Sonographic Evaluation of the Thyroid Size in Neonates

Ronald Freire, MD, PhD,[1] Osmar Monte, MD, PhD,[2] Eduardo Kiyoshi Tomimori, MD, PhD,[3] Regina Maria Catarino, MD, PhD,[4] Thais Sterza, MD,[5] Thatyana Rocha, BSc,[6] Katia Cristine Carvalho Pereira, MD,[6] Hortensio Simões Mattos Jr, Ph,[7] Leonardo Barros Fagundes, Ph,[7] Marcelo Martins Liberato, Ph,[7] Luiz Wagner Rodrigues dos Santos, CPE,[7] Adeberto Pereira, Ph,[8] Terezinha Cintra, MD,[8] Christina Hegner, MD,[8] Daniela Lube, MD,[8] Mylene Murad, MD[9]

[1] Santa Casa de São Paulo Medical School, São Paulo; Brazil and Radiology Service, Cassiano Antonio Moraes Teaching Hospital of the Federal University of Espirito Santo (HUCAM-UFES), Vitória–ES, Brazil
[2] Endocrinology and Metabolism Discipline in Santa Casa de São Paulo Medical School, São Paulo–Brazil, Brazil
[3] Santa Casa de São Paulo Medical School, São Paulo, Brazil
[4] Clinical Analysis Section, Pathology Division, Adolfo Lutz Institute, São Paulo, Brazil
[5] HUCAM-UFES, Vitória-ES, Brazil
[6] Neonatal Unit, HUCAM-UFES, Vitória–ES, Brazil
[7] São Marcos Laboratory, Vila Velha–ES, Brazil
[8] Neonatal Triage Unit, Reference Service of Espírito Santo, APAE, Vitória–ES, Brazil
[9] Department of Internal Medicine, Vila Velha School of Medicine, University of Vila, Velha–ES, Brazil

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ABSTRACT: *Purpose.* To validate the use of the ratio between the total transverse diameters of the thyroid lobes (Th) and the width of the trachea (Tr)—the Th:Tr or Yasumoto ratio—as a sonographic method for estimating thyroid size, and to determine reference values for this ratio and for thyroid volume in neonates.

Methods. In this cross-sectional study, we evaluated thyroid size according to the Yasumoto ratio and the thyroid volume calculated with the ellipsoid formula in 125 healthy, euthyroid, iodine-sufficient, full-term neonates.

Results. The mean thyroid gland volume was 1.00 ml (95% confidence interval, 0.95–1.03 ml), and the mean Yasumoto ratio was 2.29 (95% confidence interval, 2.21–2.31). The lower- and upper-limit results falling within 2 SDs of the mean were 0.45 ml and 1.53 ml for the volume and 1.71 and 2.87 for the ratio.

Conclusions. In full-term, euthyroid, iodine-sufficient neonates, the normal reference interval for thyroid volume measured on sonography was 0.45–1.53 ml and that for the Yasumoto ratio was 1.71–2.87. A ratio of 1.7 may be applied as the cutoff value for sonographic diagnosis of thyroid dysgenesis in full-term neonates with congenital hypothyroidism. © 2014 Wiley Periodicals, Inc. *J Clin Ultrasound* **00**:000–000, 2014; Published online in Wiley Online Library (wileyonlinelibrary.com). DOI: 10.1002/jcu.22244

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INTRODUCTION

Real-time sonographic (US) imaging is a valuable tool for diagnosing thyroid disorders. For accurate measurement of the thyroid, the patient must remain still with the neck slightly hyperextended for the duration of the examination. This is difficult to achieve in young children, particularly in neonates with congenital hypothyroidism, in whom thyroid US has a key diagnostic role.

