Changes of Thyroid Function Tests in Pregnancy and Contribution of Trimester Specific Reference Ranges to Diagnosis

Tiroid Fonksiyon Testlerinin Gebelikteki Değişimi ve Trimester Spesifik Referans Aralıklarının Tanıya Katkısı

Özlem ÇAKIR MADENCİ,[a]
Nihal YÜCEL,[a]
Lale KÖROĞLU DAĞDELEN,[a]
Gülşen MUTLUOĞLU,[a]
Hasan Emin KAYA,[a]
Asuman ORÇUN[b]

[a]Clinic of Biochemistry Laboratory, Dr. Lütfi Kırdar Kartal Training and Research Hospital, İstanbul
[b]Department of Radiodiagnostic, Konya Necmettin Erbakan University Meram Faculty of Medicine, Konya

Geliş Tarihi/*Received:* 26.09.2014
Kabul Tarihi/*Accepted:* 01.12.2014

This study was presented as a poster with 228 patients in IFCC WorldLab; 22-26 June 2014, İstanbul, Turkey.

Yazışma Adresi/*Correspondence:*
Özlem ÇAKIR MADENCİ
Dr. Lütfi Kırdar Kartal Training and Research Hospital,
Clinic of Biochemistry Laboratory,
İstanbul,
TÜRKİYE/TURKEY
ocmadenci@hotmail.com

ABSTRACT Objective: Non pregnant reference ranges are not appropriate in pregnancy because of the pregnancy associated changes in thyroid physiology. The aim of the study is to determine thyroid hormone status in trimesters of pregnancy and to show the clinical significance of using pregnancy associated values in thyroid stimulating hormone (TSH), free triiodothyronine (fT3) and free thyroxine (fT4) tests. **Material and Methods:** 319 pregnant women followed by the gynaecology and obstetrics clinic of our hospital were prospectively included. All tests were measured by Abbott Architect i400SR analyzer with chemiluminescent microparticle immunoassay (CMIA) method. The results were given as median and 2.5-97.5 percentiles. **Results:** The study population was composed of 319 women with a mean±SD age of 26.8±4.8 years; 96 pregnant were in the 1st trimester (9-13 weeks), 84 in the 2nd trimester (16-20 weeks) and 139 in the 3rd trimester (24-28 weeks). Median (2.5-97.5 percentile) values for TSH were found as 1.062 (0.035-2.955), 1.527 (0.334-2.70) and 1.740 (0.540-4.420) mIU/L for the 1st, 2nd and 3rd trimesters respectively. When using non-pregnant cut-off values, subclinic hypothyroid patients would be misdiagnosed; 2/96 (2.08%), 2/84 (2.38%) and 4/139 (2.87%) in the 1st, 2nd and 3rd trimesters respectively. Pregnant values found in this study were also different from the American Thyroid Association (ATA) recommended cut-off's. Use of ATA cut-off's, (4/96) 4.16% in the 1st; (2/84); 2.38% in the 2nd and (12/139) 8.6% in the 3rd trimester would be misdiagnosed. **Conclusion:** We can conclude that thyroid function test levels can change during pregnancy and laboratory specific reference ranges should be established to avoid misinterpretation for all trimesters.

