Defining Normative Sonographic Measurements of Neonatal Thyroid Volumes: Results of 165 Healthy Neonates from a Single Center in Northwest Malaysia

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Abstract

Background: Congenital hypothyroidism is the most common cause of treatable mental impairment and growth retardation in newborns. Early diagnosis requires measurement of serum thyroid-stimulating hormone (TSH) and free T4 coupled with an ultrasound of the thyroid gland. However, detailed sonographic evaluation of the thyroid gland requires comparison to the local thyroid normative volumetric values, which is currently lacking. **Methods:** A cross-sectional study was conducted from November 10, 2015, to April 18, 2018, recruiting 165 healthy neonates with normal TSH in their 1st week of life, from a single center in Northwest Malaysia. Ultrasound thyroid was done by a single ultrasonographer ($\kappa = 0.86$, percent agreement = 92.4), and the thyroid volume (TV) was calculated using the Brunn formula. **Results:** All measurements showed skewed distribution with no significant difference between the right and left lobes. The local normative values for neonatal total TV was 0.61 (interquartile range [IQR] = 0.230) cm^3, 0.31 (IQR = 0.150) cm^3 for right TV, and 0.28 (IQR = 0.110) cm^3 for left TV. There was a strong correlation between the right and left TVs, $r = 0.767$, $P < 0.001$. There were also no differences in the total TV across different genders and races. **Conclusion:** The normative values for TV determined in our study may be used accordingly in clinical practice to evaluate thyroid hypoplasia or goiter by other Asian countries due to the similarly shared biodemography.

Keywords: Congenital hypothyroidism, infant, neonatal screening, newborn, ultrasonography

Introduction

Congenital hypothyroidism (CH) is an inborn endocrine disorder resulting from the inadequate thyroid hormone production in a newborn infant. It is the most common cause of reversible mental impairment and growth retardation in newborns. The birth prevalence of CH in Malaysia is common and has been estimated to be around 1 in every 2,500 live births.[1] The most common cause of CH in the poorly developed region is iodine deficiency as compared to the more developed countries, whereby 85% of CH cases are caused by thyroid dysgenesis, which includes thyroid aplasia, hypoplasia, or ectopic. Being one of the most preventable causes of intellectual and developmental disabilities, early diagnosis and treatment are crucial.[2,3]

The first serum screening of CH was performed by Dussault in Quebec, Canada, in 1972.[4,5] It is now a standard national program in many developed countries. The screening program is important to allow timely diagnosis and management of CH as most of the infants with CH are asymptomatic at birth. In Malaysia, a nationwide stepwise CH screening program for all babies delivered in the government hospitals has been implemented by the Ministry of Health since October 1998[1] with the use of cord blood thyroid-stimulating hormone (TSH) testing.

Ultrasound assessment is among the pertinent clinical modalities to determine the underlying cause of CH and is the gold standard for assessment of the thyroid gland.[6] Ultrasound plays a role in

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CH by evaluating the size of the thyroid gland (normal, aplasia, or hypoplasia), verifying its anatomical location (normal position or ectopic), and projecting the prognostic implications.[6] Ultrasound assessment of the thyroid gland done by a trained sonographer is able to provide a precise measurement of neonatal thyroid volume (TV). Apart from the time-saving operation, ultrasound procedures do not require an additional contrast agent, and it is readily available in almost every clinical facility.

However, there is a wide discrepancy in the normative values of neonatal thyroid gland between the different geographical regions, therefore highlighting the need to establish local normative data for specific population examined.[7] This is in line with the World Health Organization (WHO) recommendation that the normal values of neonatal TV are to be clinically weighted according to the population of interest, as studies found that the TV is influenced by the differences in geographic distribution, racial, and nutritional factors.[8-10]

Furthermore, in Malaysia, there is currently no universally accepted reference range for the neonatal TV values measured by ultrasonographic imaging. Thus, this study aimed to develop a local reference range for TV in healthy neonates.

Methodology

A cross-sectional study was conducted among 165 healthy neonates within their 1st week of life. The study was conducted from November 10, 2015, to April 18, 2018, in Hospital Tuanku Fauziah, Kangar, Perlis, Malaysia, a secondary public hospital in the northwest part of Peninsular Malaysia, catering for a total population of 260,000. Neonatal ultrasound of the thyroid gland in this study was done by one dedicated study associate in the postnatal wards during the entire study period.