Most cases of congenital hypothyroidism in iodine-sufficient countries are due to thyroid dysgenesis, a malformation that occurs during the embryonic stage and leads to ectopy, aplasia, hypoplasia, or hemiaplasia of the gland.[1,2] Less frequently, congenital hypothyroidism is

Correspondence to: R. Freire

due to hereditary defects in thyroid hormone synthesis (dyshormonogenesis), in which the thyroid is located in its anatomic position and has a normal or enlarged volume.[1–3] Rarely, congenital hypothyroidism can result from central disorders or even occur in a transient form; in both situations, the thyroid is normally positioned and has a normal size.[3] In children with congenital hypothyroidism, it is important to identify which of the above causes is involved because the etiology has implications for genetic counseling, prognosis, and treatment strategy. For example, absence of the thyroid on US indicates agenesis or ectopy, whereas an enlarged gland suggests dyshormonogenesis.[4]

Thyroid US has remained relatively underused in neonates,[5,6] partly due to lack of normative data for thyroid volume in the neonatal period.[3] In 2004, Yasumoto et al[7] proposed a simple and practical method for estimating the size of the thyroid in children (neonates to 12 year olds) that uses a ratio of the total transverse diameters of the thyroid lobes (Th) divided by the width of the trachea (Tr)—the Th:Tr or Yasumoto ratio—thereby obviating the multiple measurements to calculate thyroid volume. Because the ratio can be estimated by measurements obtained on a single transverse sonogram, it requires only a few minutes to obtain. The use of this ratio to estimate thyroid size would be particularly helpful in the challenging population of neonates with confirmed congenital hypothyroidism. We therefore aimed to validate the Yasumoto ratio in neonates and to establish reference values for both the Yasumoto ratio and the thyroid volume in healthy full-term, euthyroid, iodine-sufficient neonates.

PATIENTS AND METHODS

This was a cross-sectional study evaluating 125 neonates (64 boys, 61 girls) with adequate weight and born full-term by uncomplicated delivery. None of the infants had clinical or laboratory evidence of thyroid disorders, malformations, or genetic syndromes. The maternal history in all cases was negative for thyroid autoimmune disorders, infectious diseases, use of tobacco or illicit drugs, and use of medications containing iodine or intended for treatment of thyroid disease during pregnancy. To minimize neonatal exposure to iodine, our use of topical iodine solution (povidone-iodine 10%) was restricted to antisepsis of the maternal skin and was not applied to the umbilical cord of the infant. In the last 10 neonates enrolled in the study, chlorhexidine 10% was substituted for povidone-iodine. However, povidone-iodine 2.5% eye drops were administered to all neonates.

We obtained maternal informed consent for each child before enrollment. The study was conducted at the Maternity Unit of the University Hospital of the Federal University of Espírito Santo (HUCAM-UFES) in Vitória, Brazil between February 2011 and February 2012 after approval by the Ethics Committee of the Vitória Integrated Center for Health Care Research.

US Examination

Thyroid US was performed on all neonates by one of the authors (R.F.) using a 12-MHz small-parts linear transducer connected to an EnVisor scanner (Philips Medical Systems, Bothell, WA). To obtain neck hyperextension during the exam, the infants were maintained in the supine position while sucking on an assistant's gloved finger.

We first estimated the total volume of the thyroid by calculating the volume of each lobe and of the isthmus separately using the ellipsoid formula (length × width × thickness × π/6) and adding the obtained individual values.

We then calculated the Yasumoto ratio on the transverse sonogram that displayed the largest cross-sectional area of the thyroid, by measuring the maximum width of both thyroid lobes (a and b) and that of the trachea (c). The Yasumoto ratio was defined as $a + b$ divided by c (Figure 1).

Laboratory Tests

Urinary iodine was measured in triplicate in voided urine samples stored at −20°C, using the Sandell-Kolthoff reaction modified by Pino et al.[8] All neonates were screened for congenital hypothyroidism by measuring thyroid-stimulating hormone (TSH) on a blood spot collected on filter paper (reference value, <9 μIU/ml; Auto Delfia, fluoroimmunoassay, PerkinElmer, Inc., Turku, Finland). At the same time, blood was collected for measurement of serum TSH, free T4 (FT4), thyroglobulin, antithyroid peroxidase, antithyroglobulin, and TSH-receptor antibodies. All measurements were analyzed with an electrochemiluminescence immunoassay (Roche Elecsys/cobas; Roche Diagnostics, Indianapolis, IN).

