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Sonographic evaluation of normal thyroid volume and thyroid isthmus depth among infants in the west coast of Turkey

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Abstract

Introduction: The reference values for thyroid volume (TV) suggested by the WHO are recommended for children aged 6 to 12 years and cannot be considered relevant for infants. The present study aimed to establish the normal values for TV and thyroid isthmus depth (TID) in infants aged between 1 and 12 months from the west coast of Turkey.

Material and methods: TV and TID were measured in 223 infants by a validated ultrasound technique. TV was determined by the method of Brunn et al. and Brown et al. The 3rd, 25th, 50th, 75th, and 97th percentiles of the TV and TID according to age were produced. The TV and TID measurements were compared with infants' age, gender, and standard deviation (Z) scores for weight, height, and BMI.

Results: The median (IQR) values for TV were 0.77 (0.61–1.00) and 0.84 (0.67–1.10) mL, calculated according to the formula of Brunn et al. and Brown et al., respectively. The TV was significantly associated with age, and Z scores for weight, height, and body mass index (BMI) ($r = 0.366$, $p < 0.001$; $r = 0.343$, $p < 0.0001$; $r = 0.269$, $p < 0.0001$; and $r = 0.157$, $p = 0.019$, respectively). The median (IQR) value for the TID was 1.5 (1.3–1.9) mm. The TID was significantly correlated with TV and the Z score for height ($r = 0.190$, $p = 0.004$; and $r = 0.144$, $p = 0.032$, respectively). In multivariable regression, the only independent predictor for TV was the Z score for BMI. No differences based on gender were found.

Conclusions: This is the first study to report the normative values for TV and TID in healthy Turkish infants aged up to 12 months. Our findings may serve as a basis for developing national and international references for TV and TID in infants. **(Endokrynol Pol 2022; 73 (2): 325–329)**

Key words: *thyroid volume; thyroid isthmus; Turkey; infant; ultrasonography*

Introduction

Congenital hypothyroidism (CH) is the leading cause of intellectual impairment in children, with a reported incidence of 1 in 3000 to 4500 live births worldwide [1, 2]. While early diagnosis is successfully achieved through neonatal screening programs, thyroid ultrasonography (US), increasingly used for its lack of exposure to ionizing radiation and portability, is essential in determining the aetiology of the CH [3]. In permanent CH, the thyroid gland may be small due to hypoplasia or hemiagenesis, absent due to agenesis or ectopia, and normal-sized or enlarged due to dyshormonogenesis [4]. Infants with transient CH due to prematurity, congenital malformations, or iodine deficiency may have a normal-sized or enlarged eutopic thyroid gland [1, 4]. Thus, proper diagnosis, treatment, and monitoring of infants with CH depend on the presence of relevant references for thyroid volume (TV). The reference values for TV proposed by the WHO are recommended for children aged 6 to 12 years and cannot be considered appropriate for infants [5]. As far as we are aware, no data currently exist regarding TV and thyroid isthmus depth (TID) for Turkish infants. Moreover, the successful implementation of the iodine supplementation programs in our country has prompted the need for new normative data. Therefore, the aim of the present study was to establish the normative values for TV and TID in healthy infants aged up to 12 months from the west coast of Turkey.

Material and methods

The study protocol was approved by the ethical review board of the University of Health Sciences Dr. Behçet Uz Child Disease and Paediatric Surgery Training and Research Hospital (date: 24.06.2021, ethics approval number: 2021/11-21). The principles of the Declaration of Helsinki were followed. A descriptive and cross-sectional study design was used. The US measurements of the thyroid gland were performed in 348 infants between October 2018 and February 2021. The criteria for exclusion were preterm

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delivery (n = 15); neonates (n = 32); children over 12 months of age; body weights and lengths outside the age-specific cut-offs for Turkish infants (n = 16) [6, 7]; thyroid agenesis and hemiagenesis (n = 6); thyroid parenchymal disease (n = 4); major congenital or chromosomal anomalies (n = 12); abnormal thyroid function parameters (TSH or FT4) (n = 16); and suboptimal image quality due to head movements (n = 24). A total of 223 infants with normal serum thyroid-stimulating hormone (TSH) and free thyroxine (FT4) levels were enrolled in the study analysis.

