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Trimester Specific Reference Ranges for Thyroid Hormones in Pregnancy with Multiples of Median Values

Gebelikte Tiroid Hormonlarının Medyan Değerlerin Katları ile Birlikte Trimester Spesifik Referans Aralıkları

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ABSTRACT

Aim: To establish trimester and population based laboratory-specific rational reference ranges with multiples of median (MoM) values for thyroid hormones.

Materials and Methods: The study was conducted in the obstetrics outpatient clinic of a tertiary health care center between April, 2021 and August, 2021. Healthy pregnant women without any risk factors and antithyroperoxidase positivity were recruited for all three trimesters. Serum thyroid-stimulating hormone (TSH), free thyroxine (FT4) and free triiodo-thyronine (FT3) levels were measured by the electrochemiluminescence technique. Trimester specific reference ranges were determined with 5. and 95. percentiles of TSH, FT3 and FT4 values with MoM values.

Results: Overall, 484 healthy pregnant women, including 140 women in their first trimester, 204 women in their second trimester and 140 women in their third trimester were recruited. In the first trimester, 90% (n=126) women's TSH levels were within the reference limits (0.19-3.25 uIU/mL and 0.19-3.25 MoM) and 11.1% (n=14) had TSH levels above 2.5 uIU/L. For second trimester, 90.2% (n=184) had TSH levels within the reference limits (0.65-3.83 uIU/mL and 0.4-2.36 MoM) and 8.15% (n=15) had TSH levels over 3 uIU/L. In the third trimester, 90.7% (n=127) women's TSH levels were within reference limits (0.62-3.78 uIU/mL and 0.39-2.35 MoM) and 3.15% (n=4) had TSH levels over 3 uIU/L.

Conclusion: Accurate diagnosis and management of thyroid disease for pregnant women is crucial for maternal-fetal outcomes. Established reference ranges for three trimesters in this study were all higher than the recommended fixed ranges of 2011 American Thyroid Association guideline.

Keywords: Electrochemiluminescence, pregnancy, multiples of median, thyroid hormone, trimester

ÖZ

Amaç: Popülasyon ve laboratuvara özgü tiroid hormonları için trimester spesifik rasyonel referans aralıkları oluşturmaktır.

Gereç ve Yöntem: Çalışma üçüncü basamak bir sağlık kuruluşunda kadın doğum polikliniğinde Nisan 2021-Ağustos 2021 tarihleri arasında gerçekleştirildi. Her üç trimesterde de herhangi bir risk faktörü ve antitiroperoksidaz pozitifliği olmayan sağlıklı gebeler çalışmaya alındı. Serum tiroid stimülan hormon (TSH), serbest tiroksin (FT4) ve serbest triiyodo-tironin (FT3) düzeyleri elektrokemilüminesans tekniği ile ölçüldü. Trimester spesifik referans aralıkları, medyan değerlerin katları (MoM) ile TSH, FT3 ve FT4 değerlerinin 5. ve 95. persentilleri belirlendi.

Bulgular: Toplamda, 140'ı birinci trimesterde, 204'ü ikinci trimesterde ve 140'ı üçüncü trimesterde olmak üzere 484 sağlıklı gebe çalışmaya alındı. İlk trimester için kadınların %90'ı (n=126) referans sınırlarındaydı (0,19-3,25 uIU/mL ve 0,19-3,25 MoM) ve %11,1'inin (n=14) TSH seviyeleri 2,5 uIU/L'nin üzerindeydi. İkinci trimester için, %90,2 (n=184) referans sınırlarında (0,65-3,83 uIU/mL ve 0,4-2,36 MoM) TSH seviyelerine sahipti ve

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%8,15'i (n=15) 3 uIU/L'nin üzerinde TSH seviyelerine sahipti. Üçüncü trimesterde kadınların %90,7'si (n=127) referans sınırlarında (0,62-3,78 uIU/mL ve 0,39-2,35 MoM) ve %3,15'i (n=4) 3 uIU/L'nin üzerinde TSH değerlerine sahipti.