Key Words: Reference values; pregnancy; thyroid function tests

ÖZET Amaç: Tiroid fizyolojisindeki gebeliğe bağlı değişimlerden dolayı, gebelerde gebelik dışı referans aralıklarının kullanımı uygun değildir. Bu çalışmanın amacı, farklı gebelik trimesterlerinde tiroid hormon durumunu belirlemek ve tiroid stimulan hormon (TSH), serbest triiyodotironin (sT3) ve serbest tiroksin (sT4) testlerinde gebelik ilişkili referans aralığı kullanmanın tanısal önemini belirlemektir. **Gereç ve Yöntemler:** Hastanemizin jinekoloji ve obstetrik kliniğinde izlenen 319 gebe kadın çalışmaya dâhil edildi. Tüm testler Abbott Architect i400SR cihazında, kemiluminesan mikropartikül immunoassay (CMIA) metodu ile çalışıldı. Sonuçlar median ve 2,5-97,5 persentil olarak verildi. **Bulgular:** Çalışma populasyonu yaş ortalama±SS'si 26,8±4,8 yıl olan; 96'sı 1. trimester (9-13 haftalık), 84'ü 2. trimester (16-20 haftalık), 139'u 3. trimester (24-28 haftalık) 319 kadından oluşmaktadır. TSH için median (2,5-97,5 persentil) değerleri 1, 2 ve 3. trimesterler için sırasıyla 1,062 (0,035-2,955), 1.527 (0,334-2,70) ve 1.740 (0,540-4,420) mIU/L bulundu. Gebelik dışı "cut off" (kesim) değerleri kullanıldığında 1, 2 ve 3. trimesterler için sırasıyla 2/96 (%2,08), 2/84 (%2,38) ve 4/139 (%2,87) subklinik hipotiroidi hastası tanınamaz. Bu değerler Amerikan Tiroid Birliği (ATA)'nin önerdiklerinden farklıdır ve ATA kesim noktaları kullanıldığında 1, 2 ve 3. trimesterler için sırasıyla (4/96) %4,16, (2/84) %2,38 ve (12/139) %8,6'sı yanlış tanı alır. **Sonuç:** Tiroid fonksiyon test sonuçları gebelikte değişebilir. Yanlış değerlendirmeyi önlemek için laboratuvar çalışmalarında tüm trimesterler için uygun referans aralıklarının belirlenmesi gerekmektedir.

Anahtar Kelimeler: Referans değerleri; gebelik; tiroid fonksiyon testleri

doi: 10.5336/medsci.2014-41908

Turkiye Klinikleri J Med Sci 2015;35(1):43-8

Optimal thyroid gland function is essential for all stages of life, including pregnancy and fetal development. Sufficient evidence is available showing that thyroid dysfunction during pregnancy can affect not only the maternal outcome but also the neuro physiological development of fetus.[1] Since the reported prevalence of thyroid disorders during pregnancy ranges from 2 to 5% in pregnant women, they should be diagnosed early enough both for maternal and fetal health.[2] Physiological changes in pregnancy, including plasma volume expansion, increased thyroxine-binding globulin (TBG) production and a relative iodine deficiency could affect the function of thyroid gland and interpretation of thyroid function tests.[3]

Serum Human Chorionic Gonadotropin (hCG) concentrations increase soon after fertilization and peak at 10 to 12 weeks. Besides a common alpha subunit, there is also a considerable homology of beta-subunit between hCG and TSH. As a result, hCG has weak thyroid-stimulating activity.[4] In a human thyroid cell-culture assay, 1 microU of hCG was equivalent to 0.0013 microU of TSH.[5] In a report of 63 women with extremely high hCG concentrations (>200,000 IU/L), TSH was <0.2 microU/mL in 67 percent of samples and fT4 was above 1.8 ng/dL in 32 percent of samples. All women whose hCG was greater than 400,000 IU/L had a suppressed TSH concentration.[6] During hCG peak, total serum T4 and T3 concentrations increase with a concordant increase in free forms usually within the normal range causing serum TSH concentrations to decrease.[4] Later in pregnancy, decrease in hCG secretion causes serum free T4 and T3 concentrations decline and serum TSH concentrations reciprocally rise again to the normal range.

According to the latest guidelines of the American Thyroid Association (ATA) for gestational thyroid diseases, if trimester-specific reference ranges for TSH are not available in the laboratory, the recommended reference values are 0.1-2.5 mIU/L in the 1st trimester; 0.2–3.0 mIU/L in the 2nd trimester and 0.3-3.0 mIU/L in the 3rd trimester (level I-USPSTF). Instead it recommends method-specific and trimester-specific reference ranges for fT4 (level B-USPSTF).[7]

The aim of the present study was to show the changes in thyroid hormone levels and contribution of trimester specific reference ranges to diagnosis in pregnant.

