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ORIGINAL ARTICLE

Assessment of the thymic morphometry using ultrasound in full-term newborns

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Abstract
Purpose The size of thymus is variable and depends on age of the individual. Thymus undergoes its maximum development at the time of birth, when it also has the greatest relative weight. The aim of our study was to compare the two ways of expressing the size of the newborns′ thymus, the Thymus index and estimated volume of thymus.
Methods The examined group consisted of 212 full-term newborns from Slovakia, Europe. We estimated the length, width and thickness of the left and right lobes. We used these data to calculate the approximate volume of the thymus. We also expressed size of the thymus as a multiple of the transverse diameter of the cranial part of the thymus and the sagittal area of the larger lobe of the thymus, the so-called Thymus index. Bilateral differences in thymus lobes′ sizes, as well as the thymus′ sizes between sexes and among the newborns of different types of birth were also analysed.
Results Our results show that (1) the left thymus lobe is longer and thicker than the right lobe; (2) the Thymus index and the estimated volume of the thymus have a strong significant and positive correlation; (3) boys reach significantly higher values of the Thymus index than girls; and (4) when comparing the differences in the thymus size between the newborns born in two different ways (spontaneous and operatively), no significant difference was discovered.
Conclusion Ultrasound examination is safe, effective and suitable for simple assessment of the thymus size, which has a great variability in children. In other hand, the use of the Thymus index in everyday clinical practice is limited due to different mean values in a number of studies.

Keywords Thymus · Newborns · Sonography · Morphometry

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Introduction

Thymus is a central lymphoid organ with an important endocrine function. Inside thymus, proliferation and maturation of the T-lymphocytes, responsible for cell immunity, takes place. Thymus thus plays an essential role in securing the microenvironment for the differentiation and selection of T-lymphocytes and in the development of the immunocompetence of children [15]. The main role of thymus-derived lymphocytes is the protection against the tumourous cells, intracellular parasites and viruses; through cytokine secretion they activate other cells of the immune system [6, 16].

Thymus is one of the "most mysterious" human organs. The term "thymus" was introduced in human anatomy by Claudius Galenos of Pergamon in the second century AD

[26]. As cited by Beisel et al. [3], it was J. F. Menkel who in the nineteenth century for the first time mentioned the connection between the thymus atrophy and malnutrition. This anatomical link between nutrition and immunology was recognized long before the thymus was found to be of key immunological importance. Further examination of the thymic functions was unsuccessful until 1961. In that year, Jacques Miller demonstrated the effect of the thymectomy on the immune system of the newborn mice and discovered the key role of thymus in the development of cell-mediated immunity [28].

Human thymus usually consists of two asymmetrical lobes. It is located in the superior mediastinum, but in newborns it caudally reaches to anterior mediastinum [21, 31]. Thymus undergoes its maximum development in the time of birth, when it also has the greatest relative weight [7]. Its′ morphology varies greatly even in the same age group. These anatomic variations and dynamic changes appear to be the main source of confusion with pathologic conditions. Especially radiologists play a major role in differentiating normal thymic variants, ectopic thymic tissue, and non-neoplastic thymic conditions such as rebound hyperplasia from neoplastic conditions [31]. Detailed measuring of the thymus size was preserved from 1906 when it was done by Hammar. He discovered that thymic weight reaches maximum values at about the age of 10–15 years [17]. In the following years, a number of authors studied the size of thymus, especially in connection with the mortality of children caused by a fictive enlargement of thymus. The Austrian medical examiner Arnold Paltauf was the first who introduced the term "status thymolymphaticus" in 1889. Status thymolymphaticus indicates a constitutional disorder caused by hypertrophy of the entire lymphoid tissue, including the thymus, which, thus enlarged, could cause infant sudden death [27]. It was not until the morphometric research that the reliable data about the thymus size were obtained, which helped to discover that the deaths with the "fictitious diagnosis" of status thymolymphaticus were only coincidentally put into connection with a large thymus [37].