Selection and description of participants

All healthy neonates, within their 1st week of life, who were cared for by the mother in the postnatal ward was included in the study. The exclusion criteria include prematurity of <37 completed gestational weeks, low birth weight of <2500 g, abnormal TSH values (≥25 mU/L), and the presence of any congenital malformation. Convenient sampling was used.

The procedure was explained to the attending mothers, and written consent was obtained before the ultrasound examination among the eligible study candidates.

Technical information

Ultrasound thyroid was done in a dedicated room in the postnatal wards by one dedicated study associate. The ultrasonographer had undergone adequate training and was privileged to perform the procedure in neonates. The neonatal thyroid ultrasound was done using Philips ultrasound system Philips HD7 XE equipped with Philips L12-3 linear probe (frequency range of 3.0–12.0 MHz) for TV assessment.

During the procedure, the same examination position was practiced in each session. The infants were placed in a supine position with their neck in a hyperextended position. No sedation was given throughout the procedure. The width and depth of each of the thyroid lobes were assessed on transverse images, and the length was assessed on longitudinal images [Figure 1].

Neither the isthmus nor the thyroid capsule was included in the measurement of the total thyroid gland volume. The TV was calculated according to Brunn *et al*. formula as the sum of both lobes' volumes (cm^3), counted as lobe width (cm) × depth (cm) × length (cm) ×0.479.[11]

Intra-operator variation

In order to assess for intra-operator variation, the ultrasonographer had performed the ultrasound reading twice for the first 50 neonates in the morning and afternoon of the same day. The first result was blinded before the second assessment. A κ-statistic was calculated for the first 50 paired readings with a weighing matrix defined as follows: a score of 1.0 indicates a perfect agreement, a score of 0.60 indicates two-third agreement (defined as difference in paired readings by ±0.30 cm) while a score of zero signifies complete disagreement (defined as difference in paired readings by ±0.31 cm or more).

Sample size

The sample size estimation was calculated using the population mean formulae.[12] Prior data indicate that the mean sonographic measurement of the total thyroid gland volume among Chinese newborns was 0.64 (standard deviation = 0.27)[13] cm^3, and our local population size is 300. If the Type I error probability and precision are 0.05 and 0.05, respectively, a total of 144 samples are required. Therefore, with an addition of 10% dropout rate, the minimum calculated sample size is 160 samples.

Statistical analysis

The data were analyzed using IBM SPSS Statistics for Windows, Version 23.0. Armonk, NY: IBM Corp. The categorical variables such as gender, race, and birth weight category were described in frequencies and percentages. The median values of total thyroid gland volume between the different demographic factors were

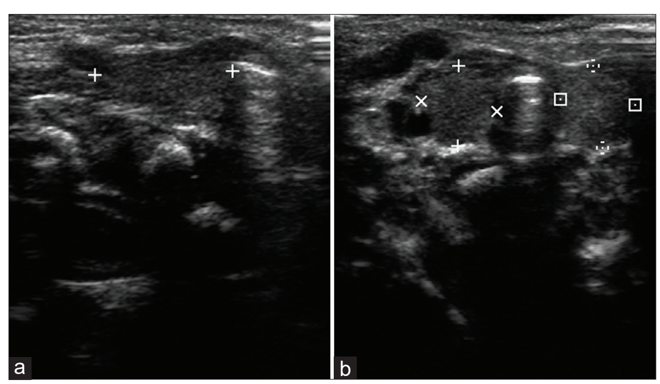

Figure 1: Sonographic diagram of the thyroid gland: (a) Longitudinal image to measure the maximum length of each lobe from sagittal sections on ultrasound. (b) Transverse image to determine the maximum transverse diameter (breadth), and the maximum anteroposterior measurement (depth)

analyzed using Mann–Whitney U-test for independent variables and Wilcoxon signed-rank test for paired readings. Median and interquartile range (IQR) were used to describe skewed data of each left and right TV.

The cutoff values for total TV are divided by the median value of the distribution.

Ethical consideration

This study was registered in the National Medical Research Register (NMRR) of Malaysia (ID: NMRR-15-212-24492) with the recommendation from the Medical Research and Ethics Committee of the Ministry of Health of Malaysia.

Results

The intra-operator variation of the ultrasonographer involved in this study showed excellent agreement between the morning and afternoon sessions ($\kappa = 0.86$, percent agreement = 92.4%). A total of 165 neonates were included in this study from November 10, 2015, to April 18, 2018, in Hospital Tuanku Fauziah, Perlis, Malaysia. There were 84 (50.9%) males and 80 (48.5%) females. Majority (n = 106, 64.2%) of the study participants had no maternal antenatal problem, whereas 16 (9.7%) had history of maternal diabetes mellitus (preexisting or gestational) and 16 (9.5%) had maternal anemia during pregnancy. None of them had previous history of maternal thyroid problem.