An Aplio 500 ultrasound machine (Toshiba Medical System, Otawara, Japan) equipped with high-frequency probes (5–15 MHz) was used for the thyroid gland evaluation. The infants were investigated in the supine position with the head slightly extended and turned opposite to the exploratory side. The thyroid gland was scanned in both the transverse and longitudinal sections. The size assessment of the thyroid gland was based on the three measurements of each thyroid lobe. The maximum width of the thyroid lobe was measured on a transverse image. The maximum depth was obtained perpendicular to the width. The maximum length was recorded from the longitudinal views. The volume (mL) of each thyroid lobe was determined by the method of Brown et al. (TV = 0.524 × width × depth × length) [8] and Brunn et al. (TV = 0.479 × width × depth × length) [9]. The total TV was estimated as the sum of both lobe volumes. The thyroid isthmus was not considered in the calculation of the TV. The maximum thyroid isthmus depth (TID) was measured on a transverse image at its thickest part. All the measurements were obtained by a European Society of Radiology board-certified radiologist.

The infants' age, gender, weight, and height were extracted from the medical files. Body mass index (BMI) was computed as weight in kilograms divided by height squared in metres. Since weight, height, and BMI are age- and gender-related, the standard deviation (Z) scores were calculated according to Turkish paediatric reference values [6, 7].

Statistical analysis

The normality of data distribution was checked with the Skewness-Kurtosis and Kolmogorov-Smirnov tests. Because the data were skewed, group differences were compared using the non-parametric Mann-Whitney and Kruskal-Wallis tests. Quantitative variables were expressed as median (interquartile range [IQR]). After a logarithmic transformation of the data with positive skewness, a multivariate stepwise regression model was conducted to determine the independent predictors of the TV and TID. Qualitative variables were summarised as percentages and compared by the chi-square test. The significance of correlations was obtained by Spearman's rank correlation tests. Statistical analyses were done using SPSS software version 20.0 (SPSS Inc., Chicago, IL, USA). P-values of ≤ 0.05 and ≤ 0.001 were accepted as statistically significant and highly significant, respectively.

Results

The present study evaluated 223 healthy infants (58.7% boys and 41.3% girls) aged 1 to 12 months (mean age ± SD, 5.05 ± 3.72 months) in University Hospital in Izmir, Turkey. Infants were subdivided into six groups according to their postnatal age: 1–2 months (n = 78; 42 males and 36 females); 3–4 months (n = 40; 24 males and 16 females); 5–6 months (n = 24; 18 males and 6 females); 7–8 months (n = 28; 17 males and 11 females); 9–10 months (n = 24; 15 males and 9 females); and 11–12 months (n = 29; 15 males and 14 females).

The weight, height, and BMI of the study group were within the normal ranges according to Turkish criteria. The median Z scores for weight, height, and BMI for infants included in our study were –0.01 (IQR: –0.81–0.79), –0.16 (IQR: –0.91–1.01), and –0.02 (IQR: –0.61–0.60), respectively.

The median (IQR) values for the depth, width, and length were 6.50 (6.00–7.50), 7.90 (7.10–8.80), and 16.80 (15.00–18.70) mm for the right thyroid lobe, respectively, and 6.20 (5.80–7.00), 7.50 (7.00–8.30), and 16.10 (14.30–17.60) mm for the left lobe, respectively.

Using the formula of Brunn et al. and Brown et al. the median (IQR) volumes were 0.40 (0.31–0.55) and 0.43 (0.34–0.60) mL for the right lobe, respectively; 0.37 (0.27–0.47) and 0.41 (0.29–0.51) mL for the left lobe, respectively; and 0.77 (0.61–1.00) and 0.84 (0.67–1.10) mL for both lobes, respectively. The sonographic measurements of the thyroid lobes and TV in infants of different age groups are shown in Table 1.