Sonuç: Gebe kadınlarda tiroid hastalığının doğru teşhisi ve yönetimi maternal-fetal sonuçlar için çok önemlidir. Bu çalışmada üç trimester için belirlenen referans aralıklarının tümü, 2011 Amerikan Tiroid Birliği kılavuzunun önerilen sabit aralıklarından daha yüksek bulunmuştur.

Anahtar Kelimeler: Elektrokemilüminesans, gebelik, medyan değer, tiroid hormonu, trimester

INTRODUCTION

Diagnosis and management of thyroid disorders are important for a healthy pregnancy. Thyroid dysfunction in pregnancy can lead to adverse pregnancy outcomes including miscarriage, preterm birth, low birth weight, preeclampsia, abruptio placentae, and stillbirth[1-3]. The thyroid gland of the fetus does not function until the 10th-12th weeks of gestation and therefore, cannot produce hormones properly until the 20th week[3]. During these weeks, maternal thyroid hormones reach the embryo through the placenta and play a crucial role in the development of the fetus[4]. In addition, substantial new evidence supports the importance of thyroid hormone in the neurological development of the fetus[5].

Diagnosis of thyroid dysfunction is mainly based on the measurement of thyrotrophin or thyroid-stimulating hormone (TSH) and free thyroxine (FT4)[6]. Pregnancy is associated with increased renal iodine excretion, thyroxine binding globulin, thyroid hormone synthesis, and human chorionic gonadotropins (hCG) thyroid stimulatory actions[7]. Thyroid function tests in pregnant women are affected by all of these factors[7]. The prevalence of thyroid dysfunction during pregnancy is 2-4%[3] but the diagnosis is challenging due to undetermined population-based cut-off levels. The laboratory reference ranges do not indicate the relatioshipn between thyroid hormone levels and clinical illness[8]. A reference range for TSH with an upper limit of 2.5 mU/l for the first trimester and 3.0 mU/l for the second or third trimester to diagnose subclinical and overt hypothyroidism are generally used[3]. With the use of fixed cut-off values for upper limits (2.5-3 mU/l), 8-28% of TSH measurements are accepted as high[9]. If population-based pregnancy-specific reference range was used for the upper limit for TSH, 3-4% of the measurements would be accepted as high and these population-based pregnancy-specific upper limits were generally found to be above 2.5 or 3 mU/l in the literature[9]. Recently, the 2017 American Thyroid Association (ATA) and the American College of Obstetricians and Gynecologists guidelines recommended calculating and using pregnancy-specific and laboratory-specific reference ranges for TSH and FT4 to diagnose thyroid dysfunction in pregnancy[10].

The aim of this study was to establish trimester and population based laboratory-specific rational reference ranges with multiples of median values (MoM) for thyroid hormones.

MATERIALS AND METHODS

The study was conducted in the obstetrics outpatient clinic of a tertiary health care center between April, 2021 and August, 2021. The University of Health Sciences Turkey, Sancaktepe Şehit Prof. Dr. İlhan Varank Training and Research Hospital Scientific Research Ethics Committee approved the study (decision number: 2021/146 date: 21.04.2021). The study was registered to ClinicalTrials.gov Protocol Registration and Results System with NCT04860622 clinical trial number. Written consent was obtained from the participating women.

The women with a singleton pregnancy in any trimester, who applied to the outpatient clinic for routine antenatal obstetric care with iodized salt consumption or iodine supplementation, were recruited for the study.

Exclusion Criteria

- Pregnant women with *in vitro* fertilisation pregnancy, family history of thyroid disease, pre-existing thyroid disease, using thyroid interfering medication, with other autoimmune diseases and any pregnancy complications (gestational diabetes, hyperemesis, hypertension) were excluded from the study in the first evaluations.

- The pregnant women with a history of diabetes or pregnancy complications in previous pregnancies were also excluded.

- If pregnancy complications like gestational diabetes, hypertensive disorders occurred in follow-up of pregnancy before final analysis, the pregnant women recruited within the first trimester were excluded.

- The women who had anti-thyroperoxidase (anti-TPO) over 34 IU/mL and with any reported abnormality in the sonographic thyroid evaluation were excluded as the second step of exclusion from reference interval assessment.

