

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

Hakan Aytan,¹ Pelin Aytan,² Fazlı Demirtürk,³ Ahmet Cantuğ Çalışkan,⁴ Şemsettin Şahin,⁵ Filiz Erdoğan⁶

¹ Mersin University, Faculty of Medicine, Department of Obstetrics and Gynecology, Mersin, Turkey

² Çukurova University, Faculty of Medicine, Department of Internal Medicine Hematology, Adana, Turkey

³ Gaziosmanpaşa University, Faculty of Medicine, Department of Obstetrics and Gynecology, Tokat, Turkey

⁴ Samsun Education and Research Hospital, Department of Obstetrics and Gynecology, Samsun, Turkey

⁵ Gaziosmanpaşa University, Faculty of Medicine, Department of Biochemistry, Tokat, Turkey

⁶ Muratlı State Hospital, Tekirdağ, Turkey

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 (μ IU/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 (μ IU/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.

Key Words: Thyroid hormones, reference values, pregnancy, first-trimester, women. *Nobel Med* 2014; 10(1): 25-29

ORTA KARADENİZ BÖLGESİNDE YAŞAYAN TÜRK GEBE KADIN POPÜLASYONUNDA BİRİNCİ TRİMESTER TİROİD HORMON REFERANS DEĞERLERİ

ÖZET

Amaç: Türk kadınlarında gebeliğin birinci trimesterine spesifik tiroid hormon referans değerleri henüz belirlenmemiştir. Bu çalışmanın amacı Türkiye'nin Orta Karadeniz bölgesinde yaşayan ve üniversitemizden hizmet alan Türk gebe kadınlarda gebeliğin birinci trimesterinde tiroid hormonlarının referans değerlerini hesaplamaktır.

Materyal ve Metod: Ocak 2005 ile Ocak 2009 yılları arasında Gaziosmanpaşa Üniversitesi Tıp Fakültesi Hastanesi Kadın Hastalıkları ve Doğum Kliniğine gebelik ilk viziti için başvuran 1144 gebe kadın retrospektif olarak incelendi. Laboratuvar değerlendirmenin bir parçası olarak istenen tiroid hormonları analiz edildi.

Bulgular: 1144 kadının 250'sinde antitiroid peroksidaz ve antitiroglobulin antikorları ölçülmüştü. Bunlardan 166 tanesinde değerler normal sınırlarda idi. Bu 166 antikor negatif kadının tiroid hormon değerlerinin 2,5 ve 97,5 persentilleri şöyleydi: TSH (μ IU/mL): 0,043-3,968, serbest T4 (ng/dL): 0,840-1,638 ve serbest T3 (pg/mL): 2,059-4,386. Geri kalan tiroid antikor durumu bilinmeyen 894 hastanın 2,5 ve 97,5 persentilleri ise TSH (μ IU/mL): 0,059-4,196, sT4 (ng/dL): 0,634-1,527 ve sT3 (pg/mL): 2,340-4,143 olarak bulundu.

Sonuç: Tiroid anormalliklerin tanısı için popülasyon, laboratuvar ve hatta metoda dayalı referans değerleri belirlenmelidir. Bu çalışma Türk gebe kadınlarda bu konuda yapılan ilk çalışmalardan biridir.

Anahtar Kelimeler: Tiroid hormonları, referans değerleri, gebelik, birinci trimester, kadınlar **Nobel Med** 2014; 10(1): 25-29

INTRODUCTION

Thyroid physiology changes significantly during gestation.¹ 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.² 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.^{3,4} 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.²⁻⁵

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.⁶⁻⁸ It has been reported that the interpretation of screening thyroid function tests from obstetric patients is quite variable from practice to practice.⁹ 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.¹⁰ 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 6/7 days 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 μ IU/mL), total thyroxine (tT4) (4.5-14 μ g/dL), total triiodothyronine (tT3) (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 fT3, 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 Lillefor'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, gravidiy 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 tT4 7 (5.51%) and for tT3 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.