In clinical practice it is the conventional radiography (front chest radiographs) that is usually used to depict the thymic size, even though, currently this method is being gradually replaced by the computed tomography (CT) and magnetic resonance imaging (MRI) [29]. Nowadays, ultrasound is the prevailing method to depict the thymic size, too. Most frequent indications for a thymus control include a suspicion of an acquired or inborn defect of the thymus or a suspicion of a cyst or tumour.

In the ultrasound image, thymus' echogenicity is comparable to that of the liver [39]. Multiple of two sizes is used in determining the size of the thymus during ultrasonography: the biggest transversal width of the thymus and the sagittal plane of the bigger thymus lobe. Thus expressed, thymus size is described as Thymus (Thymic) index [19]. Thymus index has been shown to correlate with thymus weight at autopsy and has been used to show that the human thymus is sensitive to environmental influences during infancy [11, 30]. Determination of the thymus size through the Thymus index has been used by a number of authors, for example by Benn et al. [4], Garly et al. [14], Iscan et al. [23], Jeppesen et al. [24], Jeppesen et al. [25], Park et al. [33] and Zeyrek et al. [43].

The main goal of our study was to compare the two ways of expressing the size of the newborns′ thymus: the Thymus index (from two dimensions of thymus) and estimated volume of thymus (from six dimensions of thymus). Bilateral differences in thymus lobes′ sizes, as well as the thymus′ sizes between sexes and among the newborns of different types of birth were also analysed.

Patients and methods

The examined group consisted of 212 full-term newborns in the years 2005 and 2006 at the Department of Gynaecology and Obstetrics of General Hospital in Komarno (Slovakia, Europe). There were 122 boys and 90 girls. The newborns were born between weeks 38 and 42 of the gestation age. 169 of the newborns were born spontaneously and 43 were born by a Caesarean section. We did not include prematurely born babies and newborns with congenital infection symptoms, chromosomal anomaly and malformation into the study. We determined the thymus size within the first four days after delivery, approximately on the third day.

In our study, we measured the thymus size using the ultrasound equipment HITACHI EUB-525 CFM. The examination was conducted by a 10 MHz linear probe from the suprasternal or subxiphoid (transcardial) access, as well as through the nonossified sternum and intercostal spaces. We estimated the length, width and thickness of the left and right lobes. We used these data to calculate the approximate volume of the thymus: we imagined the two lobes as two prisms, the length of sides of which is known. The final volume of the thymus is given by the sum of the volume of the two prisms (volume of both lobes).

We also expressed the size of the thymus using the method by Hasselbalch et al. [19], the so-called "Thymus index". We established the Thymus index as a multiple of the transverse diameter of the cranial part of the thymus and the sagittal area of the larger lobe of the thymus (Figs. 1, 2, 3). All measurements were performed by a single sonographer.

We compared both ways of expressing the size of the thymus through the Spearman correlation. The closer is the

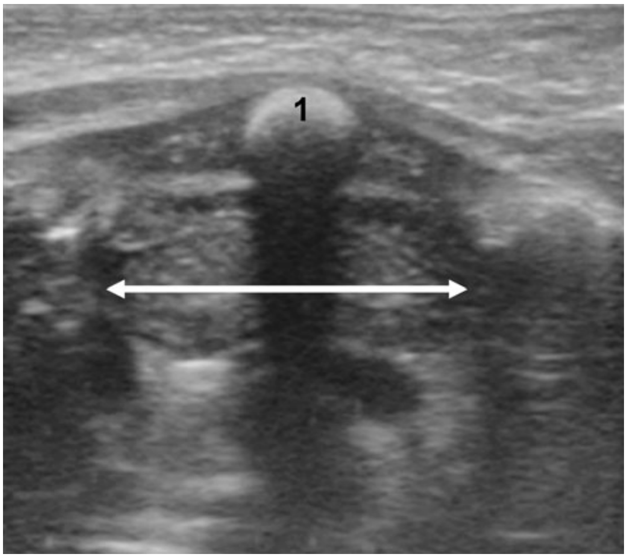

Fig. 1 The largest transversal diameter (width) of the thymus on the computer monitor (*1* ossification centre of sternum)