The gestational age, gravidity, parity, and the number of abortions were all questioned in the routine obstetric care of pregnant women. The initially selected cohort of pregnant women were tested for beta-hCG, TSH, FT4, free triiodothyronine (FT3) and anti-TPO. In addition, women were directed to sonographic thyroid evaluation if possible. The size of the anti-TPO negative study cohort was determined according to previous recommendations in this subject about thyroid function reference intervals during pregnancy[3].

Gestational age of women was determined by the last menstrual period and crown-rump-length measurement

by ultrasound scan together. When there was a significant difference between the two dates, the ultrasound scan was used to determine the gestational age. The first trimester of pregnancy was defined as between 7 weeks and 13 weeks and 6 days, the second trimester between 14 weeks and 27 weeks and 6 days, and the third trimester as ≥28 weeks until birth.

Serum TSH, FT4 and FT3 and anti-TPO were measured by the electrochemiluminescence (ECL) technique with Elecsys 801 analyzer using commercially available kits of Roche Diagnostics (Mannheim, Germany). Venous blood samples were collected from each recruited subject after 8-10 hours of fasting and tested for TSH, FT4, FT3 and anti-TPO. Reference ranges for adults used in the laboratory in which the assay was performed were as follows: TSH: 0.50-5.10 uIU/mL, FT4: 0.93-1.7 ng/dL, FT3: 2.04-4.4 pg/dL. The inter and intraassay variations were 1.0% and 1.5%, respectively, for TSH, 1.6% and 3.2%, respectively, for FT4 and 1.9% and 2.2%, respectively, for FT3.

Thyroid sonographic evaluation was performed by an experienced sonographer using Toshiba Aplio 300 (Toshiba Medical Systems, Tokyo, Japan) with 7.5 MHZ linear transducer. Any abnormality reported by the sonographer was taken for the exclusion of the subject from the present study.

Statistical Analysis

The collected data were analyzed using the Statistical Package for the Social Sciences software version 22.0 (IBM Corp., Armonk, NY, USA). The normality of the demographic data was assessed using the Shapiro-Wilk test. Demographic data are summarized as the median±interquartile range for non-normally distributed data and as the mean±standard deviation for normally distributed data. One-way ANOVA and Kruskal-Wallis tests were used for comparing continuous variables when appropriate. Since the subjects were clinically selected as healthy, outlier exclusion was not performed. TSH, FT3 and FT4 values were log-transformed for normality assumption. Trimester specific reference ranges were determined with 5. and 95. percentiles of TSH, FT3 and FT4 values. MoM values of TSH, FT3 and FT4 values were calculated and reference ranges of each trimester were found at 5. and 95. percentiles. A p value of <0.05 was considered to indicate a significant difference.

RESULTS

In total, 526 women were enrolled in this study. Forty women due to high anti-TPO levels and 2 women with thyroiditis findings in the sonographic evaluation were excluded. Ultrasonography/thyroid sonographic evaluation could only be applied to 50 pregnant women due to limited resources. Overall, 484 healthy pregnant women, including 140 women in the first trimester, 204 women in the second trimester and 140 women in the third trimester, were recruited for the final analysis of the study. Demographic and obstetric characteristics of women and laboratory results are summarized in Table 1 in accordance with each trimester. Reference intervals (median, 5th and 95th percentiles) for thyroid hormone levels and MoM values are presented in Tables 2, 3, and 4.

For the first trimester, TSH levels of 90% (n=126) women were within the reference ranges (0.19-3.25 uIU/mL) and 11.1% (n=14) out of 126 women had TSH levels above the fixed upper limit of the first trimester (2.5 uIU/L) (Figure 1). With regard to the second trimester, 90.2% (n=184) had TSH levels within the reference ranges (0.65-3.83 uIU/mL) and 8.15% (n=15) of 184 women had TSH levels over the fixed upper limit (3 uIU/L) (Figure 2). In the third trimester, 90.7% (n=127) of women's TSH levels were within reference ranges (0.62-3.78 uIU/mL) and 3.15% (n=4) of 127 women had TSH levels over the fixed upper limit (3 uIU/L) (Figure 3).

Within the reference ranges of first, second and third trimester TSH levels, 5 (3.97%), 7 (3.80%), and 5 (3.94%) pregnant women had FT4 level below the 5th percentile FT4 level of first, second and third trimesters, respectively.