Statistical Analysis

Data were entered into a database (Afrodite Olimpo 2005–2012) and later imported for

FIGURE 1. Calculation of the Yasumoto ratio on a transverse sonogram of the thyroid. The sum of the maximum width of each thyroid lobe (a + b) divided by the width of the trachea at the level of the thyroid (c) on a transverse sonogram yields the Yasumoto ratio. (NOTE: This sonogram was obtained with an equipment other than the EnVisor scanner used in our study and on a subject who was not part of the study for the purpose of illustrating the measurement technique.)

statistical analysis into Minitab 16 (Minitab, Inc., State College, PA) and SPSS (SPSS Inc., Chicago, IL). We tested the normality of the distribution of the data using the Kolmogorov-Smirnov test. To analyze data without normal distribution (TSH on filter paper, serum TSH, and thyroglobulin), we applied the Mann-Whitney and Kruskal-Wallis tests. For data with normal distribution (urinary iodine, FT4, thyroid volume, and Yasumoto ratio), we used Student's *t*, Tukey, and analysis of variance testing.

To establish a reference range for thyroid volume and Yasumoto ratio for neonates, we calculated the interval representing ±2 SDs of the mean for each method. We considered *p* values ≤0.05 to be statistically significant.

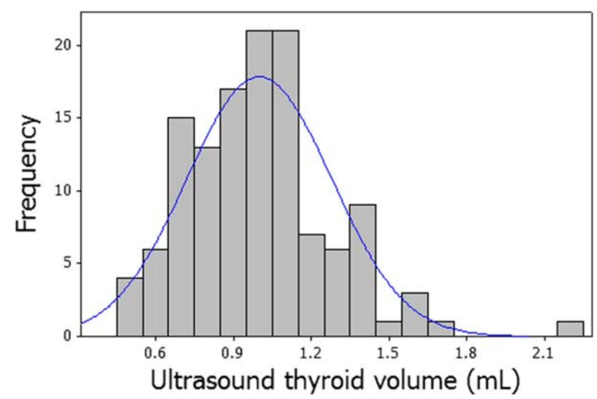

FIGURE 2. Histogram shows the distribution of the calculated thyroid volumes in 125 neonates. The mean (± SD) volume was 1.00 ± 0.28 ml.

RESULTS

The mean age of the neonates at the time of thyroid US examination was 2.5 days (median, 1.0 day). The examination was conducted during the first week of life in 113 neonates, whereas it was performed during the second week in nine and in the third week in three.

The mean thyroid volume was 1.00 ml (SD = 0.28 ml; 95% confidence interval, 0.95–1.03 ml). The lower- and upper-limit results falling within 2 SDs of the mean for the volume were 0.45 and 1.53 ml. There were no significant differences in volumes of the right and left lobes ($p = 0.06$) or between sexes ($p = 0.99$). Similarly, there was no correlation between the volume of the thyroid and the age of the newborn (Pearson's $r = 0.064$; $p = 0.48$), nor was any difference in thyroid volumes among newborns evaluated during the first, second, and third weeks of the neonatal period ($p = 0.55$). Figure 2 shows the distribution of the thyroid volumes.

When we compared nine neonates born from mothers with gestational diabetes with the remaining 116 without a maternal history of