The TV was slightly higher in boys; however, these changes did not reach the significance level (0.77 *vs.* 0.72, p = 0.985). The TV increased gradually with the age of the study group (r = 0.366, p < 0.001). The 3rd, 25th, 50th, 75th, and 97th percentiles of the TV according to age are presented in Figure 1.

There were significant positive correlations of Z scores for weight, height, and BMI with the TV of the infants (r = 0.343, p < 0.0001; r = 0.269, p < 0.0001; and r = 0.157, p = 0.019; respectively). The results of the multivariate regression analysis revealed that the Z score for BMI was the only independent predictor of the logarithmic value of the TV [F (1, 18) = 7.004, p = 0.016, R^2 = 0.280]. The correlations of the age and Z scores for BMI with the TV of the infants are shown in Figure 2.

The median (IQR) value for the TID was 1.5 (1.3–1.9) mm. Although not statistically significant, the 75th percentile of the TID was slightly higher in boys compared to girls (2.0 *vs.* 1.8, p = 0.176). The median values for the TID in infants of different age groups are described in Table 1.

The TID was positively correlated with TV and Z score for height (r = 0.190, p = 0.004; and r = 0.144, p = 0.032; respectively), but not correlated with age, and Z scores for weight and BMI (r = 0.122, p = 0.069; r = 0.110, p = 0.102; and r = –0.017, p = 0.796; respectively). The TV was the only significant independent predictor of the logarithmic value of the TID in the multivariable regression model [F (1, 45) = 5.561, p = 0.023, R^2 = 0.110]. A comparison of the TID in infants of different ages is presented in Figure 3.

Discussion

Thyroid US is an initial imaging tool for investigating paediatric patients with suspected CH. It provides valuable information for the presence, size, and parenchy-

Table 1. *The sonographic measurements of the thyroid gland in infants according to age*

Age [months]	Right thyroid lobe [mm]			Left thyroid lobe [mm]			Thyroid isthmus [mm]	Total thyroid volume (Brunn et al.) [mL]	Total thyroid volume (Brown et al.) [mL]
	Depth	Width	Length	Depth	Width	Length	Depth		
1–2	6.5 (5.7–7.0)	7.9 (7.0–8.6)	14.5 (12.7–16.3)	6.0 (5.5–7.0)	7.1 (6.5–8.3)	14.2 (12.3–15.6)	1.5 (1.2–1.8)	0.66 (0.51–0.82)	0.72 (0.56–0.89)
3–4	6.5 (6.2–7.0)	7.7 (7.2–8.1)	16.4 (15.0–17.5)	6.0 (5.5–7.0)	7.1 (7.0–8.0)	15.6 (14.1–17.3)	1.6 (1.4–2.0)	0.68 (0.60–0.92)	0.74 (0.66–1.00)
5–6	6.4 (6.0–7.9)	7.2 (6.9–8.9)	17.3 (16.2–19.4)	7.0 (5.9–7.1)	7.5 (7.1–8.0)	16.9 (15.9–18.9)	1.6 (1.4–1.7)	0.80 (0.62–1.02)	0.88 (0.68–1.12)
7–8	6.5 (6.3–7.2)	7.9 (7.1–8.7)	18.4 (17.6–19.4)	6.1 (5.9–6.9)	7.5 (7.0–8.0)	17.5 (17.0–18.5)	1.4 (1.2–1.7)	0.88 (0.68–1.03)	0.96 (0.74–1.12)
9–10	7.00 (6.4–7.9)	7.9 (7.2–9.1)	19.1 (17.6–21.1)	6.5 (6.1–7.4)	8.0 (7.0–9.4)	18.1 (17.1–19.8)	1.7 (1.2–2.0)	0.89 (0.80–1.26)	0.97 (0.88–1.37)
11–12	7.8 (6.3–8.3)	8.4 (7.4–9.5)	18.0 (16.5–20.6)	7.0 (6.2–7.5)	7.5 (7.1–8.4)	16.8 (15.8–18.7)	1.7 (1.5–2.0)	1.11 (0.69–1.28)	1.21 (0.75–1.40)