All of the study participants had normal blood TSH level, 165 (100.0%). Majority (n = 164, 99.4%) had the thyroid gland located in the anterior neck. Majority had normal parenchyma and smooth outline (n = 164, 99.4%). Most of the patients also reported no calcification (n = 164, 99.4%), with no mass (n = 164, 99.4%) and absence of lymph nodes (n = 164, 99.4%).

The median total volume of the thyroid gland among the study participants was 0.61 (IQR = 0.230) cm^3 whereas 0.31 (IQR = 0.150) cm^3 for right TV and 0.28 (IQR = 0.110) cm^3 for left TV. The normal reference range for total thyroid gland volume in our population is further divided into low normal (0.360–0.610 cm^3) and high normal (0.611–1.520 cm^3) based on the distribution of data [Figure 2].

There was a strong correlation between the right TV and the left TV, $r = 0.767$, $P < 0.001$. The median depth of both the right and left thyroid glands among the study participants was 0.70 (IQR = 0.200) cm. The median width of the right thyroid gland was 0.70 (IQR = 0.100) cm, whereas the median width of the left thyroid gland was 0.70 (IQR = 0.200) cm. The median length of the right thyroid gland was 1.30 (IQR = 0.300) cm, whereas the median length of the left thyroid gland was 1.30 (IQR = 0.400) cm.

Table 1 shows the association between thyroid gland volume and demographic characteristics among study participants.

The sonographic measurements of the thyroid gland in 165 healthy newborn infants within the 1st week of life are shown in Table 2.

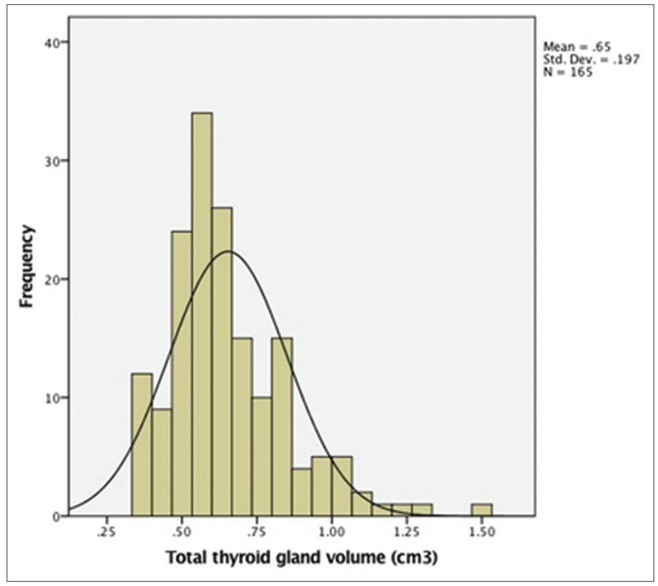

Figure 2: Histogram showing the data distribution of thyroid gland volume among study participants

Simple logistic regression found that neither gender ($P = 0.821$), race ($P = 0.921$), nor birth weight ($P = 0.251$) predicts the total TV of the healthy neonates. Similarly, multiple logistic regressions also did not find a significant model to predict the outcome of total TV using the selected demographic characteristics of our study participants.

Discussion

Establishment of a local reference range for normal thyroid gland in neonates is crucial when defining abnormality in cases of suspected thyroid anomaly, either due to the abnormal gland size or anatomic location. The median total TV among our local population was 0.61 (IQR = 0.230) cm^3. Our findings were comparable to the data from China[13] established in the year 2011. However, findings from European studies such as Germany,[14] Belgium,[15] and Scotland[16] found that the mean total thyroid gland volume in neonates was between 0.84 (0.38) cm^3 and 1.62 (0.41) cm^3, which were considerably bigger as compared to the Asian population. Therefore, this further highlights the need for local establishment of normal reference range of thyroid gland volume, which is in accordance with the WHO recommendation as the different geographical region, gender, height, weight, race, age, maternal antenatal iodine intake, and other disease factors may affect the neonatal thyroid size. Our study found no difference in the median total TV across the different genders and races within our locality. This is supported by similar reports from China[13] and Scotland.[16] However, our study found a significant association between the birth weight and the median thyroid gland volume, similar to a report from China published in 2011.[13]