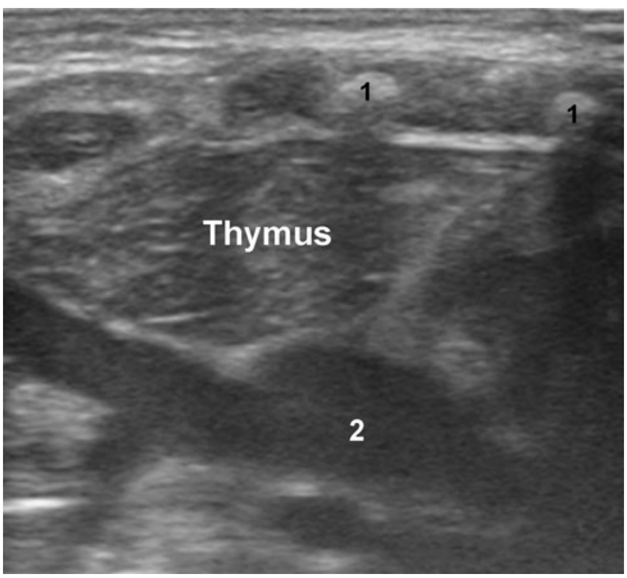

Fig. 2 The sagittal area (longitudinal scan plane) of the right thymic lobe on the monitor (*1*ossification centres of sternum; *2* vena cava superior)

Spearman's correlation coefficient (r) to the value of 1, the stronger is the correlation between two analysed indicators. Bilateral differences in the thymus lobes sizes, as well as the thymus sizes between sexes and among the newborns with different types of birth (spontaneous or operative) were analyzed by Mann–Whitney nonparametric test. We considered the results of the level of significance of $P < 0.05$ as statistically significant. Statistical calculations were done through the software Statistical Package for the Social Sciences (SPSS) for Windows version 13.0.

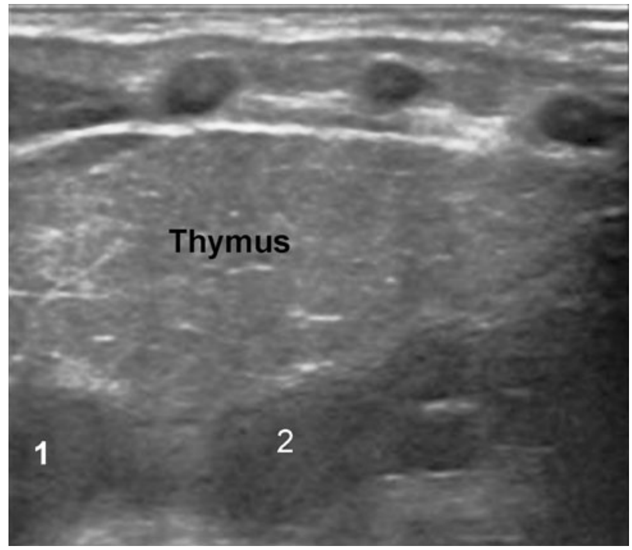

Fig. 3 The sagittal area (longitudinal scan plane) of the left thymic lobe on the monitor (*1* ascending aorta; *2* arch of aorta)

The study was approved by the local ethical committee of General Hospital in Komarno, Slovakia.

Results

Human thymus most often consists of two lobes. During examination of the group of 212 newborns, we noticed an anatomic variation of the thymus shape three times. Two of the newborns had a cranial accessory lobe, which stretched to the neck. It was 15 mm long and 8 mm thick with the girl born in the 39th week, and 14 mm long and 7 mm thick with the girl born in the 40th week. It did not cause any health problems in either of the cases. We presume that it is the remnant of the embryonic descent of the thymus. The third case of the discovered anomaly (girl, 39th week) completely lacked the left lobe. Since the mother of the newborn has been treated for epilepsy, the variation could have been a result of the anti-epileptic medication. However, the disturbed development of left thymic lobe did not relate on the anti-epileptic medication and can be only a random anatomical variation in the shape and size of thymus.

