Developmental variations and clinical importance of the fetal thyroid gland

A morphometric study

Aynur E. Cicekcibasi, *MD,* ***Ahmet Salbacak,*** *PhD,* ***Muzaffer Seker,*** *PhD,*
Taner Ziylan, *PhD,* ***Isik Tuncer,*** *MD,* ***Mustafa Buyukmumcu,*** *PhD.*

ABSTRACT

Objectives: To investigate the morphologic structures and developmental anomalies of the thyroid gland in human fetuses.

Methods: This study performed in the Department of Anatomy, Meram Faculty of Medicine between February and April in 2002. Fetuses were obtained from the Gynecology Department of the Meram Faculty of Medicine, Selçuk University, and Dr. Faruk Sukan Maternity Hospital (Konya, Turkey). Sixty spontaneously aborted fetuses (30 boys and 30 girls) between the ages of 13.5th and 32.5th weeks, which had no detectable anomalies, were evaluated. The gland was dissected under the microscope. The location of the gland was determined according to the tracheal ring levels and laryngeal cartilage levels. The length, width and thickness of both lobes and isthmus of the gland were measured and then, the developmental anomalies were noted. The obtained data were statistically analyzed by Least Squares in variant analysis.

Results: Although there was no significant difference regarding to the gender for all parameters except in width of the right lobe ($p<0.05$), difference in the length and width of lobes and the length of isthmus between trimesters was significant ($p<0.05$). All measured parameters were increasing with advancing gestational age. The pyramidal lobe was observed in 18.3% of the cases.

Conclusion: Normal dimensions and developmental anomalies of the fetal thyroid, which was shown in this study, may provide useful information for the prenatal diagnosis and in-utero treatment of thyroid dysfunctions.

Saudi Med J 2007; Vol. 28 (4): 524-528

From the Department of Anatomy, Meram Faculty of Medicine, Selcuk University, Konya, Turkey.

Received 12th April 2006. Accepted 9th December 2006.

Address correspondence and reprint request to: Dr. Aynur E. Cicekcibasi, Department of Anatomy, Meram Faculty of Medicine, Selcuk University, 42080, Konya, Turkey. Tel. +90 (332) 2237246. Fax. +90 (332) 2236181. E-mail: aynurcicekcibasi@yahoo.com.tr

The thyroid gland is the first endocrine gland which appears in about the 3rd week of embryonic development as an epithelial proliferation in the floor of the pharynx, at a point later indicated by the foramen caecum. With further development, the gland descends in front of the hyoid bone and the laryngeal cartilages. It reaches its final position in front of the trachea in the 7th week. During this migration, the gland remains connected to the tongue by a narrow canal named as thyroglossal duct. This duct later becomes solid and finally disappears. Then, the thyroid gland acquires a small median isthmus and 2 lateral lobes.[1,2] The lateral lobes extend up to the sides of the thyroid cartilage and their bases are at the level of the fourth or fifth tracheal ring. The isthmus is usually anterior to the second and third tracheal cartilages.[3] Until the fetal thyroid completely develops into a follicular structure and becomes functionally active in about 12 weeks of embryonic development, normal maternal thyroid function is compulsory.[2,4] Fetal serum thyrotropin (TSH) levels increases between 18 and 22 weeks, coincident with the maturation of the hypothalamic-pituitary axis.[5] Thyroid hormone is essential for normal fetal growth and maturation of the central nervous system and both hypo- and hyperthyroidism may be harmful to brain development. Although undiagnosed thyroid disorders during intrauterine life significantly increase fetal, neonatal morbidity and mortality successful in utero treatment is possible.[4,6-10] Congenital hypothyroidism is the most common congenital endocrine disorder (one newborn