DISCUSSION

Reference levels for the TSH, FT4 and FT3 values were determined in a healthy cohort of pregnant women for our institution. The upper reference limits were found to be above

Table 1. Demographic and obstetric characteristics and laboratory results of women in accordance with each trimester

	1st trimester (n=140)	2nd trimester (n=204)	3rd trimester (n=140)	p
	Mean±SD (min-max)	Mean±SD (min-max)	Mean±SD (min-max)	
Age (year)	27.9±5.2 (18-46)	27.7±5.6 (24-42)	28.2±5.2 (19-41)	0.534
BMI (kg/m^2)	26.3±8.8 (16.81-39.30)	26.8±4.6 (18.21-45.49)	28.8±5.0 (19.10-47.11)	0.001
	Median±IQR (min-max)	Median±IQR (min-max)	Median±IQR (min-max)	
Gravidity	2±2 (1-11)	2±1 (1-10)	2±3 (1-9)	0.501
Parity	1±2 (0-8)	1±2 (0-9)	1±2 (0-5)	0.530
Gestational age (week)	8±4.5 (7-13)	21±8 (14-30)	32±4 (28-39)	
	Mean±SD (min-max)	Mean±SD (min-max)	Mean±SD (min-max)	
Beta-hCG (mIU/mL)	85104.1±42370.0 (3689-191450)	23882.0±20462.1 (1361-127444)	20139.6±15733.1 (1838-77793)	N/A
TSH (uIU/mL)	1.33±1 (0.02- 6.59)	1.84±1 (0.01- 6.1)	1.75±0.9 (0.35- 5.81)	0.000
FT4 (ng/dL)	1.2±0.16 (0.75-1.65)	1.04±0.14 (0.68-1.52)	0.97±0.12 (0.66- 1.22)	0.000
FT3 (pg/dL)	3.29±0.44 (2.1-4.93)	3.02±0.37 (2.14-4.28)	2.8±0.16 (0.75-1.65)	0.000

TSH: Thyroid-stimulating hormone, FT4: Free thyroxine, FT3: Free triiodothyronine, BMI: Body mass index, SD: Standard deviation, Min-max: Minimum-maximum, beta-hCG: Beta-human chorionic gonadotrophin, IQR: Interquartile range

Table 2. Reference intervals (median, 5th and 95th percentiles) for TSH levels (uIU/mL) and MoM values

	5th percentile (CI) value	5th percentile MoM value	Median	CI value	95th percentile MoM value
First trimester (n=140)	0.19 (0.09-0.31)	0.19	1.02	3.31 (2.75-3.60)	3.25
Second trimester (n=204)	0.65 (0.48-0.79)	0.4	1.62	3.83 (3.34-4.46)	2.36
Third trimester (n=140)	0.62 (0.50-0.73)	0.39	1.61	3.78 (2.91-4.08)	2.35

TSH: Thyroid-stimulating hormone, MoM: Multiples of median, CI: Confidence interval

Table 3. Reference intervals (median, 5th and 95th percentiles) for FT4 levels (ng/dL) and MoM values

	5th percentile (CI) value	5th percentile MoM value	Median	95th percentile (CI) value	95th percentile MoM value
First trimester (n=140)	0.97 (0.95-1)	0.82	1.19	1.51 (1.4- 1.57)	1.27
Second trimester (n=204)	0.83 (0.8-0.86)	0.81	1.03	1.29 (1.26-1.4)	1.25
Third trimester (n=140)	0.78 (0.72- 0.82)	0.81	0.96	1.17 (1.14-1.2)	1.22

FT4: Free thyroxine, MoM: Multiples of median, CI: Confidence interval

Table 4. Reference intervals (median, 5th and 95th percentiles) for FT3 levels (pg/dL) and MoM values

	5th percentile (CI) value	5th percentile MoM value	Median	95th percentile (CI) value	95th percentile MoM value
First trimester (n=140)	2.59 (2.47-2.73)	0.78	3.32	3.98 (3.86- 4.14)	1.20
Second trimester (n=204)	2.44 (2.35- 2.54)	0.81	3.01	3.61 (3.53- 3.78)	1.20
Third trimester (n=140)	2.2 (2.14- 2.35)	0.81	2.73	3.52 (3.3-3.82)	1.29

FT3: Free triodothyronine, MoM: Multiples of median, CI: Confidence interval

the recommended-fixed upper limits of 2.5 uIU/L and 3 uIU/L at the 2011 ATA guideline. The fixed upper limits of 2.5 uIU/L and 3 uIU/L would lead to overdiagnosis and overtreatment of 11.1%, 8.15%, and 3.15% of the first, second and third trimesters, respectively, when compared with new reference values in this study.