Maternal dietary iodine intake during pregnancy is also one of the factors that may affect neonatal total TV. In addition, the overall proportion of Malaysian households with an

Table 1: Association between demographic data and thyroid gland volume in healthy neonates

Variable(s)	*n* (%)	Median thyroid gland volume in cm³ (IQR)		*P*[a]	Total thyroid gland volume in cm³, median (IQR)	*P*
		Right	Left			
Gender						0.944[b]
Male	87 (51.5)	0.31 (0.160)	0.29 (0.120)	0.005*	0.61 (0.230)	
Female	81 (47.9)	0.31 (0.140)	0.28 (0.150)	0.450	0.61 (0.230)	
Race						0.193[c]
Malay	154 (93.3)	0.31 (0.140)	0.28 (0.110)	0.002*	0.61 (0.230)	
Chinese	2 (1.2)	0.23 (.)	0.28 (.)	0.180	0.52 (.)	
Siamese	8 (4.8)	0.28 (0.220)	0.49 (0.260)	0.128	0.73 (0.480)	
Birth weight (kg)						0.037[c,*]
2.5-3.0	77 (45.6)	0.28 (0.130)	0.28 (0.080)	0.047*	0.58 (0.220)	
3.1-3.5	65 (38.5)	0.34 (0.130)	0.32 (0.130)	0.182	0.66 (0.240)	
3.6-3.9	19 (11.2)	0.32 (0.150)	0.30 (0.130)	0.507	0.60 (0.250)	

[a]Wilcoxon signed-rank test, [b]Mann–Whitney U-test, [c]Kruskal–Wallis H-test (described in median and IQR), *Statistically significant. IQR: Interquartile range

Table 2: Ultrasound measurements of the thyroid gland in 165 healthy newborns

Variable(s)	Site	Mean±SD	Range
Length (cm)	Right	1.37±0.307	0.90-2.00
	Left	1.43±0.313	1.00-2.00
Breadth (cm)	Right	0.76±0.143	0.40-1.00
	Left	0.75±0.144	0.50-1.00
Depth (cm)	Right	0.74±0.165	0.00-1.00
	Left	0.73±0.157	0.00-1.00
Volume (cm³)	Right	0.33±0.106	0.17-0.84
	Left	0.32±0.107	0.15-0.76

SD: Standard deviation

adequate iodized salt intake of 20–30 ppm as recommended by the Malaysian Food Act 1983 was only at 6.8%.[17] Even though data on maternal iodine intake during pregnancy were not captured in our study, the nutritional aspect of the mother during pregnancy should be monitored as it contributes to neonatal birth weight and influences the TV of the neonate.

Overall, there was a strong correlation between the left and right thyroid lobes, hence validating a symmetrical gland as normal. However, further analyses noted that those with male gender have a significantly asymmetrical thyroid gland, with the right lobe being larger than the left ($P = 0.005$). Despite the statistical significance, it is not clinically relevant in practice. A study report analyzing normal TV among healthy neonates also found similar finding.[13] Therefore, in general, discrepancies may exist in the size of the thyroid gland, in its depth, width, length, or volume between the right and left lobes and still be considered as a normal variant.

Among the neonates with Malay ethnicity, there was a statistically significant difference between the size of the right thyroid lobe and the left thyroid lobe, with the right appearing larger than the left. Again, this finding is statistically significant but is not clinically relevant in practice. Our study also found that among the non-Malay descendants, which include the Chinese and Siamese, the left thyroid gland was significantly larger than the right, a reversed finding to the Malay population, even though the values did not reach statistical significance.

There was no significant difference between the right and left lobes of the thyroid gland across the different birth weights in neonates. Despite these findings, extensive literature searches were not able to correlate between the effect of various ethnicities and birth weight, on the symmetry of the thyroid gland, due to the paucity of research projects studying the thyroid gland in healthy neonates.

Ultrasonography is a highly operator-dependent modality and hence may inadvertently influence the observation. Therefore, it is recommended for individual health-care centers to establish their own normative data for use in neonatal TV assessment. In addition, our study findings may act as a platform for more researches in developing local cutoff point and reference values for thyroid gland depth, length, width, and volume in neonates.

Conclusion

The value for total TV among the neonates in the Northwest Malaysian population was 0.61 (IQR = 0.230) cm³.

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Conflicts of interest

There are no conflicts of interest.

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