in 3000) and represents the most common cause of preventable mental retardation.[11,12] In the literature, some different techniques such as amniotic fluid assessment, cordocentesis or fetal blood sampling with ultrasonography (USG). have been described to evaluate and manage intrauterine fetal thyroid disorders.[13-17] Fetal goiter most commonly occurs as an indirect result of maternal ingestion of goitrogenic drugs, including propylthiouracil, methimazole, and iodine in large doses or as a direct result of fetal hyperthyroidism and thyrotoxicosis. Untreated fetal hyperthyroidism may lead to intrauterine growth retardation, oligohydramnios, malpresentation during labor, neonatal tracheal obstruction, tachycardia, craniosynostosis and death. Other reported complications include delayed perceptual-motor, visual-spatial, and language development.[5,8,9,18-20] Newborn screening programs have been widely implemented, and early treatment in infants has been shown to have a beneficial effect on cognitive performance.[8] Evaluation of the fetal thyroid as well as surrounding neck structures is an important part of the sonographic evaluation. The fetal thyroid can be figured out as early as in the middle of the second trimester, and fetal goiters can be identified in utero.[5] Clearly, the most important role of the ultrasound examination is to determine if there is thyroid tissue in its right position in the neck or not. Establishing whether the thyroid is small, normal, or enlarged is also important because mild enlargement of this gland may be one of the first signs of fetal thyroid dysfunction.[5,21] The antenatal diagnosis of potentially treatable thyroid disease in the fetus frequently depends on the detection of abnormal growth of the fetal thyroid gland.[8] Mostly, assessing the fetal thyroid rely on a subjective impression of increased thyroid size. The presence of fetal head extension as an adjunct for diagnosing enlargement of the fetal thyroid has been used, but this is present only in fetuses with very large goiters. Due to the fact that the early diagnose lesser degrees of fetal thyroid enlargement a nomogram is necessary for an accurate diagnose and several nomograms have been published.[9] There are many variations in the shape, size and relative level of the gland.[22] The object of this study was not only to establish the normal dimensions and the location of the thyroid gland in human fetuses, but also to compare our normative data with those reported in ultrasonic studies of other authors. In addition, the developmental anomalies of the gland were described.

Methods. This study was performed in spontaneously aborted 60 fetuses (30 boys and 30 girls) (40 second trimester and 20 third trimesters) with no detectable congenital malformations or maternal history of risky pregnancy. The fetuses were obtained from the Gynecology Department of the Meram Faculty of Medicine, Selçuk University, and Dr. Faruk Sükan Maternity Hospital (Konya, Turkey). In order to use the fetuses as experimental materials, the signed consents were obtained from the families and the experimental procedures were ethically approved by the official laws and regulations of Turkish Ministry of Health and Selcuk University. The fetuses with external and internal anomalies which were seen after dissection such as gastroschisis, renal agenesis, ectopic kidneys, agenesis of external genitalia, spinal cord abnormality, vertebral column anomalies, polydactyl and so forth, were also excluded from the study. The ages of the fetuses were determined to be between the 13.5th and 32.5th postmenstrual weeks base on the crown-rump length (CRL) measurements.[23] The fetuses were fixed using the immersion technique in 10% formalin. In the neck region, the thyroid gland was examined after the skin and regional surrounding soft tissues were dissected under the microscope (Colposcope Plus; Carl Zeiss, Oberkochen, Germany). The location of the gland was determined according to the tracheal ring levels and laryngeal cartilage levels. The measured parameters by a single observer were as follows: 1) The maximal length between superior pole border and inferior pole border of the right, left lobes and isthmus. 2) The maximal transverse width of the right and left lobes. 3) The maximal anteroposterior thickness of the right, left lobes and isthmus (**Figures 1a & 1b**). All measurements were carried out using electronic digital calipers (150 x 0.01 mm). The obtained data were statistically analyzed by Least-Squares in variant analysis (Minitab-7 for windows).[24] The developmental anomalies were evaluated and photographed.

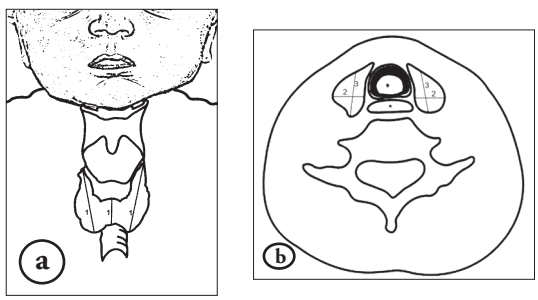

Figure 1 - Photograph of **a)** the maximal length of the right, left lobes and isthmus. Number 1 = length of right lobe, length of left lobe, length of isthmus. **b)** The maximal width of the right and left lobes. The maximal thickness of the right, left lobes and isthmus. Number 2 = width of right lobe, width of left lobe, number 3 = thickness of right lobe, thickness of left lobe, thickness of isthmus, o = esophagus, tr = trache,

