.08-2.82</td>
<td>10.55-18.28 (pmol/l)</td>
</tr>
<tr>
<td>&lt;11 wk</td>
<td>Spain</td>
<td>Abbott Architect</td>
<td>0.10-2.65</td>
<td>0.86-1.36 (ng/dl)</td>
</tr>
<tr>
<td>1st trimester</td>
<td>China</td>
<td>Diagnostic Products</td>
<td>0.13-3.33</td>
<td>12.0-23.34 (pmol/l)</td>
</tr>
<tr>
<td>1st trimester</td>
<td>USA</td>
<td>Bayer Diagnostics</td>
<td>0.04-3.6</td>
<td></td>
</tr>
<tr>
<td>10-13 wk</td>
<td>USA</td>
<td>Beckman Coulter UniCel Dlx</td>
<td>0.04-2.98</td>
<td>7.35-14.19 (pmol/l)</td>
</tr>
<tr>
<td>10-13 wk</td>
<td>USA</td>
<td>Roche Modular Analytics E170</td>
<td>0.03-3.40</td>
<td>11.09-18.32 (pmol/l)</td>
</tr>
<tr>
<td>1st trimester</td>
<td>Turkey</td>
<td>Beckman Coulter</td>
<td>0.049-3.988</td>
<td>0.64-1.63 (pmol/l)</td>
</tr>
</tbody>
</table>

G.A.: Gestational age; TSH: Thyroid stimulating hormone; T4: Thyroxine; T3: Triiodothyronine; USA: United States of America.