There is a debate about universal screening for thyroid dysfunction and screening mainly recommended for pregnant women with risk[6,11,12]; however, healthcare providers are widely performing universal screening[13]. Furthermore, there is an ongoing debate about whom to treat, when to treat, and whether treatment is useful based on currently available data[12]. In this regard, locally established reference ranges for thyroid function at the population level in pregnant women without thyroid disease were recommended[6,10].

Several studies were carried out following the recommendations of recent guidelines about population-based reference intervals of thyroid hormones in pregnant women[3,14-16]. To the best of our knowledge, there were only two studies that emerged from our country[14,15] at the time of writing this paper. In these studies, 2.5 and 97.5 percentiles were taken as reference intervals. In the study of Akarsu et al.[14], reference intervals of 0.49-2.33 mIU/L, 0.51-3.44 mIU/L, and 0.58-4.31 mIU/L for TSH were found for the first, second and third trimesters, respectively. The first trimester upper reference limit was lower than the fixed upper limit of the 2011 ATA guideline and lower than the upper limit found in the present study. Bulur et. al.[15] found their reference intervals for TSH as 0.005-3.65 mIU/L for the first, 0.011-3.63 mIU/L for the second and 0.2-3.46 mIU/L for the third trimesters. The upper limits in that study were higher than the fixed 2011 ATA guideline upper limits and our upper reference limits. Regarding FT4 limits, the limits were lower in this study compared to the present study and the limits were declining from the first to the third trimester, similar to our study.

In the present study, ECL kits were used for the measurement of thyroid hormone levels. The other studies using ECL kits proposed higher reference limits for TSH than the fixed ATA limits of 2011[17-19]. In the studies of Marwaha et al.[18] and Kurioka et al.[19], the TSH mean values were found to be increasing from the first through the third trimester, and FT4 and values were declining with advancing pregnancy. These findings were similar to our study findings. However, another study of Kumar et al.[17] revealed that FT4 and FT3 values were increasing from first to the second trimester and declining from second to third trimester. In our opinion, in pregnant women, TSH was first suppressed and then increased pertinently with changes in FT4, FT3, and beta-hCG levels as mentioned in a study from China[20].

The recent ATA guideline makes an exception for anti-TPO positive women and suggests that treatment can be considered if the TSH level is above 2.5 mU/L. Another study investigated this subject and reported that treatment for TSH levels above 4 mU/L in anti-TPO positive women was beneficial in reducing the rate of preterm delivery[21]. This beneficial effect has also existed for the anti-TPO negative women[22]. However, the data about the treatment of euthyroid women or subclinical hypothyroid

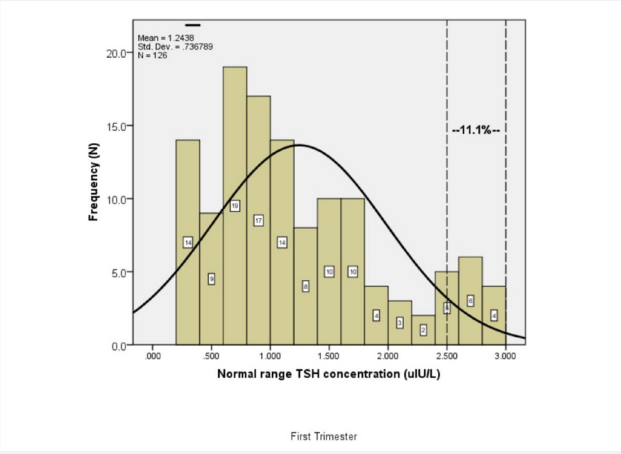

Figure 1. Distribution of serum TSH values within the normal percentile interval (5th-95th percentiles) in the first trimester