Basic morphometric proportions of the individual lobes can be found in Table 1. Our results show that the left thymus lobe is longer and thicker than that in the right lobe. Meanwhile the width and the estimated calculated volume of the right lobe are bigger than those of the left lobe. The data might be distorted since the contours of thymus are not always clearly visible and the shape of the thymus also changes during breathing, as well as with the heart activity.

We expressed the size of the thymus also using the Thymus index. Resultant values of the Thymus index in the studied group, as well as the values of both parameters for

Table 1 Morphometry of thymus in group of 212 full-term newborns

$n = 212$		Right lobe of thymus	Left lobe of thymus
Length of lobe (mm)	Mean	34.64	36.19
$P = 0.117$	SD	4.51	4.20
Width of lobe (mm)	Mean	13.79	12.76
$P = 0.035$	SD	2.68	2.53
Thickness of lobe (mm)	Mean	13.57	14.01
$P = 0.004$	SD	1.78	1.77
Volume of lobe (cm^3)	Mean	6.66	6.56
$P = 0.194$	SD	2.34	2.20
Volume of two lobes together (cm^3)	Mean	13.22	
	SD	3.82	

Table 2 Values of Thymus index in group of 212 full-term newborns

Thymus index	Mean	9.08
	SD	2.46
Transverse diameter of thymus (cm)	Mean	2.37
	SD	0.32
Sagittal area of thymus (cm^2)	Mean	3.80
	SD	0.73

the index calculation, can be found in Table 2. Statistical analysis helped us discover that the Thymus index (obtained from 2 morphometric data) and the estimated volume of the thymus (based on the three diameters of each of the lobes) have a strong significant and positive correlation ($r = 0.675$; $P < 0.001$; Fig. 4). Since both indicators of the thymus size positively correlate it is well-founded in clinical practice to use the easier Thymus index that requires examination of two diameters only rather than calculate the volume based on six diameters.

Analysing sex differences in thymus sizes with newborns, we discovered that boys reached statistically more significantly higher values of the Thymus index than girls. We did not prove a significant difference between sexes in estimated thymus volume (Table 3).

Birth presents natural stress for the newborn. We presumed that spontaneous birth is more stressful. When comparing the differences in thymus size between the newborns born in two different ways (spontaneous and operatively), no significant difference was discovered between the two groups ($P = 0.686$). Results can be found in Table 4.

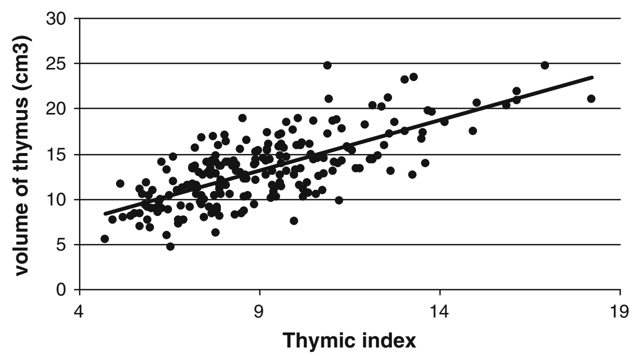

Fig. 4 Scatter plot of volume of thymus against value of Thymus index (Spearmans' $r = 0.675$; $P < 0.001$)

Discussion

Human thymus consists of two lobes divided by connective tissue. The pair embryonic primordia of both lobes are derived from the pharyngeal region of human embryo [40]. Literature mentions few records concerning anomalies in shape and location of thymus. About 100 cases have been described in the literature, ten per cent of which occurred in neonates. The most interesting clinical symptoms are