Data are presented as median (interquartile range [IQR])

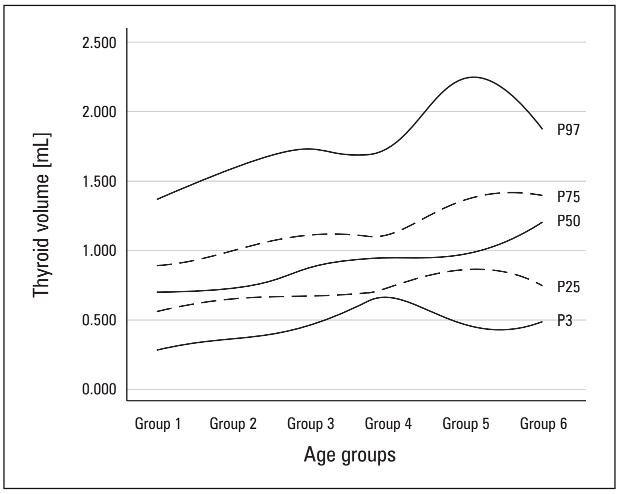

Figure 1. *Comparison of the 3rd, 25th, 50th, 75th, and 97th percentiles (P) of the thyroid volume in infants of different ages*

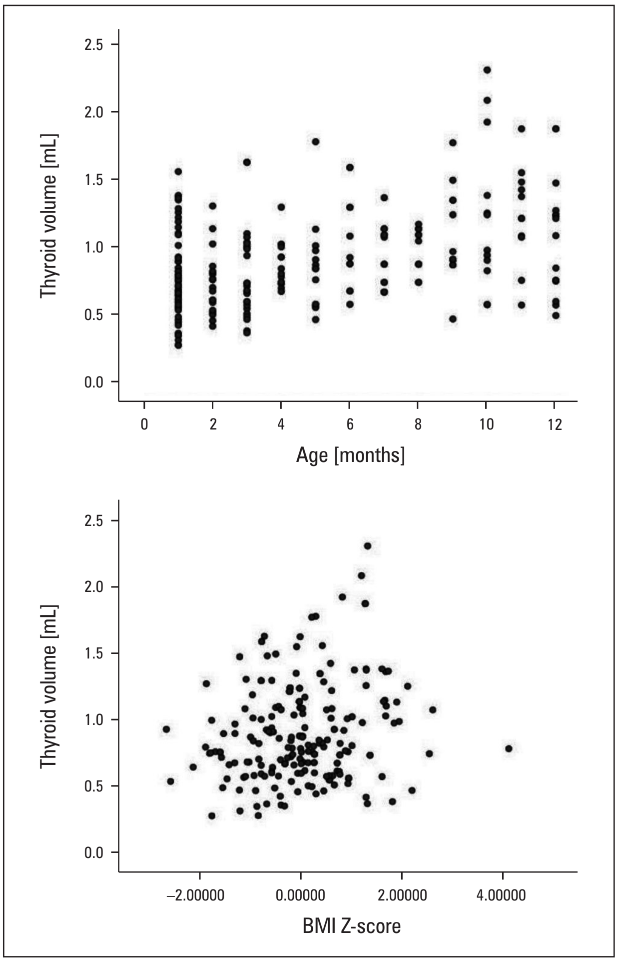

Figure 2. *Association of the age and Z scores for body mass index (BMI) with the thyroid volume of all infants included in the study*

mal echogenicity of the thyroid gland [1, 3]. Determining if the thyroid gland as small, normal, or enlarged is important for proper diagnosis, treatment decision, and prognosis of patients with CH [1, 10]. The normative values for the TV in infants have been strongly influenced by the geographical location, nutritional status of iodine during pregnancy, and ethnic and genetic factors. A recent study by Vural et al. reported a prevalence of iodine deficiency of 74% among pregnant women and 51% among newborns in Turkey. In the western part of Turkey, the median (IQR) urinary iodine concentration was 83 (49–134) μg/L indicating moderate iodine deficiency among pregnant women and 93 (34–172) μg/L indicating mild iodine deficiency among newborns [11]. Therefore, the WHO/ICCIDD underlines the importance of obtaining normative data for TV on national and regional levels [5, 12]. Current