TABLE 1
Summary of Studies Assessing Thyroid Volume on Sonography in Neonates*

Authors	Year	NB Full-Term	Ellipsoid Model Correction Factor	Thyroid Volume (ml)†	Urinary Iodine (μg/l)†	Iodine Deficiency Status (in Locale)
Einenkel[11]	1989	50	(0.479)	1.0–3.9 (min–max)	33.2 (mean)	Severe (Magdeburg, DE)
Chanoine et al[12]	1991	85	(π/6)	0.83 (mean)	No record	Mild (Brussels, BE)
Böhles et al[28]	1993	65	(0.479)	0.61 (median)	30.0 (median)	None (Frankfurt, DE)
Glinoer et al[14]	1995	180	(π/6)	● 0.75 ○1.05 (mean)	○ 43.0 ● 80.0 (mean)	Mild (Brussels, BE)
Liesenkötter et al[13]	1996	108	(0.479)	● 0.70 ○1.5 (median)	○ 65.0 ● 83.0 (median)	Moderate (Berlin, DE)
Vade et al[3]	1997	68	(π/6)	0.95 (mean)	Not performed	(?) (Illinois, USA)
Tajtakova et al[10]	1999	227	(0.479)	0.62 (mean)	113.0 (mean), 66.0 (median)	None (Slovakia)
Kurtoglu et al[29]	2002	42	(π/6)	1.21 (mean)	(?)	(?) (Kayseri, TR)
Perry et al[5]	2002	100	(π/6)	1.62 (mean)	Not performed	(?) (Glasgow, UK)
Köksal et al[26]	2008	100	(π/6)	0.82 (mean)	Not performed	Moderate (Bursa, TR)
Yao et al[30]	2011	85	(0.479)	0.64 (mean)	Not performed	(?) (Hangzhou, CN)
Mutlu et al[15]	2012	38	(π/6)	0.72 (mean)	Not performed	(?) (Trabzon, TR)
Freire et al‡	2013	125	(π/6)	1.00 (mean = median)	299.20 (mean) 300.0 (median)	None (Vitória, BR)

Abbreviations: NB, newborn; DE, Germany; BE, Belgium; USA, United States of America; TR, Turkey; UK, United Kingdom; CN, China; BR, Brazil.
*Adapted from Tajtakova et al[10] and Köksal et al.[26]
†Key to symbols: ●, iodine supplementation; ○, no iodine supplementation; (?), information not available.
‡Our current study.

gestational diabetes, we also found no significant differences in thyroid volume measurements ($p = 0.57$, Student's t test).

The mean Yasumoto ratio was 2.29 (SD = 0.29, 95% confidence interval, 2.21–2.31). The lower and upper values falling within 2 SDs of the mean were 1.71 and 2.87. There was no significant difference in mean ratio between sexes ($p = 0.32$, Student's t test).

We found a weak correlation between thyroid volume measurements and the Yasumoto ratio ($r = 0.43$). There was also a weak correlation between thyroid volume and ratio with TSH from filter paper, serum TSH, FT4, thyroglobulin, urinary iodine, birth length and weight, body surface area at birth, gestational age, and age at thyroid US ($r < 0.26$ for all parameters).

Five neonates had hypoechoic nodular areas with well-defined borders in the thyroid parenchyma, measuring from 0.2 to 0.56 cm in diameter. No difference in thyroid volume was found between these neonates and those without nodules ($p = 0.13$, Mann-Whitney test).

Blood tests yielded normal results in all neonates. The mean (±1 SD) urinary iodine concentration was 299 (±72) μg/l. We did not find a statistically significant difference in mean urinary iodine levels when we compared neonates born after maternal antisepsis with povidone-iodine 10% ($n = 115$) with those born after antisepsis with chlorhexidine ($n = 10$), nor did we find a difference between neonates born via cesarean section ($n = 73$) and those delivered vaginally ($n = 52$).

DISCUSSION

According to Yasumoto et al,[7] when the ratio indicates a small, normal, or enlarged gland, the corresponding sensitivities are 99%, 93.5%, and 92%. However, their study included children up to 12 years old and only a small number of neonates.

In our study, the lowest and highest values of thyroid volumes (0.48 ml and 2.17 ml) corresponded to Yasumoto ratios of 2.20 and 2.45, respectively. Both of these values fall within the normal reference levels for the ratio and have a probability of 93.5% of representing the normal thyroid volume in infants, as determined by Yasumoto et al.[7] We took great care to exclude thyroid disorders and iodine deficiency or excess in our cohort.

Our lower ratio limit of 1.7 is identical to that published by Yasumoto et al, thereby validating this value as the cutoff point for full-term neonates and for the diagnosis of thyroid dysgenesis, the most common cause of permanent congenital hypothyroidism in iodine-sufficient countries.[1,9] In thyroid dysgenesis, screening based on serum thyroid tests alone is insufficient to establish the diagnosis. In contrast, US screening, with its sensitivity of 85% for detection of dysgenesis, should be useful in genetic counseling, establishing prognosis, and planning treatment strategy.