Results. After determination of location and variation types, the results are listed as follows: according to the tracheal ring levels, the inferior pole border of the thyroid gland was determined as given below: For right lobes: 1st: 3.3%, 2nd: 10%, 3rd: 58.3%, 4th: 20%, 5th: 8.3%. For left lobes: 1st: absent, 2nd: 3.3%, 3rd: 56.7%, 4th: 31.7%, 5th: 8.3%. According to the thyroid (1/3) and cricoid cartilage levels, the superior pole border of the thyroid gland was observed as below: For right lobes: 10% upper, 61.6% middle, 16.6% lower 1/3 of the thyroid cartilage levels and 11.6% of the cricoid cartilage level. For left lobes: 3.3% upper, 38.3% middle, 38.3 % lower 1/3 of the thyroid cartilage levels and 20% of the cricoid cartilage level. There was no significant difference regarding to the gender for all parameters except the width of the right lobe ($p<0.05$). The mean values of the gland in boys were greater than girls in all parameters excluding the thickness of the left lobe (**Table 1**). There were significant differences in the length and width of lobes ($p<0.05$). The length of isthmus between trimesters were showing meaningful differences ($p<0.05$) (**Table 2**). Distributions of the values according to gender in trimesters are shown in

Table 1 - Comparison of the data (mm, mean ± standard deviation) of the thyroid gland in human fetuses according to gender.

Parameter (mm)	Boys (n = 30)	Girls (n = 30)	Total (n = 60)	*P* value
Length of right lobe	11.09 ± 0.43	10.66 ± 0.43	**10.87 ± 0.30**	>0.05
Width of right lobe	6.05 ± 0.29	5.16 ± 0.29	**5.61 ± 0.20**	<0.05
Thickness of right lobe	3.02 ± 0.18	2.92 ± 0.18	**2.97 ± 0.13**	>0.05
Length of left lobe	10.47 ± 0.45	10.20 ± 0.45	**10.33 ± 0.32**	>0.05
Width of left lobe	5.38 ± 0.27	5.06 ± 0.27	**5.22 ± 0.19**	>0.05
Thickness of left lobe	2.98 ± 0.18	3.00 ± 0.18	**2.99 ± 0.13**	>0.05
Length of isthmus	4.34 ± 0.26	3.86 ± 0.26	**4.10 ± 0.19**	>0.05
Thickness of isthmus	1.46 ± 0.11	1.38 ± 0.11	**1.42 ± 0.08**	>0.05
		$p<0.05$		

Table 2 - Comparison of the data (mm, mean ± standard deviation) of the thyroid gland in human fetuses according to trimesters.

Parameter (mm)	Second trimester (n = 40)	Third trimester (n = 20)	Total (n = 60)	*P* value
Length of right lobe	8.75 ± 0.35	12.99 ± 0.49	**10.87 ± 0.30**	<0.01
Width of right lobe	4.57 ± 0.24	6.64 ± 0.33	**5.61 ± 0.20**	<0.05
Thickness of right lobe	2.83 ± 0.15	3.11 ± 0.21	**2.97 ± 0.13**	>0.05
Length of left lobe	8.48 ± 0.37	12.19 ± 0.52	**10.33 ± 0.32**	<0.05
Width of left lobe	4.57 ± 0.22	5.87 ± 0.31	**5.22 ± 0.19**	<0.05
Thickness of left lobe	2.87 ± 0.15	3.11 ± 0.21	**2.99 ± 0.13**	>0.05
Length of isthmus	3.47 ± 0.22	4.73 ± 0.30	**4.10 ± 0.19**	<0.05
Thickness of isthmus	1.29 ± 0.09	1.55 ± 0.12	**1.42 ± 0.08**	>0.05
		$p<0.05$		

Table 3 - Comparison of the data (mm, mean ± standard deviation) of the thyroid gland in human fetuses according to gender and trimesters.