- the ectopic thymus causing severe dyspnoe, stridor or dysphagia [5, 36];
- the ectopic thymus mimicking thyroid gland enlargement [12];
- the ectopic thymus mimicking subglottic mass as congenital haemangioma [32]; and

Table 3 Analysis of sex differences in size of thymus in group of 212 full-term newborns

	n	Thymus index ($P = 0.011$)		Estimated volume of thymus ($P = 0.137$)	
		Mean	SD	Mean	SD
Boys	122	9.41	2.48	13.57	3.95
Girls	90	8.62	2.38	12.73	3.60

Table 4 Mean value of Thymus index in group of newborns borne spontaneously and operatively ($P = 0.686$)

	n	Mean	SD
Spontaneous delivery	169	9.03	2.42
Sectio Caesarea	43	9.26	2.64

- the ectopic thymus causing snoring at sleep [33].

Given the variability in shape and size of the thymus, familiarity with the broad spectrum of imaging appearance of the normal thymus will help radiologists minimize the number of invasive procedures. Thymic morphology varies greatly. For instance, in young adults, it is typically bilobed and V-shaped, with two small processes extending into the neck; however, it can also be unilobed, trilobed, or shaped like an X or inverted V [31]. Our group of 212 newborns included 3 anomalies in the thymus shape (twice it was a triple lobe thymus and once a single lobe), but without clinical symptoms.

In our study we focused on setting up of normative of the thymus diameters in the population of the full-term Slovak newborns. The significance of the thymus size in relation to age and immunity functions is being researched intensely. Even though some of the studies confirmed a close connection between the thymus size and weight and length of the babies' bodies, the significance of the big thymus in relation to the baby's health has not been confirmed. For example, only 25% of children with Di George's syndrome that suffer from hypoplasia or aplasia of thymus suffer from immunodeficiency, too [38]. On the other hand, it is known that malnutrition in young age causes thymus atrophy, which is in close relation to the dysfunction of the immune system. This state is described as nutrition thymectomy [9, 35].

Steinmann et al. [37] studied the weight and volume of thymus by necropsy in individuals of various age groups who suffered sudden death. The average value of thymus volume with children during the first year of their life is 26.8 ± 16.1 cm^3. The value of our calculated thymus volume is 13.22 ± 3.82 cm^3. Double values in the Steinmann et al. [37] group may be ascribed to the low number of individuals in the analysed group ($n = 6$), and the fact that the group did not consist of newborns only but included also babies of age up to one year. Thymus size in ultrasound imaging reaches largest values between the fourth and sixth months, and it gradually decreases after sixth or eighth month of age [42].

Ultrasound examination of the thymus has been introduced as part of the clinical practice abroad in the 1990s. It proved to be a simple and highly effective diagnostic procedure when identifying changes of this organ with foetuses, newborns and children. Despite all that there are relatively few studies that would provide a more detailed study of thymus morphometry in full-term newborns. However, ultrasound examination of thymus is a simple, non-invasive and effective method. It enables depiction of the individual parts of thymus, such as cortex, medulla and interlobular septum with blood vessels [18]. Despite the ultrasound imaging of children being often complicated by a significant variability of the thymus' size and shape, it does not expose the young patient to harmful radiation and does not require sedation when compared with CT scan and MRI [39]. Hasselbalch et al. [19] introduced new method of expressing the thymus size into clinical practice, the Thymus index. This index has been shown to correlate with thymus volume and weight at autopsy. We reached a similar result when comparing thymus volume based on measuring all the diameters of each lobe with the Thymus index.

Use of the Thymus index in everyday clinical practice is limited due to different average values in a number of studies. These depend on the skill of the sonographist, though differences between populations can also be found. That is why we compared our results with those of other authors (Table 5). In the study of Park et al. [33] the newborns' Thymus index was determined by six different radiologists and the average values of the Thymus index significantly differed based on the physician and the equipment used. Average values of the Thymus index moved between 8.1 and 13.2.