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

	Mean ± SD	Median (IQR)	2.5 th %	97.5 th %
Thyroid antibody negative				
TSH (μIU/mL) (n:166)	1.71 ± 1.14	1.53 (1.62)	0.043	3.968
fT4 (ng/dL) (n:161)	1.24 ± 0.29	1.20 (0.28)	0.840	1.638
fT3 (pg/mL) (n:157)	3.04 ± 0.57	3.03 (0.59)	2.059	4.386
tT4 (μg/dL) (n:127)	10.54 ± 2.24	10.31 (3.09)	7.484	15.240
tT3 (ng/dL) (n:123)	141.31 ± 28.75	132.8 (37.0)	99.950	212.20
Thyroid antibody status unknown				
TSH (μIU/mL) (n:893)	1.49 ± 1.09	1.24 (1.39)	0.059	4.196
fT4 (ng/dL) (n:813)	0.99 ± 0.55	0.92 (0.32)	0.634	1.527
fT3 (pg/mL) (n:757)	3.11 ± 0.46	3.08 (0.54)	2.340	4.143

TSH: thyroid stimulating hormone, fT4: free thyroxine, fT3: free triiodothyronine, tT4: total thyroxine, tT3: total triiodothyronine, SD: standard deviation, IQR: interquartile range

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

	Antibody negative (n:166)	Antibody status unknown (n:894)	
	Median (IQR)	Median (IQR)	p*
Maternal Age (years)	28.00 (5)	27 (6)	0.003
Gestational week	8.0 (3)	8 (5)	0.181
Gravidity	2 (2)	2 (2)	0.773
Parity	1 (1)	1 (1)	0.673

IQR: Interquartile range, *: Mann-Whitney U test

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

	G.A.	Country	Method	TSH	Free T4	Free T3
Stricker et al.	<6-12 wk	Switzerland	Abbott Architect	0.08-2.82	10.53-18.28 (pmol/l)	3.52-6.22 (pmol/l)
Bacos-Terraz et al.	<11 wk	Spain	Abbott Architect	0.10-2.65	0.88-1.38 (ng/dl)	2.34-4.34 (pg/ml)
Shan et al.	1 st trimester	China	Diagnostic Products	0.13-3.93	12.0-23.34 (pmol/l)	3.46-7.70 (pmol/l)
Pearce et al.	1 st trimester	USA	Bayer Diagnostics	0.04-3.6		
Wyness et al.	10-13 wk	USA	Beckman Coulter UniCel Dx	0.04-2.98	7.35-14.19 (pmol/l)	
	10-13 wk	USA	Roche Modular Analytics E170	0.03-3.40	11.09-18.32 (pmol/l)	
Aytan et al.	1 st trimester	Turkey	Beckman Coulter	0.043-3.968	0.84-1.63 (ng/dl)	2.05-4.38 (pg/ml)

G.A.: Gestational age, TSH: Thyroid stimulating hormone, T4: thyroxine, T3: triiodothyronine, USA: United States of America

status of pregnant women should be considered when constructing trimester specific ranges because elevated serum anti-TPO antibody levels were associated with higher TSH and lower T4 values.¹³ In the studied population the mean (\pm SD) and median (IQR) of the anti-TPO positive women were 2.894 \pm 2.162 and 2.58 (2.71) respectively which were higher than the antibody negative and antibody unknown groups. The United States National Academy of Clinical Biochemistry (NACB) also recommends establishment of “trimester-specific reference values and paying particular attention to the fact that specimens used for such studies should not contain thyroid antibodies.⁵ For this reason, data obtained from antibody negative women are more reasonable for establishment of reference values for this studied Turkish population. In literature, population and laboratory specific different ranges have been reported. Table 3 shows some reference values from different populations with different measurement methods.¹⁴⁻¹⁷ There seems to be variations that may be due to differences in studied populations and measurement methods. The reference values in anti-

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 Dx method Wyness et al.’s results and the results of the present study.¹⁷ 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 μ IU/mL.¹³⁻¹⁷ Because hypothyroidism has catastrophic effects on growing embryo/fetus, it has been recommended to consider 2.5 μ IU/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.¹⁸ For this reason there may also be need for method-specific reference intervals for all thyroid analytes.¹⁷

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.