Parameter (mm)	Second trimester		Third trimester		*P* value
	Boys (n = 20)	Girls (n = 20)	Boys (n = 10)	Girls (n = 10)	
Length of right lobe	9.01 ± 0.49	8.49 ± 0.49	13.17 ± 0.69	12.83 ± 0.70	>0.05
Width of right lobe	4.92 ± 0.33	4.22 ± 0.33	7.19 ± 0.47	6.09 ± 0.47	>0.05
Thickness of right lobe	2.87 ± 0.21	2.79 ± 0.21	3.18 ± 0.30	3.05 ± 0.30	>0.05
Length of left lobe	8.74 ± 0.52	8.22 ± 0.52	12.20 ± 0.74	12.18 ± 0.74	>0.05
Width of left lobe	4.88 ± 0.31	4.27 ± 0.31	5.89 ± 0.44	5.85 ± 0.44	>0.05
Thickness of left lobe	2.97 ± 0.21	2.77 ± 0.21	2.98 ± 0.29	3.24 ± 0.29	>0.05
Length of isthmus	3.79 ± 0.30	3.15 ± 0.30	4.89 ± 0.43	4.57 ± 0.43	>0.05
Thickness of isthmus	1.45 ± 0.12	1.12 ± 0.12	1.46 ± 0.17	1.64 ± 0.17	>0.05
		$p<0.05$			

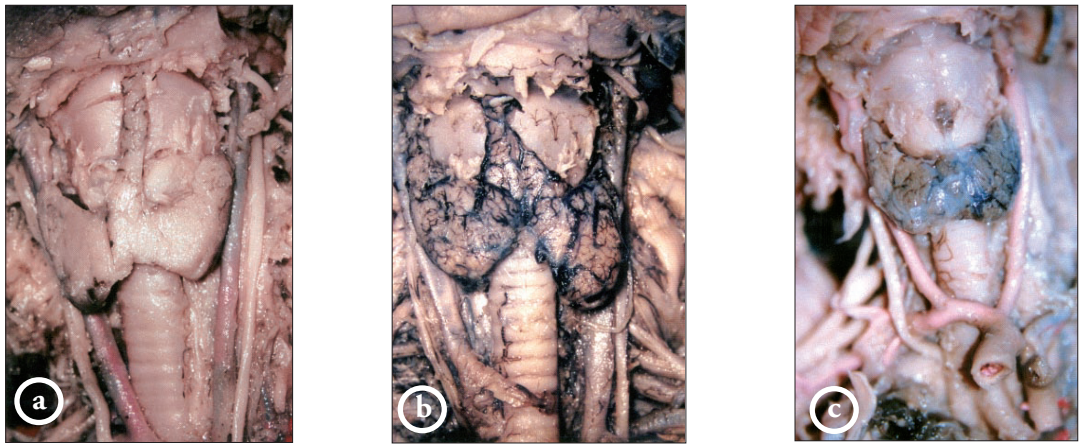

Figure 2 - a-c) Photograph of different developmental variations in the shape, size and relative level of the thyroid gland.

Table 3 and the results were not statistically significant. The thyroid gland was in normal structure in 49 of all fetuses while, developmental anomalies were observed in the rest 11 thyroid gland. The pyramidal lobe was present in 18.3% (6 boys and 5 girls) of the cases (**Figures 2a, 2b & 2c**).

Discussion. Several studies previously reported that the fetal thyroid can be evaluated in utero by using different ultrasound parameters such as thyroid diameter, circumference and volume.[5,8,25-27] Because some reported results differ from one another, it was mentioned that such differences could be related to variations in ambient iodine. Some part of the differences in fetal thyroid size can be attributed to the anthropometric differences between races. Besides, it is believed that the published data were largely different due to methodological approaches of the studies.[4,8] Perry et al[21] have studied normal ranges of volume and linear measurements of thyroid gland in 100 neonates (49 boys and 51 girls) in the United Kingdom. They reported that there were no significant differences between the right and left lobes in dimensions of the gland. The mean ± SD (range) length, width and thickness were 1.94 ± 0.24 cm (0.9-2.5), 0.88 ± 0.16 cm (0.5-1.4), 0.96 ± 0.17 cm (0.6-2.0), respectively. In their study, comparison of the thyroid dimensions according to gender showed no difference except longer right lobe in boys, and deeper left lobe in girls. By ultrasonic examination, Bromley et al[5] evaluated the transverse width and circumference of the gland in 31 fetuses in 23 and 40 weeks in gestational ages that resulted at low risk for perinatal thyroid disease. They noted an increase in size with advancing gestational age. The thyroid width and circumference increased by 0.36 mm and by 0.94 mm in a sequence per week of gestation to their calculated regression equation. Achiron et al[8] found an approximately 2-fold greater increase in thyroid width and circumference of 0.68 mm and 2.30 mm per week of gestation. While the estimates of Bromley et al[5] were 17.4 mm and 21.0 mm at 20 and 30 weeks, respectively, Achiron et al[8] predict a thyroid width of 9.7 mm and 16.5 mm at 20 and 30 weeks of gestation according to their measurements. Achiron et al[8] reported that the mean ± SD thyroid width was 11.7 ± 4.1 mm and circumference was 39.5 ± 14.1 mm. In a study made by Vade et al[27] the mean measurements for the sum of both lobes for transverse dimension was 13.9 mm, anteroposterior was 15.1 mm, and longitudinal was 34.6 mm. No significant correlation of these measurements was found with gestational age. These studies do not take the size of the thyroid isthmus into account, but the dimensions of the isthmus were measured in this study. In addition, the mean values of the gland were greater in boys for all parameters except the thickness of the left lobe. Variations of the thyroid gland commonly associated with its development such as the ectopic gland, hemiagenesis or agenesis.[28,29] The congenital hypothyroidism, which caused by an absent or defective thyroid gland classified as agenesis (22-42%), ectopy (35-42%) and place defects (24-36%).[12] Most of the variations in the gland are due to a partial persistence of the median or thyroglossal duct. The most obvious example of this persistence is the lobus pyramidalis. The pyramidal lobe represents a persistent portion of the inferior end of the thyroglossal duct and may extend superiorly from the isthmus for a variable distance. It is usually attached to the isthmus on the left side of the median plane, but it may join either of the lateral lobes. The isthmus may be incomplete,