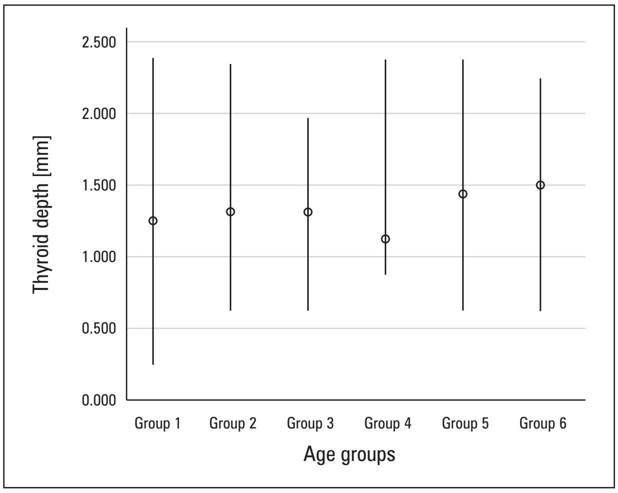

Figure 3. *Comparison of the 3rd, 50th, and 97th percentiles of the thyroid isthmus depth in infants of different ages*

data for infants have been based on a limited number of studies with variable age ranges [13, 14]. Moreover, no study to date has reported the normal values for the TV among Turkish infants from different age groups. In the present study, we have attempted to fill the gap in knowledge of the normative data for TV and TID in healthy infants aged up to 12 months from the west coast of Turkey. Current results were also compared with previously published data.

While the importance of establishing reference ranges for TV is a worldwide trend, it is striking that limited data are available for infants up to 1 year of age. Yao et al. measured the TV by US in 408 healthy Chinese infants in the age range of 0–12 months [13]. The median values for TV in our infants aged 1 to 10 months were more than 10% lower than those found in Chinese infants. The TV in infants aged 11–12 months was similar to the values reported for Chinese infants. The discrepancy between the results is probably due to the differences in geographical location, dietary iodine intake, and race.

A recent study by Prabhu et al. calculated the TV in 157 Indian neonates and infants under 18 months of age [14]. The median values for TV in Indian infants aged 1 to 12 months were approximately 70% lower than those measured in our infants. A lesser volume in Indian infants might be related to the ethnic factor of lower BMI of the Indian population because BMI is the most important predictor deciding the TV.

According to Klingmuller et al., the TV values of German infants aged 1 to 12 months were between 0.30 and 1.70 cm^3 [15]. The TV in our infants ranged between 0.67 and 1.10 mL. Studies from iodine-deficient regions suggested that children of mothers with inadequate iodine intake during pregnancy had higher TV than those from iodine-sufficient areas [16]. The higher lower limits of TV values in our infants proposed that iodine deficiency is still a public health problem in our country. The TV might be also affected by maternal smoking before and during pregnancy. Barrere et al. reported a nearly 25% higher TV in smokers compared to non-smokers [17]. The higher TV measurements might be explained in part by the rising prevalence of smoking in young women in the west of Turkey. A seasonal variation was reported as well with nearly 20% higher TV values during the winter months [18].

Studies covering a wide age range (0–18 years) of children have reported the TV measurements from different regions of Turkey. The mean TV measurements in 0- to 1-year-old infants from Central Anatolia [19], Marmara [20], and the Aegean region [21] of Turkey were 1.8 ± 0.7, 0.81 ± 0.28, and 0.81 cm^3, respectively. These studies were based on small sample sizes, ranging from 19 to 23 infants, and hence should be interpreted with caution. Nonetheless, our results were 50% lower than those found in Central Anatolia [19] and similar to those found in Marmara [20] and the Aegean region [21] of Turkey. These results confirmed that the dietary iodine intake varies not only across countries but also across geographical regions in the same country.