MATERIAL AND METHODS

SUBJECTS

Between March 2013 and April 2014 a total of 415 pregnant women attending gynaecology and obstetrics department of our hospital were evaluated cross sectionally. Ninety six pregnants with a thyroid disease or a family history of thyroid disease, abortus of unknown etiology, multiple fetuses, hyperemesis gravidarum, high risk in prenatal screening test, grade 1-2 goiter in thyroid physical examination, high levels of anti-thyroid peroxidase or anti-thyroglobulin were excluded. Remaining 319 women were evaluated for thyroid function tests. Fasting blood specimens were taken BD Vacutainer® SST™ II Advance Blood Collection Tubes (Becton, Dickinson and Company, Franklin Lakes, NJ, USA). Sera were separated and preserved at -20 °C until the date of analysis.

All tests were measured by Abbott Architect i400SR analyser with chemiluminescent microparticle immunoassay (CMIA). Reagent reference numbers were; 6C48 34-1580/R3 for TSH, 6C50 34-3159/R2 for fT3 and 7K62 68-5842/R1 for fT4. The functional sensitivity was presented as <0.01 IU/mL and analytical specificity >90% and recovery as 99.4% of for the TSH assay. The analytical sensitivities of fT3 and fT4 were presented as 1.536 and 5.136 pmol/L respectively. Analytical specificities of both assays were over 90%. We also calculated our laboratory total CVs for 3 assays according to EP15-A protocol and presented external quality control results for accuracy.

Trimester based reference ranges were calculated using MedCalc (Medical Calculation Version 12.4.0; Belgium). The results were given as median and 2.5-97.5 percentiles. Comparison of groups was done by Kruskal Wallis and Mann Whitney U test. Normality of groups were tested by D'Agostino-Pearson test and outliers were detected by Tukey

test. Manufacturer recommended reference ranges were used as non-pregnant values.

Study was approved by our institute's scientific and ethical commitee and the patients signed an informed consent.

RESULTS

Study population consisted of 319 pregnant women with mean±SD ages of 26.8±4.8 years; 96 women were in the 1st trimester (9-13 weeks), 84 in 2nd trimester (16-20 weeks) and 139 in 3rd trimester (24-28 weeks) (min-max). Trimester based distribution of the pregnant women was shown in figure 1. Median (2.5-97.5 percentile) values for TSH were found as 1.062 (0.035-2.955), 1.527 (0.334-2.70) and 1.740 (0.540-4.20) mIU/L; for fT3 5.596 (3.874-6.388), 5.065 (3.840-6.360) and 4.825 (3.08-6.562) pmol/L; for fT4 14.050 (10.644-17.388), 12.945 (9.938-15.220) and 11.7 (5.911-15.50) pmol/L for 1st, 2nd and 3rd trimesters respectively.

Our laboratory total coefficient of variation (CVs) of the methods were, 3.7% for TSH level of 5.41 mlU/L, 3.1% for fT3 level of 6 pmol/L and 3% for fT4 level of 12 pmol/L performed according to EP15-A protocols. Correlation coefficient of regression line analysis vs peer group for fT3, fT4 and TSH were found as 0.987, 0.997 and 0.999 in last cycle of external quality control (EQAS Dec 2013-Dec 2014 Cycle 10 Lot No: 230900) results.

Thyroid hormone levels in trimesters of pregnancy were shown in Table 1. There were significant differences among all trimesters for all parameters (Kruskal Wallis p<0.0001). In nonparametric comparison of two groups; TSH and fT4 showed significant differences between any two

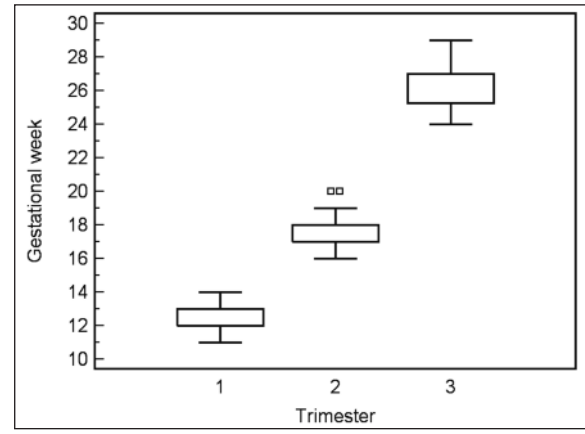

FIGURE 1: Trimester based distribution of the pregnant women.