In our experience, the Yasumoto ratio is a simple and practical parameter for estimating the size of the thyroid gland in neonates and has the potential to replace the traditional calculation of volume in congenital hypothyroidism.

In neonates, thyroid volume calculated by US ranges from 0.61 ml to 1.62 ml (Table 1). Tajtakova et al[10] established 0.5 ml as the lower limit value for the neonatal thyroid gland. Thyroid volumes greater than 1.5 ml have been considered indicative of goiter in various studies.[11–13] In contrast, the upper limit in neonates born from iodine-deficient mothers has been reported as 2.5–2.6 ml.[13,14] In our study, which included only iodine-sufficient infants, only one neonate had a thyroid volume of less than 0.5 ml, whereas six of them had volumes greater than 1.5 ml. In these cases, thyroid function and antibodies as well as urinary iodine levels were within the neonatal period reference ranges.[15–22]

In our study, there was no difference in urinary iodine between neonates born from mothers who had undergone the use of povidone-iodine and those from mothers in whom chlorhexidine was used as a topical antiseptic during delivery. This finding is in line with the results of a study that compared neonates exposed versus those not exposed to iodine during delivery.[17] Although we tried to minimize exposure of the infant to iodine during delivery, our hospital requires prophylaxis of neonatal conjunctivitis with povidone-iodine 2.5% eye drops. These eye drops have a very low concentration of free iodine and appear to be minimally absorbed, with little effect on the concentration of urinary iodine in neonates. This finding has also been reported by others.[23–25]

Most studies assessing thyroid volume on US in neonates have been carried out in the first half of the neonatal period, with the vast majority conducted in the first week of life.[3,5,12,14,26] In our study, no significant difference in thyroid volume was observed between newborns examined during the first, second, or third weeks of the neonatal period. We also did not find a significant difference in thyroid volume when we compared infants born from mothers with gestational diabetes with those without diabetes, as reported by others.[26]

The nodular areas seen in the thyroid parenchyma in five of our neonates were similar to those described by Segni et al,[27] who considered these areas likely to represent ectopic thymus tissue.

In conclusion, our study has validated the Yasumoto ratio as a simplified US method for estimating the size of the thyroid in neonates and has also established the reference intervals of 1.7–2.9 for the ratio and 0.45–1.53 ml for thyroid volume in full-term, euthyroid, iodine-sufficient neonates. The cutoff point of 1.7 for the Yasumoto ratio may be adopted for US diagnosis of thyroid dysgenesis in full-term neonates with congenital hypothyroidism.

REFERENCES

1. Rastogi MV, LaFranchi SH. Congenital hypothyroidism. Orphanet J Rare Dis 2010;5:17.
2. Kreisner E, Camargo-Neto E, Maia CR, et al. Accuracy of ultrasonography to establish the diagnosis and aetiology of permanent primary congenital hypothyroidism. Clin Endocrinol 2003;59:361.
3. Vade A, Gottschalk ME, Yetter EM, et al. Sonographic measurements of the neonatal thyroid gland. J Ultrasound Med 1997;16:395.
4. Ueda D, Mitamara R, Suzuki N, et al. Sonographic imaging of the thyroid gland in congenital hypothyroidism. Pediatr Radiol 1992;22:102.
5. Perry RJ, Hollman AS, Wood AM, et al. Ultrasound of the thyroid gland in the newborn: normative data. Arch Dis Child Fetal Neonatal Ed 2002;87:F209.
6. Chang YW, Lee DH, Hong YH, et al. Congenital hypothyroidism: analysis of discordant US and scintigraphic findings. Radiology 2011;258:872.
7. Yasumoto M, Inoue H, Ohashi I, et al. Simple new technique for sonographic measurement of the thyroid in neonates and small children. J Clin Ultrasound 2004;32:82.
8. Pino S, Fang SL, Braverman LE. Ammonium persulfate: a safe alternative oxidizing reagent for measuring urinary iodine. Clin Chem 1996;42:239.
9. Dora JM, Maia AL, Krug BC, et al. Clinical protocol and therapeutic guidelines–-congenital hypothyroidism [in Portuguese]. October 31, 2002. Available at: http://dtr2001.saude.gov.br/sas/dsra/protocolos/do_h26_01.pdf. Accessed on September 18, 2014.
10. Tajtakova M, Capova J, Bires J, et al. Thyroid volume, urinary and milk iodine in mothers after delivery and their newborns in iodine-replete country. Endocr Regul 1999;33:9.
11. Einenkel D. [Sonographic volume determination of the thyroid in newborn infants.] Padiatr Grenzgeb 1989;28:79.
12. Chanoine JP, Topet V, Lagasse R, et al. Determination of thyroid volume by ultrasound from the neonatal period to late adolescence. Eur J Pediatr 1991;150:395.
13. Liesenkötter KP, Göpel W, Bogner U, et al. Earliest prevention of endemic goiter by iodine supplementation during pregnancy. Eur J Endocrinol 1996; 134:443.
14. Glinoer, De Nayer P, Delange F, et al. A randomized trial for the treatment of mild iodine deficiency during pregnancy: maternal and neonatal effects. J Clin Endocrinol Metab 1995;80:258.
15. Mutlu M, Karagüzel G, Aliyazicioglu Y, et al. Reference intervals for thyrotropin and thyroid hormones and ultrasonographic thyroid volume during the neonatal period. J Matern Fetal Neonatal Med 2012;25:120.