The TV was significantly associated with Z scores for weight and height, which is consistent with the results reported by Yao et al. [13]. Moreover, we found that the Z score for BMI was the only independent predictor of the TV. No gender differences were found in either of the previous studies as well as this study [13, 14]. This might be because the body surface area in infants is not significantly different between boys and girls.

Comparison of our TID measurements was limited by the lack of generally accepted reference values. To date, only Yao et al. have reported the TID by US in Chinese infants [13]. The median values for TID in our infants aged between 1 and 10 months were nearly 10% higher than those reported in Chinese infants. The slight differences observed might be attributed to the dietary iodine intake, ethnic, and geographical factors.

The limitations of our study deserve a mention. This was a single-centre study with a relatively small sample size in each age group. Data regarding urinary iodine excretions were not collected. However, the infants included in our study had normal TSH levels on newborn screening with repeated normal serum TSH and FT4 values. TSH is a preferred biomarker for the evaluation of potential CH. Information on maternal smoking, nutritional, and iodine status during pregnancy were not available. Finally, we noticed a lack of studies and consensus regarding reference values for TV and TID in infants; therefore, further studies with larger samples are needed to interpret our results appropriately.

Conclusions

This is the first study to report the normative values for TV and TID in healthy infants aged up to 12 months from the west coast of Turkey. The wide variation in the TV and TID measurements between countries is largely attributable to differences in geographical location, demographic status, and racial and environmental factors, which underlines the importance of establishing normative data for infants on a regional and national level.

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Author contributions

All authors have accepted responsibility for the entire content of this manuscript and approved its submission.

Competing interests

The authors state no conflict of interest.