trimesters. For fT3, there was no significant difference between 1st and 2nd trimesters although significant difference was observed between 2nd and 3rd and 1st and 3rd trimesters (Table 2). Ranges of all trimesters were also significantly different from non-pregnant values except for 1st trimester fT4.

Using non-pregnant cut-offs, a total of 8/319 (2.5%) subclinic hypothyroid pregnant 2/96 (2.08%), 2/84 (2.38%) and 4/139 (2.87%) in the 1st, 2nd and the 3rd trimesters respectively would be misdiagnosed. By ATA cut-off's, a total of 18 (5.64%) subclinic hypothyroidic pregnant; 4/96 (4.16%), 2/84 (2.38%) and 12/139 (8.6%) in the 1st, 2nd and the 3rd trimesters respectively would be misdiagnosed.

DISCUSSION

During the 1st trimester, hCG induces a transient increase in fT4 levels, which is followed by a decrease in TSH concentrations. Following this period, serum fT4 concentrations decrease as ~10-15%, and serum TSH values progressively in-

TABLE 1: Thyroid hormone levels in trimesters of pregnant and non-pregnant women.

Variable	Non-pregnant	1st trimester	2nd Trimester	3rd Trimester
Gestational Week (min-max)		9-13 week	16-20 week	24-28 week
No. subjects	549	96	84	139
TSH (mIU/L)	(0.35-4.94)	(0.035-2.955)	(0.334-2.70)	(0.540-4.20)
fT3 (pmol/L)	(2.6-5.7)	(3.874-6.388)	(3.840-6.360)	(3.08-6.562)
fT4 (pmol/L)	(9.0-19.04)	(10.644-17.388)	(9.938-15.220)	(5.911-15.50)

Results are presented as 2.5-97.5 percentiles.

TABLE 2: Comparison of thyroid hormone levels in trimesters of pregnants.

Variables	1st trimester	2nd Trimester	3rd Trimester	Significance (p)		
Gestational week (min-max)	9-13 week	16-20 week	24-28 week	Multiple group comparison	Comparison of two groups	
No. subjects	96	84	139			
TSH (mIU/L)	1.062	1.527	1.740	<0.0001	I-II	0.2494
					I-III	0.0002
					II-III	0.0106
fT3 (pmol/L)	5.596	5.065	4.825	0.001	I-II	<0.0001
					I-III	<0.0001
					II-III	0.0001
fT4 (pmol/L)	14.050	12.945	11.7	<0.0001	I-II	0.0080
					I-III	<0.0001
					II-III	0.0003

Results were presented as median.

crease and finally reach non-pregnant values at the end of pregnancy. Also starting at early gestation, there is a marked increase in serum TBG concentrations, which peak around midgestation and are maintained thereafter. This event, in turn is responsible for a significant rise in total T4 and T3. Thus, both free thyroid hormone and TSH reference ranges change throughout pregnancy, method and gestation-specific reference ranges are strongly recommended for interpreting thyroid functions in pregnancy.[8] Our results showed similar variations in thyroid hormone status in pregnant women (Figure 2 a, b and c shows TSH, fT3 and fT4 levels during pregnancy). Only the first trimester increase mentioned in thyroxine levels wasn't seen in fT4. This is mostly because our study didn't consist of pregnant in early weeks of gestation. The smallest gestational age was 9 weeks in the first trimester and probably the mentioned fT4 peak took place before and we couldn't demonstrate it.