16. Roche Diagnostics. Reference intervals for children and adults. Elecsys thyroid tests. Elecsys systems 1010/2010. Modular analytics E170. Mannheim, Germany: Roche Diagnostics; 2004, p 6.
17. Zimmermann MB, Dorey CM. Reference values for spot urinary iodine concentrations in iodine-sufficient newborns using a new pad collection. Thyroid 2008;18:347.
18. Knobel RB. Thyroid hormone levels in term and preterm neonates. Neonatal Netw 2007;26:252.
19. Kratzsch J, Schubert G, Pulzer F, et al. Reference intervals for TSH and thyroid hormones are mainly affected by age, body mass index and number of blood leucocytes, but hardly by gender and thyroid autoantibodies during the first decades of life. Clin Biochemistry 2008;41:1091.
20. Fisher DA. Disorder of the thyroid in the newborn and infant. In: Sperling MA, editor. Pediatric Endocrinology, 2nd ed. Rio de Janeiro: Saunders; 2002, p 189.
21. Fisher DA. Disorder of the thyroid in the newborn and infant. In: Sperling MA, editor. Pediatric Endocrinology. 2nd ed. Rio de Janeiro: Saunders; 2002, p 176.
22. Delange F. Optimal iodine nutrition during pregnancy, lactation and the neonatal period. Int J Endocrinol Metab 2004;2:1.
23. Richter R, Below H, Kadow I, et al. Effect of topical 1.25% povidine–iodine eyedrops use for prophylaxis of ophthalmia neonatorum on renal iodine excretion and thyroid-stimulating hormone level. J Pediatr 2006;148:401.
24. Pyati SP, Ramamurthy RS, Krauss MT, et al. Absorption of iodine in the neonate following topical use of povidone iodine. J Pediatr 1977;91:825.
25. Gordon CM, Rowitch DH, Mitchell ML, et al. Topical iodine and neonatal hypothyroidism. Arch Pediatr Adolesc Med 1995;149:1336.
26. Köksal N, Aktürk B, Saglam H, et al. Reference values for neonatal thyroid volumes in a moderately iodine-deficient area. J Endocrinol Invest 2008;31:642.
27. Segni M, di Nardo R, Pucarelli I, et al. Ectopic intrathyroidal thymus in children: a long-term follow-up study. Horm Res Paediatr 2011;75:258.
28. Böhles H, Aschenbrenner M, Roth M, et al. Development of thyroid gland volume during the first 3 months of life in breast-fed versus iodine-supplemented and iodine-free formula-fed infants. Clin Investig 1993;71:13.
29. Kurtoglu S, Akcakus M, Gunes T, et al. Urinary iodine levels of the term newborns in Kayseri province [in Turkish]. Erciyes Tip Dergisi (Erciyes Med J) 2002;24:69.
30. 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;30:895.