References

1. Kiess W, Penke M, Gesing J, et al. Congenital hypothyroidism. J Pediatr Endocrinol Metab. 2018; 31(6): 595–596, doi: 10.1515/jpem-2018-0197, indexed in Pubmed: 29804102.
2. Kor Y, Kor D. Current status of the congenital hypothyroidism neonatal screening program in Adana Province, Turkey. J Pediatr Endocrinol Metab. 2018; 31(6): 619–624, doi: 10.1515/jpem-2017-0433, indexed in Pubmed: 29750648.
3. Livett T, LaFranchi S. Imaging in congenital hypothyroidism. Curr Opin Pediatr. 2019; 31(4): 555–561, doi: 10.1097/MOP.0000000000000782, indexed in Pubmed: 31145126.
4. Kara C, Günindi F, Can Yılmaz G, et al. Transient Congenital Hypothyroidism in Turkey: An Analysis on Frequency and Natural Course. J Clin Res Pediatr Endocrinol. 2016; 8(2): 170–179, doi: 10.4274/jcrpe.2345, indexed in Pubmed: 27086592.
5. Zimmermann MB, Hess SY, Molinari L, et al. New reference values for thyroid volume by ultrasound in iodine-sufficient schoolchildren: a World Health Organization/Nutrition for Health and Development Iodine Deficiency Study Group Report. Am J Clin Nutr. 2004; 79(2): 231–237, doi: 10.1093/ajcn/79.2.231, indexed in Pubmed: 14749228.
6. Demir K, Özen S, Konakçı E, et al. A Comprehensive Online Calculator for Pediatric Endocrinologists: ÇEDD Çözüm/TPEDS Metrics. J Clin Res Pediatr Endocrinol. 2017; 9(2): 182–184, doi: 10.4274/jcrpe.4526, indexed in Pubmed: 28443820.
7. Neyzi O, Bundak R, Gökçay G, et al. Reference Values for Weight, Height, Head Circumference, and Body Mass Index in Turkish Children. J Clin Res Pediatr Endocrinol. 2015; 7(4): 280–293, doi: 10.4274/jcrpe.2183, indexed in Pubmed: 26777039.
8. Brown MC, Spencer R. Thyroid gland volume estimated by use of ultrasound in addition to scintigraphy. Acta Radiol Oncol Radiat Phys Biol. 1978; 17(4): 337–341, doi: 10.3109/02841867809127937, indexed in Pubmed: 717046.
9. Brunn J, Block U, Ruf G, et al. [Volumetric analysis of thyroid lobes by real-time ultrasound (author's transl)]. Dtsch Med Wochenschr. 1981; 106(41): 1338–1340, doi: 10.1055/s-2008-1070506, indexed in Pubmed: 7274082.
10. Ramo Akgün N. Assistive Technology for Children with Intellectual Disabilities. In: İşcan A, Baskın S. ed. Recent Studies of Education in Various Occasions. Lambert Academic Publishing, Mauritius: 26–51.
11. Vural M, Koc E, Evliyaoglu O, et al. Turkish Iodine Survey Group. Iodine status of Turkish pregnant women and their offspring: A national cross-sectional survey. J Trace Elem Med Biol. 2021; 63: 126664, doi: 10.1016/j.jtemb.2020.126664, indexed in Pubmed: 33075737.
12. Zimmermann MB, Molinari L, Spehl M, et al. Toward a consensus on reference values for thyroid volume in iodine-replete schoolchildren: results of a workshop on inter-observer and inter-equipment variation in sonographic measurement of thyroid volume. Eur J Endocrinol. 2001; 144(3): 213–220, doi: 10.1530/eje.0.1440213, indexed in Pubmed: 11248739.
13. Yao D, He X, Yang RL, et al. Sonographic measurement of thyroid volumes in healthy Chinese infants aged 0 to 12 months. J Ultrasound Med. 2011; 30(7): 895–898, doi: 10.7863/jum.2011.30.7.895, indexed in Pubmed: 21705721.
14. Prabhu SR, Mahadevan S, Jagadeesh S, et al. Normative Data of Thyroid Gland Volume in South Indian Neonates and Infants. Indian J Pediatr. 2018; 85(12): 1045–1049, doi: 10.1007/s12098-017-2528-5, indexed in Pubmed: 29423669.
15. Klingmüller V, Fiedler C, Otten A. [Characteristics of thyroid sonography in infants and children]. Radiologe. 1992; 32(7): 320–326, indexed in Pubmed: 1509029.
16. Aghini-Lombardi F. Effect of Iodized Salt on Thyroid Volume of Children Living in an Area Previously Characterized by Moderate Iodine Deficiency. Journal of Clinical Endocrinology & Metabolism. 1997; 82(4): 1136–1139, doi: 10.1210/jc.82.4.1136, indexed in Pubmed: 9100585.
17. Barrère X, Valeix P, Preziosi P, et al. Determinants of thyroid volume in healthy French adults participating in the SU.VI.MAX cohort. Clin Endocrinol (Oxf). 2000; 52(3): 273–278, doi: 10.1046/j.1365-2265.2000.00939.x, indexed in Pubmed: 10718824.
18. Hegedüs L, Rasmussen N, Knudsen N. Seasonal variation in thyroid size in healthy males. Horm Metab Res. 1987; 19(8): 391–392, doi: 10.1055/s-2007-1011833, indexed in Pubmed: 3311957.
19. Taş F, Bulut S, Eğilmez H, et al. Normal thyroid volume by ultrasonography in healthy children. Ann Trop Paediatr. 2002; 22(4): 375–379, doi: 10.1179/027249302125002047, indexed in Pubmed: 12530288.
20. Aydıner Ö, Karakoç Aydıner E, et al. Normative Data of Thyroid Volume-Ultrasonographic Evaluation of 422 Subjects Aged 0-55 Years. J Clin Res Pediatr Endocrinol. 2015; 7(2): 98–101, doi: 10.4274/jcrpe.1818, indexed in Pubmed: 26316430.
21. Çolak E, Özkan B, Genç S, et al. Ultrasonographic determination of thyroid volume in infants and children from Aegean region of Turkey and comparison with national and international references. J Pediatr Endocrinol Metab. 2021; 34(4): 457–464, doi: 10.1515/jpem-2020-0514, indexed in Pubmed: 33626602.