Almost all studies agreed on decrease of TSH levels in pregnancy compared to non pregnants; but some had conflicting results about free hormones.[9-11] Direct fT4 measurements were said to be unreliable during pregnancy. Measurement of fT4 in the dialysate or ultrafiltrate of serum samples using liquid chromatography/tandem mass spectrometry appears to be the most reliable method and when this is used, fT4 concentrations were shown to decrease gradually with advancing gestational age, particularly between the 1st and 2nd trimester.[12,13] This assay is relatively expensive and not universally available. Routine fT4 assays (and probably fT3 assays) frequently fail to meet performance standards in pregnant women, owing to increases in TBG and decreases in albumin concentrations that cause the immunoassay to be unreliable.[10] To compensate, some kits have provided different fT4 normal ranges for pregnant patients. Thus ATA says method and trimester-specific reference ranges of serum fT4

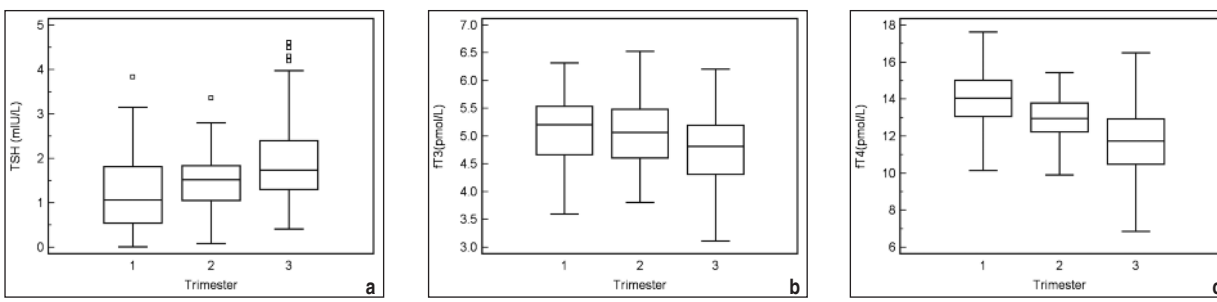

FIGURE 2: a) TSH levels during pregnancy, **b)** fT3 levels during pregnancy, **c)** fT4 levels during pregnancy.

TABLE 3: Reference Ranges from different populations with different measurement methods.

		1st trimester			2nd trimester			3rd trimester		
Study	**Method**	**fT4**	**fT3**	**TSH**	**fT4**	**fT3**	**TSH**	**fT4**	**fT3**	**TSH**
2008 India[1]	ECLIA Elecys 1010, Roche Diagnostics	12-19.45	1.92-5.86	0.6-5	9.48-19.58	3.2-5.73	0.44-5.78	11.32-17.7	3.3-5.18	0.74-5.7
2014 Turkey[11]	LEIA Access, Beckman Coulter Unicel DXI	10.8-21.08	3.17-6.75	0.043-3.968	-	-	-	-	-	
2008 Italy[17]	RIA (fT4), IRMA (TSH)	11.9-20.8	-	0.03-2.3	10.4-18.7	-	0.29-2.8	10.3-16.4	-	0.34-3.0
2014 India[18]	ELISA	8.24-25.74	-	0.25-3.35	6.82-27.28	-	0.78-4.96	8.24-25.48	-	0.89-4.6
2014 Ireland[19]	ECLIA Modular E170, Roche Diagnostics	12.1-18.7	3.8-6.3	0.1-3	10.4-17.1	3.6-5.7	0.2-3.2	9-15.7	3.4-5.3	0.3-3.4
2013 Chinese[20]	CMIA Architect I 2000, Abbott	11.49-18.84	-	0.03-3.6	10.02-14.19	-	0.54-3.26	9.63-17.94	-	0.61-5.54
	ECLIA Cobas Elecsys 600, Roche Diagnostics	12.9-22.35	-	0.05-5.17	9.74-14.19	-	0.77-4.23	8.96-14.82	-	0.97-7.58
2013 Iran[21]*	IRMA			0.2-3.9			0.5-4.1			0.6-4.1
Our study	CMIA Architect i400SR, Abbott	10.64-17.38	3.87-6.38	0.035-2.955	9.93-15.22	3.84-6.36	0.33-2.70	5.91-15.50	3.08-6.56	0.54-4.20

*The reference intervals were calculated as 5th and 95th percentiles.

fT3 and fT4 values were represented as pmol/L and TSH as mIU/L.