failing to join the lateral lobes. There may be one or more fragments of thyroid tissue separate from main gland. The pyramidal lobe is present in about 50% of all humans and more commonly is associated with the left side of the isthmus.[30,31] In this study, the pyramidal lobe was observed in 18.3% of the cases. As a rule, the 2 lateral lobes are almost equally well-developed, but occasionally they are unequal in size, and the right lobe may be twice as large as the left.[31,32] In rare cases, one lobe may be absent. The isthmus varies greatly in size and is frequently not developed. In the adult it usually overlies the second, third and fourth tracheal rings.[22] The thyroid gland may also be absent. The presence of thyroid tissue within the tracheal lumen is an unusual cause of upper respiratory obstruction.[31] Consequently, knowledge of formation, position and developmental anomalies of the thyroid gland are of great practical importance for the radiologists, gynecologists and pediatricians to prevent both maternal and fetal complications in the fetal and neonatal period.

References

1. Sadler TW. Langman's Medical Embryology. 6th ed. Baltimore: Williams and Wilkins; 1990. p. 312-313.
2. Moore KL, Persaud TVN. The developing human-clinically oriented embryology. 5th ed. Philadelphia: W. B. Saunders Company; 1993. p. 200-203.
3. Williams PL, Warwick R, Dyson M, Bannister LH. Gray's Anatomy. 37th ed. Edinburg: Churchill Livinstone; 1989. p. 1459-1460.
4. Radaelli T, Cetin I, Zamperini P, Ferrazzi E, Pardi G. Intrauterine growth of normal thyroid. ***Gynecol Endocrinol*** 2002; 16: 427-430.
5. Bromley B, Frigoletto FD, Cramer D, Osathanondh R, Benacerraf BR. The fetal thyroid: normal and abnormal sonographic measurements. ***J Ultrasound Med*** 1992; 11: 25-28.
6. Gillam MP, Kopp P. Genetic regulation of thyroid development. ***Curr Opin Pediatr*** 2001; 13: 358-363.
7. Van Wassenaer AG, Kok JH, Briet JM, Pijning AM, de Vijlder JJ. Thyroid function in very preterm newborns: possible implications. ***Thyroid*** 1999; 9: 85-91.
8. Achiron R, Rotstein Z, Lipitz S, Karasik A, Seidman DS. The development of the foetal thyroid: in utero ultrasonographic measurements. ***Clin Endocrinol*** 1998; 48: 259-264.
9. Ranzini AC, Ananth CV, Smulian JC, Kung M, Limbachia A, Vintzileos AM. Ultrasonography of the fetal thyroid: nomograms based on biparietal diameter and gestational age. ***J Ultrasound Med*** 2001; 20: 613-617.
10. LaFranchi S. Congenital hypothyroidism: etiologies, diagnosis, and management. ***Thyroid*** 1999; 9: 735-740.
11. Van Vliet G. Development of the thyroid gland: lessons from congenitally hypothyroid mice and men. ***Clin Genet*** 2003; 63: 445-455.
12. Klett M. Epidemiology of congenital hypothyroidism. ***Exp Clin Endocrinol Diabetes*** 1997; 105: 19-23.
13. Avni EF, Rodesch F, Vandemerckt C, Vermeylen D. Detection and evaluation of fetal goitre by ultrasound. ***Br J Radiol*** 1992; 65: 302-305.