TSH: Thyroid-stimulating hormone

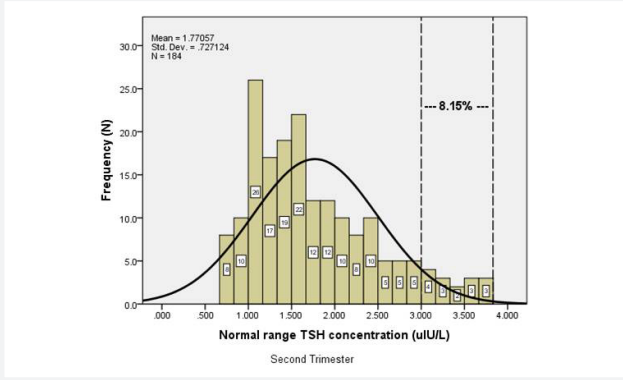

Figure 2. Distribution of serum TSH values within the normal percentile interval (5th-95th percentiles) in the second trimester

TSH: Thyroid-stimulating hormone

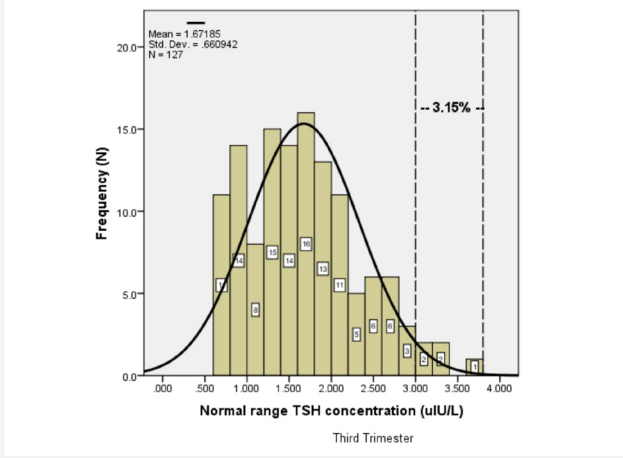

Figure 3. Distribution of serum TSH values within the normal percentile interval (5th-95th percentiles) in the third trimester

TSH: Thyroid-stimulating hormone

women with thyroid autoimmunity were limited and future randomized controlled studies with large sample sizes were needed[2]. In the present study, adjunct to the exclusion of known thyroid disease, anti-TPO negative pregnant women were recruited for the purpose of constituting a qualified reference population.

Overt hyperthyroidism is a rare condition that affects 0.1 to 0.4% of all pregnancies[23]. A suppressed (0.1 mU/L) or undetectable (0.01 mU/L) serum TSH value, as well as a FT4 and/or FT3 (or total T4 and/or total T3) measurement that exceeds the normal range for pregnancy, should be used to diagnose overt hyperthyroidism during pregnancy[10]. For the second and third trimesters, the recommended lower limits for TSH are 0.2 and 0.3 mU/L[10]. In the present study, the lower limits for TSH were above the recommended lower limits; however, it was similar to the other study from Turkey[14]. The TSH and FT4 values were expressed as MoM in this study, this was suggested for interpreting and comparing these values obtained by different assays[3,8]. In a previous study that summarized the reference intervals as MoM values of TSH and FT4 during early pregnancy, the TSH MoM values changed between 0.04-0.44 for the lower limit and 2.34-3.37 MoM for the upper limit, and regarding FT4 MoM values changed between 0.71-0.80 MoM for the lower limit and 1.25-1.60 for the upper limit[3]. The MoM values for TSH and FT4 were within these limits in this study.

Study Limitations

The urinary iodine concentration could not be measured in the present study. The median urinary iodine concentration of the population has been used for iodine sufficiency or deficiency status of reference population[24]. The pregnant women's iodine requirements increase with the increase in renal iodine clearance and with an increase in maternal thyroxine production for being sufficient to mother and fetus particularly at the beginning of pregnancy[3,24]. The urinary iodine concentration was not considered in the studies of Sun and Xia[25], Donovan et al.[26], Akarsu et al.[14], and Bulur et al.[15] and in a study of Kostecka-Matyja et al.[27], pregnant women taking iodine prophylaxis were recruited as a study cohort. In the study of Azizi et al.[28], the urinary iodine level measurement and thyroid ultrasonography evaluation were considered. In the present study, the pregnant women consuming iodized salt and iodine supplementation were recruited for minimizing the possible effect of iodine deficiency.