ECLIA: Electrochemiluminescence immunoassay; ELISA: Enzyme-linked immunosorbent assay; IRMA: Immunoradiometric assay, LEIA: Luminescence immunoassay; CMIA: Chemiluminescent microparticle immunoassay.

should be established (level B-USPSTF).[7] Instead, for TSH, if trimester-specific reference ranges are not available in the laboratory, it recommends reference ranges of 0.1-2.5 mIU/L for the 1st trimester 0.2-3.0 mIU/L for the 2nd trimester and 0.3-3.0 mIU/L for the 3rd trimester (level I-USPSTF).

Pregnant in this study had a 97.5 percentile of 2.955, 2.70 and 4.2 mIU/L for the 1st, 2nd and the 3rd trimesters respectively for TSH. Our study showed that using non-pregnant cut offs, a total of 8/319 (2.5%) subclinic hypothyroidic pregnant would be misdiagnosed. These values were also all different from the ATA recommended cut-off's. If we used ATA cut-off's, a total of 18 (5.64%) subclinical hypothyroid pregnant would be misdiagnosed.

There were several studies examining thyroid function in pregnancy which reported different reference ranges for fT3, fT4 and TSH in several countries. Table 3 shows some reference values from different populations with different measurement methods. There are many factors that contribute to this variation. Thyroid test levels are affected from the large variability in race, culture, diet, iodine status and environment.[14] Also different analytical systems produce significantly different results.[15] There are no available trimester based reference ranges of thyroid hormones including all trimesters in Turkish pregnant women. Only one established ranges for only first trimester pregnancy.[16] In this study distribution of pregnant had a discrete scale rather than a continuous one. Therefore we could not represent our data as reference ranges of trimesters, instead we presented monthly intervals of all trimesters. This was the limitation of our study. Nevertheless this seems to be the first study providing trimester based thyroid hormone levels in Turkish pregnant women living in İstanbul and can be useful from the clinical point of view. Statistical significance among trimester specific thyroid hormone levels in pregnancy does not contribute any significance to clinical decision because of overlapping values. The more important aspect is the difference of cut-off levels between pregnant and non-pregnant that is used as clinical decision point especially for TSH that is on the primary step of screening and diagnosis.

In conclusion, although thyroid hormone pattern of pregnant women have been clearly demonstrated, differences in assays used, ethnicity, geographical location and iodine status may influence the reference ranges produced. Therefore, laboratory specific ranges must be used for accurate diagnosis and management of thyroid disorders in pregnancy.