14. Heckel S, Favre R, Schlienger JL, Soskin P. Diagnosis and successful in utero treatment of a fetal goitrous hyperthyroidism caused by maternal Graves' disease. A case report. ***Fetal Diagn Ther*** 1997; 12: 54-58.
15. Nachum Z, Rakover Y, Weiner E, Shalev E. Graves' disease in pregnancy: prospective evaluation of a selective invasive treatment protocol. ***Am J Obstet Gynecol*** 2003; 189: 159-165.
16. Porreco RP, Bloch CA. Fetal blood sampling in the management of intrauterine thyrotoxicosis. ***Obstet Gynecol*** 1990; 76: 509-512.
17. Wenstrom KD, Weiner CP, Williamson RA, Grant SS. Prenatal diagnosis of fetal hyperthyroidism using funipuncture. ***Obstet Gynecol*** 1990; 76: 513-517.
18. Cohen O, Pinhas-Hamiel O, Sivan E, Dolitski M, Lipitz S, Achiron R. Serial in utero ultrasonographic measurements of the fetal thyroid: a new complementary tool in the management of maternal hyperthyroidism in pregnancy. ***Prenat Diagn*** 2003; 23: 740-742.
19. Soliman S, McGrath F, Brennan B, Glazebrook K. Color Doppler imaging of the thyroid gland in a fetus with congenital goiter: a case report. ***Am J Perinatol*** 1994; 11: 21-23.
20. Zimmerman D. Fetal and neonatal hyperthyroidism. ***Thyroid*** 1999; 9: 727-733.
21. Perry RJ, Hollman AS, Wood AM, Donaldson MDC. Ultrasound of the thyroid gland in the newborn: normative data. ***Arch Dis Child Fetal Neonatal Ed*** 2002; 87: 209-211.
22. Anson BJ, McVay CB. Surgical anatomy. 5th ed. Philadelphia: W. B. Saunders Co; 1971. p. 265.
23. Hensinger RN. Standards and measurements: Fetus and neonate. In: Polin RA, Fox WW, editors. Fetal and Neonatal Physiology. Philadelphia: W. B. Saunders Co; 1992. p. 1687-1696.
24. Harwey WR. Mixed model Least-Squares and maximum likelihood computer program-user's guide for LSMLMW PC-1 version. Ohio: Ohio State University; 1987.
25. Ho SS, Metreweli C. Normal fetal thyroid volume. Ultrasound ***Obstet Gynecol*** 1998; 11: 118-122.
26. Ohnishi H, Inomata H, Watanabe T, Wataki K, Sato H, Sanayama K, Noda H, Yasuda T, Niimi H. Clinical utility of thyroid ultrasonography in the diagnosis of congenital hypothyroidism. ***Endocr J*** 2002; 49: 293-297.
27. Vade A, Gottschalk ME, Yetter EM, Subbaiah P. Sonographic measurements of the neonatal thyroid gland. ***J Ultrasound Med*** 1997; 6: 395-399.
28. De Felice M, Di Lauro R. Thyroid development and its disorders: genetics and molecular mechanisms. ***Endocr Rev*** 2004; 25: 722-746.
29. Sarı O, Ciftci I, Törü M, Erbas B. Thyroid agenesis. ***Clin Nucl Med*** 2000; 25: 766-768.
30. Hansen JT. Embryology and surgical anatomy of the lower neck and superior mediastinum; in Falk SA(ed): Thyroid disease endocrinology, surgery, nuclear medicine, and radiotherapy. 2nd ed. Phidelphia: Lippincott-Raven Publishers; 1997. p. 15-21.
31. Bergman RA, Afifi AK, Miyauchi R. Available from URL: http://www.vh.org/adult/provider/anatomy/AnatomicVariants/OrganSystem/Text/ThyroidGland.html
32. Netter FH. Endocrine system and selected metabolic diseases. 3rd ed. The CIBA Collection of Medical Illustrations. Vol. 4. New Jersey: West Caldwell; 1974. p. 41-45.