Table 5 Mean values of Thymus index (from the lowest to the highest value), according to several authors

Authors	n	Description of evaluated newborns	Mean value of Thymus index
Jeppesen et al. [25]	80	Pre-term newborns from Denmark	5.20
Jeppesen et al. [24]	12	Newborns born to mothers with HIV from Denmark	8.60
Zeyrek et al. [43]	50	Newborns of smoking mothers from Turkey	8.79
	92	Control group of newborns from Turkey	13.26
Our results	212	Full-term newborns from Slovak Republic	9.08
Park et al. [33]	982	Full-term newborns from east Slovakia	9.60
Benn et al. [4]	149	Full-term newborns from Denmark	11.90
Iscan et al. [23]	65	Full-term newborns from Turkey	13.60
Moore et al. [30]	1168	Full-term newborns from rural Bangladesh	27.6

According to our findings, the Thymus index is significantly higher in newborns of male sex. Our results do not correspond with those of Chen et al. [8], De Leon-Luis et al. [13], Hasselbalch et al. [20], Iscan et al. [23] and Jeppesen et al. [25]. According to their results, the difference in thymus size in newborns is not based on the sex. Aaby et al. [1] and Park et al. [33] recorded significantly higher values of the Thymus index in males.

We did not discover significant difference in thymus size based on the type of birth (spontaneous or operatively) in our group. Chen et al. [8] reached the same conclusion.

The most frequent thymic disorders according to Nasseri and Eftekhari [31] are thymic hyperplasia, thymic cyst and thymic tumours (thymoma, thymic carcinoma, lymphomas, Langerhans cell histiocytiosis, thymolipoma and thymic carcinoid). One of the most interesting phenomena in dynamic changes in morphology of thymus is the thymic enlargement after atrophy (during prolonged period of illness or after chemotherapy for malignancies). In some cases, the thymus after atrophy not only regrows, but occasionally overgrows or "rebounds" (regrowth 50% greater than baseline volume) [10, 41]. When the thymus increases in size after chemotherapy and/or radiation therapy, it may be difficult to differentiate rebound thymic hyperplasia from recurrence of lymphoma. A biopsy may be necessary in some patients. Bangerter et al. [2] demonstrate the utility of mini-invasive fine needle aspiration cytology as a front-line investigative procedure in the diagnosis of thymic hyperplasia, but also radiological methods, such as chemical shift MR imaging, can be used to differentiate thymic hyperplasia from thymic tumours [22].

Ultrasound imaging is among the easiest imaging methods of thymus in children since it allows for observation of shape and size of this organ. Ultrasound examination is safe, effective and suitable for simple assessment of the thymus size, which has a great variability in children. The thymic size and development is influenced by both nutritional and environmental exposures in early life, and quantitative reduction in children's tymic size could serve as an indirect marker of abnormal thymopoiesis and thymic insufficiency [13, 30]. The long-term functional implications of these findings require further investigation.

Conclusion

The main aim of our study was to compare the two ways of expressing the size of the thymus: the Thymus index (from two dimensions of thymus) and estimated volume of thymus (from six dimensions of thymus). Bilateral differences in thymus lobes′ sizes, as well as the thymus′ sizes between sexes and among the newborns of different types of birth were also analysed.

Our results show that

- the left thymus lobe is longer and thicker than the right lobe;
- the Thymus index and the estimated volume of the thymus have a strong significant and positive correlation;
- boys reach significantly higher values of the Thymus index than girls; and
- when comparing the differences in the thymus size between the newborns born in two different ways (spontaneous and operatively), no significant difference was discovered.

Ultrasound examination is safe, effective and suitable for simple assessment of the thymus size, which has a great variability in children. On the other hand, the use of the Thymus index in everyday clinical practice is limited due to different mean values in a number of studies.

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Conflict of interest There is no financial or other relationship that might be perceived as leading to a conflict of interest (i.e. affecting author objectivity).

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