REFERENCES

1. 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(5):602-6.
2. Allan WC, Haddow JE, Palomaki GE, Williams JR, Mitchell ML, Hermos RJ, et al. Maternal thyroid deficiency and pregnancy complications: implications for population screening. J Med Screen 2000;7(3):127-30.
3. Cotzias C, Wong SJ, Taylor E, Seed P, Girling J. A study to establish gestation-specific reference intervals for thyroid function tests in normal singleton pregnancy. Eur J Obstet Gynecol Reprod Biol 2008;137(1):61-6.
4. Ballabio M, Poshychinda M, Ekins RP. Pregnancy-induced changes in thyroid function: role of human chorionic gonadotropin as putative regulator of maternal thyroid. J Clin Endocrinol Metab 1991;73(4):824-31.
5. Yamazaki K, Sato K, Shizume K, Kanaji Y, Ito Y, Obara T, et al. Potent thyrotropic activity of human chorionic gonadotropin variants in terms of 125I incorporation and de novo synthesized thyroid hormone release in human thyroid follicles. J Clin Endocrinol Metab 1995;80(2):473-9.
6. Lockwood CM, Grenache DG, Gronowski AM. Serum human chorionic gonadotropin concentrations greater than 400,000 IU/L are invariably associated with suppressed serum thyrotropin concentrations. Thyroid 2009;19 (8):863-8.
7. Stagnaro-Green A, Abalovich M, Alexander E, Azizi F, Mestman J, Negro R, et al. Guidelines of the American Thyroid Association for the diagnosis and management of thyroid disease during pregnancy and postpartum. Thyroid 2011;21(10):1081-125.
8. Moleti M, Trimarchi F, Vermiglio F. Thyroid physiology in pregnancy. Endocr Pract 2014;20(6):589-96.
9. Glinoer D. The regulation of thyroid function in pregnancy: pathways of endocrine adaptation from physiology to pathology. Endocr Rev 1997;18(3):404-33.
10. Lee RH, Spencer CA, Mestman JH, Miller EA, Petrovic I, Braverman LE, et al. Free T4 immunoassays are flawed during pregnancy. Am J Obstet Gynecol 2009;200(3): 260.e1-6.
11. Soldin OP, Tractenberg RE, Hollowell JG, Jonklaas J, Janicic N, Soldin SJ. Trimester-specific changes in maternal thyroid hormone, thyrotropin, and thyroglobulin concentrations during gestation: trends and associations across trimesters in iodine sufficiency. Thyroid 2004;14(12):1084-90.
12. Kahric-Janicic N, Soldin SJ, Soldin OP, West T, Gu J, Jonklaas J. Tandem mass spectrometry improves the accuracy of free thyroxine measurements during pregnancy. Thyroid 2007;17(4):303-11.
13. Yue B, Rockwood AL, Sandrock T, La'ulu SL, Kushnir MM, Meikle AW. Free thyroid hormones in serum by direct equilibrium dialysis and online solid-phase extraction--liquid chromatography/tandem mass spectrometry. Clin Chem 2008;54(4):642-51.
14. Zhang GQ, Sang ZN, Liu H, Zhang SF, Wei W, Zhao N, et al. [Study on the iodine status of pregnant women and thyroid function of neonate in high iodine area]. Zhonghua Yu Fang Yi Xue Za Zhi 2012;46 (3):225-7.
15. Springer D, Bartos V, Zima T. Reference intervals for thyroid markers in early pregnancy determined by 7 different analytical systems. Scand J Clin Lab Invest 2014;74(2):95-101.
16. Aytan H, Aytan P, Demirtürk F, Çalışkan AC, Şahin Ş, Erdoğan F, et al. First-trimester thyroid hormone reference data in a Turkish pregnant women population living in Middle Blacksea Region. Nobel Medicus 2014;10(1): 25-9.
17. Moleti M, Lo Presti VP, Campolo MC, Mattina F, Galletti M, Mandolfino M, et al. Iodine prophylaxis using iodized salt and risk of maternal thyroid failure in conditions of mild iodine deficiency. J Clin Endocrinol Metab 2008;93(7): 2616-21.
18. Maji R, Nath S, Lahiri S, Saha Das M, Bhattacharyya AR, Das HN. Establishment of Trimester-Specific Reference Intervals of Serum TSH & fT4 in a Pregnant Indian Population at North Kolkata. Indian J Clin Biochem 2014;29(2):167-73.
19. Khalid AS, Marchocki Z, Hayes K, Lutomski JE, Joyce C, Stapleton M, et al. Establishment of Trimester-Specific Reference Intervals of Serum TSH & fT4 in a Pregnant Indian Population at North Kolkata. Indian J Clin Biochem 2014;29(2):167-73.
20. Fan JX, Han M, Tao J, Luo J, Song MF, Yang S, et al. Reference intervals for common thyroid function tests, during different stages of pregnancy in Chinese women. Chin Med J (Engl) 2013;126(14):2710-4.
21. Mehran L, Amouzegar A, Delshad H, Askari S, Hedayati M, Amirshekari G, et al. Trimester-specific reference ranges for thyroid hormones in Iranian pregnant women. J Thyroid Res 2013;2013:651517 doi: 10.1155/ 2013/651517.