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C	CORRESPONDING AUTHOR: Hakan Aytan Fath Mah., Adnan Menderes Bulvarı, 30014. Sok. Yalı Apt, 7/14, Mezitli, Mersin, Turkey drhakanaytan@yahoo.com
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REFERENCES

- Glinoe D. The regulation of thyroid function in pregnancy: pathways of endocrine adaptation from physiology to pathology. *Endocr Rev* 1997; 18: 404-433.
- Feldt-Rasmussen U, Bliddal Mortensen AS, Rasmussen AK, et al. Challenges in interpretation of thyroid function tests in pregnant women with autoimmune thyroid disease. *J Thyroid Res* 2011; 2011: 598712.
- Lazarus JH. Thyroid function in pregnancy. *British Medical Bulletin* 2011; 97: 137-148.
- Yan YQ, Dong ZL, Dong L, et al. Trimester- and method-specific reference intervals for thyroid tests in pregnant Chinese women: methodology, euthyroid definition and iodine status can influence the setting of reference intervals. *Clin Endocrinol (Oxf)* 2011; 74: 262-269.
- Baloch Z, Carayon P, Conte-Devolx B, et al. Guidelines Committee, National Academy of Clinical Biochemistry. Laboratory medicine practice guidelines: laboratory support for the diagnosis and monitoring of thyroid disease. *Thyroid* 2003; 13: 3-126.
- Dashe JS, Casey BM, Wells CE, et al. Thyroid-stimulating hormone in singleton and twin pregnancy: importance of gestational age-specific reference ranges. *Obstet Gynecol* 2005; 106: 753-757.
- Walker JA, Illions EH, Huddleston JF, Smallridge RC. Racial comparisons of thyroid function and autoimmunity during pregnancy and the postpartum period. *Obstet Gynecol* 2005; 106: 1365-1371.
- Haddow JE, Knight GJ, Palomaki GE, McClain MR, Pulkkinen AJ. The reference range and withinperson variability of thyroid stimulating hormone during the first and second trimesters of pregnancy. *J Med Screen* 2004; 11: 170-174.
- Haddow JE, McClain MR, Palomaki GE, Kloza EM, Williams J. Screening for thyroid disorders during pregnancy: results of a survey in Maine. *Am J Obstet Gynecol* 2006; 194: 471-474.
- Lambert-Messertian G, McClain M, Haddow JE, et al. FaSTER Research

Consortium. First- and second- trimester thyroid hormone reference data in pregnant women: a FaSTER (First- and Second-Trimester Evaluation of Risk for aneuploidy) Research Consortium study. *Am J Obstet Gynecol* 2008; 199: 62.

11. Morreale de Escobar G, Obregon MJ, Escobar del Rey F. Role of thyroid hormone during early brain development. *Eur J Endocrinol* 2004; 151: U25-37.
12. Glinoe D. What happens to the normal thyroid during pregnancy? *Thyroid* 1999; 9: 631-635.
13. Pearce EN, Oken E, Gillman MW, et al. Association of first-trimester thyroid function test values with thyroperoxidase antibody status, smoking, and multivitamin use. *Endocr Pract* 2008; 14: 33-39.
14. Stricker R, Echenard M, Eberhart R, et al. Evaluation of maternal thyroid function during pregnancy: the importance of using gestational age-specific reference intervals. *Eur J Endocrinol* 2007; 157: 509-514.
15. Bocos-Terraz JP, Izquierdo-Alvarez S, Bancalero-Flores JL, et al. Thyroid hormones according to gestational age in pregnant Spanish women. *BMC Res Notes* 2009; 2: 237.
16. Shan ZY, Chen YY, Teng WP, et al. A study for maternal thyroid hormone deficiency during the first half of pregnancy in China. *Eur J Clin Invest* 2009; 39: 37-42.
17. Wyness SP, La'ulu SL, Roberts WL. First-trimester reference intervals for thyrotropin, free thyroxine, free thyroxine index and thyroxine for the Beckman Coulter UniCel® DxI 800 and Roche Modular Analytics E170 analyzers. *Clin Chim Acta* 2011; 412: 2346-2348.
18. Mandel SJ, Spencer CA, Hollowell JG. Are detection and treatment of thyroid insufficiency in pregnancy feasible? *Thyroid* 2005; 15: 44-53.