The other limitations of the current study are that the small number of patients were evaluated with thyroid ultrasonography due to limited facility and technical difficulties, and that the

present study did not last enough to be able to investigate all the maternal and neonatal outcomes of the study population.

CONCLUSION

Accurate diagnosis and management of thyroid disease for pregnant women is crucial for maternal-fetal outcomes. In the current study, trimester and laboratory-specific rational reference ranges for thyroid hormone levels with MoM values for diagnosing thyroid dysfunction were established. Established reference ranges for three trimesters were all higher than the recommended fixed ranges of the 2011 ATA guideline. Well-designed studies including maternal-fetal outcomes should be conducted to create population-based laboratory specific reference limits for pregnant women.

Ethics

Ethics Committee Approval: The University of Health Sciences Turkey, Sancaktepe Şehit Prof. Dr. İlhan Varank Training and Research Hospital Scientific Research Ethics Committee approved the study (decision number:2021/146 date: 21.04.2021).

Informed Consent: Retrospective study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: A.B.T., M.Y., G.T., D.E., D.B., B.D.T., Concept: A.B.T., M.Y., B.D.T., M.A.S., N.T., Design: A.B.T., M.Y., G.T., D.E., B.D.T., M.A.S., N.T., Data Collection or Processing: A.B.T., M.Y., G.T., D.E., D.B., B.D.T., Analysis or Interpretation: A.B.T., M.Y., D.E., D.B., N.T. Literature Search: A.B.T., M.Y., D.E., D.B., M.A.S., Writing: A.B.T., M.Y., M.A.S., N.T.

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REFERENCES

1. Andersen SL, Olsen J, Wu CS, Laurberg P. Low Birth Weight in Children Born to Mothers with Hyperthyroidism and High Birth Weight in Hypothyroidism, whereas Preterm Birth Is Common in Both Conditions: A Danish National Hospital Register Study. Eur Thyroid J. 2013;2:135-44.
2. Ge GM, Leung MTY, Man KKC, Leung WC, Ip P, Li GHY, et al. Maternal Thyroid Dysfunction During Pregnancy and the Risk of Adverse Outcomes in the Offspring: A Systematic Review and Meta-Analysis. J Clin Endocrinol Metab. 2020;105:dgaa555.
3. Medici M, Korevaar TI, Visser WE, Visser TJ, Peeters RP. Thyroid function in pregnancy: what is normal? Clin Chem. 2015;61:704-13.
4. Chan SY, Vasilopoulou E, Kilby MD. The role of the placenta in thyroid hormone delivery to the fetus. Nat Clin Pract Endocrinol Metab. 2009;5:45-54.
5. Korevaar TIM, Medici M, Visser TJ, Peeters RP. Thyroid disease in pregnancy: new insights in diagnosis and clinical management. Nat Rev Endocrinol. 2017;13:610-22.
6. ACOG (The American College of Obstetricians and Gynecologiest). Clinical Management Guidelines for Obstetrician – Gynecologists. Thyroid Disease in Pregnancy. Obstet Gynecol. 2020;135:261-8.
7. Glinoer D. The regulation of thyroid function in pregnancy: pathways of endocrine adaptation from physiology to pathology. Endocr Rev. 1997;18:404-33.
8. Bestwick JP, John R, Maina A, Guaraldo V, Joomun M, Wald NJ, et al. Thyroid stimulating hormone and free thyroxine in pregnancy: expressing concentrations as multiples of the median (MoMs). Clin Chim Acta. 2014;430:33-7.
9. Korevaar TIM. The upper limit for TSH during pregnancy: why we should stop using fixed limits of 2.5 or 3.0 mU/l. Thyroid Res. 2018;11:5.
10. Alexander EK, Pearce EN, Brent GA, Brown RS, Chen H, Dosiou C, et al. 2017 Guidelines of the American Thyroid Association for the Diagnosis and Management of Thyroid Disease During Pregnancy and the Postpartum. Thyroid. 2017;27:315-89.
11. Günkaya OS, Kıyak H, Ekiz A, Gedikbaşı A. Gestational outcomes of thyroid function in the first trimester. Perinat J. 2017;25:121-6.
12. van der Spek AH, Bisschop PH. Universal screening for thyroid disease SHOULD NOT be recommended before and during pregnancy. Best Pract Res Clin Endocrinol Metab. 2020;34:101429.
13. Stagnaro-Green A, Dong A, Stephenson MD. Universal screening for thyroid disease during pregnancy should be performed. Best Pract Res Clin Endocrinol Metab. 2020;34:101320.
14. Akarsu S, Akbiyik F, Karaismailoglu E, Dikmen ZG. Gestation specific reference intervals for thyroid function tests in pregnancy. Clin Chem Lab Med. 2016;54:1377-83.
15. Bulur O, Atak Z, Ertugrul DT, Beyan E, Gunakan E, Karakaya S, et al. Trimester-specific reference intervals of thyroid function tests in Turkish pregnants. Gynecol Endocrinol. 2020;36:413-6.
16. Derakhshan A, Shu H, Broeren MAC, de Poortere RA, Wikström S, Peeters RP, et al. Reference Ranges and Determinants of Thyroid Function During Early Pregnancy: The SELMA Study. J Clin Endocrinol Metab. 2018;103:3548-56.
17. Kumar A, Gupta N, Nath T, Sharma JB, Sharma S. Thyroid function tests in pregnancy. Indian J Med Sci. 2003;57:252-8.
18. Marwaha RK, Chopra S, Gopalakrishnan S, Sharma B, Kanwar RS, Sastry A, et al. Establishment of reference range for thyroid hormones in normal pregnant Indian women. BJOG. 2008;115:602-6.
19. Kurioka H, Takahashi K, Miyazaki K. Maternal thyroid function during pregnancy and puerperal period. Endocr J. 2005;52:587-91.
20. Panesar NS, Li CY, Rogers MS. Reference intervals for thyroid hormones in pregnant Chinese women. Ann Clin Biochem. 2001;38:329-32.
21. Nazarpour S, Ramezani Tehrani F, Simbar M, Tohidi M, Alavi Majd H, Azizi F. Effects of levothyroxine treatment on pregnancy outcomes in pregnant women with autoimmune thyroid disease. Eur J Endocrinol. 2017;176:253-65.
22. Nazarpour S, Ramezani Tehrani F, Simbar M, Tohidi M, Minooee S, Rahmati M, et al. Effects of Levothyroxine on Pregnant Women With Subclinical Hypothyroidism, Negative for Thyroid Peroxidase Antibodies. J Clin Endocrinol Metab. 2018;103:926-35.
23. Krassas GE, Poppe K, Glinoer D. Thyroid function and human reproductive health. Endocr Rev. 2010;31:702-55.
24. Zimmermann MB. Iodine deficiency. Endocr Rev. 2009;30:376-408.
25. Sun R, Xia J. The Reference Intervals of Thyroid Hormones for Pregnant Women in Zhejiang Province. Lab Med. 2017;49:5-10.
26. Donovan LE, Metcalfe A, Chin A, Yamamoto JM, Virtanen H, Johnson JA, Krause R. A Practical Approach for the Verification and Determination of Site- and Trimester-Specific Reference Intervals for Thyroid Function Tests in Pregnancy. Thyroid. 2019;29:412-20.
27. Kostecka-Matyja M, Fedorowicz A, Bar-Andziak E, Bednarczuk T, Buziak-Bereza M, Dumnicka P, et al. Reference Values for TSH and Free Thyroid Hormones in Healthy Pregnant Women in Poland: A Prospective, Multicenter Study. Eur Thyroid J. 2017;6:82-8.
28. Azizi F, Mehran L, Amouzegar A, Delshad H, Tohidi M, Askari S, et al. Establishment of the trimester-specific reference range for free thyroxine index. Thyroid. 2013;23:354-9.