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Fetal thymus reference range in healthy singleton pregnancies

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Abstract

Objective: To present the reference range of the fetal thymus gland according to gestational age groups.

Methods: In this prospective study, fetal thymus size was assessed in singleton, uncomplicated pregnancies between 19 and 38 weeks of gestation in our outpatient clinic between 2019 and 2020. Based on their monthly pregnancy follow-ups, fetal thymus measurement was divided into 5 gestational age groups (Group 1: 19–22 weeks, Group 2: 23–26 weeks, Group 3: 27–30 weeks, Group 4: 31–34 weeks, and Group 5: 35–38 weeks).

Results: Fetal thymus measurements of 210 patients were performed over one year, and as a result, 184 pregnant patients were included for assessment. Fetal thymus could be visualized at a rate of 93.5%. The 5th percentile of thymus transverse diameter, antero-posterior diameter, perimeter, thymus anterior-posterior diameter to thoracic diameter, and thymus perimeter to thoracic circumference were 11.03 mm, 5.60 mm, 32.52 mm, 0.33, and 0.32 in Group 1; 13.53 mm, 7.66 mm, 43.67 mm, 0.34, and 0.32 in Group 2; 20.43 mm, 11.22 mm, 47.72 mm, 0.33, and 0.32 in Group 3; 27 mm, 12.98 mm, 55.88 mm, 0.32, and 0.30 in Group 4; 28 mm, 13.59 mm, 63.4 mm, 0.32, and 0.30 in Group 5; respectively. Spearman's rho correlation coefficients for the thymic measurements were 0.879, 0.869, 0.846, 0.236, and 0.267 respectively, and all p-values were less than 0.001. As a result of linear regression analysis between thymus measurements and BPD; the equations for the optimal models are as follows: thymus transverse diameter= -3.49+0.4×BPD (mm) (r=0.826, R^2=0.682, p<0.001), thymus anterior-posterior diameter= -2.48+0.22×BPD (mm) (r=0.808, R^2=0.653, p<0.001), thymus perimeter= -14.37+1.21×BPD (mm) (r=0.814, R^2=0.663, p<0.001), thymus anterior-posterior diameter /thoracic diameter= 0.38+7.76E-4×BPD (r=0.213, R^2=0.045, p=0.004) and thymus perimeter/thoracic circumference= 0.35+1.02E-3×BPD (r=0.263, R^2=0.069, p<0.001). Thymus transverse diameter, anterior-posterior diameter, and perimeter increased linearly with increasing biparietal diameter (BPD).

Conclusion: We established the reference ranges of fetal thymus size. Thymus transverse diameter, antero-posterior diameter, and thymus perimeter have a strong relationship with gestational age and are easy and reproducible. Therefore, the knowledge of reference ranges of fetal thymus will enable the evaluation of thymic aplasia/hypoplasia.

Keywords: Fetal thymus, obstetric ultrasound, reference range.

Introduction

The thymus gland, which is a lymphoepithelial organ, plays a key role in the fetal immune system.[1,2] Evaluation of fetal thymus measurements in the neonatal period may allow the diagnosis of congenital absence or hypoplasia of the thymus.[3] It is known that 22q11.2 chromosome deletion syndromes including Di George syndrome, conotruncal facial anomalies and Shprintzen syndrome, chondroplasia punctata, Ellis-van Creveld syndrome, and ethanol exposure are often associated with thymus aplasia/hypoplasia.[1,4] Disorders in the immune system due to thymus hypoplasia will increase the susceptibility to

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infections.[5] Thymic hypoplasia is also a common finding in preterm premature rupture of membranes (PPROM), chorioamnionitis, maternal preeclampsia, Down syndrome, and other aneuploidies.[6–9] This finding can be considered as the cause of impaired immune functions in such pregnancy complications.[8]

Evaluation of the presence of thymus hypoplasia according to the week of gestation will be based on the knowledge of normal measurements of the fetal thymus gland. Owing to the developments in ultrasonographic imaging and the skills of clinicians, by the early second trimester, the thymus gland can be visualized and measurements can be taken in a short time provided the correct technique is used. In our study, it was aimed to determine the size of the fetal thymus gland according to weeks of gestation.

Methods

Fetal thymus measurements, which were performed only once for each patient with singleton pregnancies, for those who were routinely checked between 19–38 weeks of gestation in our outpatient clinic between November 2019 and November 2020 were included. If fetal thymus measurement was included once in the pregnancy follow-up, no re-measurement of the same patient in another week of gestation was included. Multiple pregnancies, pregnancies with fetuses with known chromosomal or major structural anomalies, preterm delivery (<37 weeks), intrauterine growth retardation, low birth weight (<2500 g), macrosomia (>4500 g), pregnancies with PPROM, chorioamnionitis, preeclampsia, and insulin-dependent gestational diabetes were excluded from the study. Also, the patients whose fetal thymus measurements could not be performed due to fetal position or maternal factors were not included. Fetal position was considered insufficient provided that the thymus could not be visualized due to shadowing of the surrounding bones.

Age, gravidity, parity, height, weight, body mass index, and weeks of gestation of the pregnant patients were recorded. The week of gestation was arranged according to the first day of the last menstrual period of the pregnant patient or due to the ultrasonography performed in the first three months of the pregnancy. The delivery process of the pregnant patients who had fetal thymus measurement was followed up. Birth week, birth weight and gender of the newborn, and any complications were recorded. Delivery information of the patients who delivered in other centers was obtained by phone calls.

The patients, whose fetal thymus measurements were performed starting from the 19 weeks of gestation, were divided into five groups as Group 1 (19+0 – 22+6 weeks), Group 2 (23+0 – 26+6 weeks), Group 3 (27+0 – 30+6 weeks), Group 4 (31+0 – 34+6 weeks), and Group 5 (35+0 – 38+6 weeks), based on their monthly pregnancy follow-ups.

All ultrasonographic examinations were performed transabdominally using Voluson E8 (5-8 MHz 3D transducer General Electric Healthcare; Little Chalfont, UK) device. Biometric measurements including biparietal diameter (BPD), femur length (FL), and abdominal circumference (AC) were performed. As described by Yagel et al., after the four-chamber view was obtained in the upper abdomen transverse section and angled towards the cranial, 3-vessel view was obtained and fetal thymus measurements were performed by 2 experienced ultrasonographers.[10] Maximum thymus diameter in the transverse section, the distance from the sternum to the end of the thymus in the anterior-posterior section, the distance between the sternum and the spine, thymus perimeter, and thoracic circumference were measured (**Fig. 1**). The ratio of thymic anteroposterior diameter to

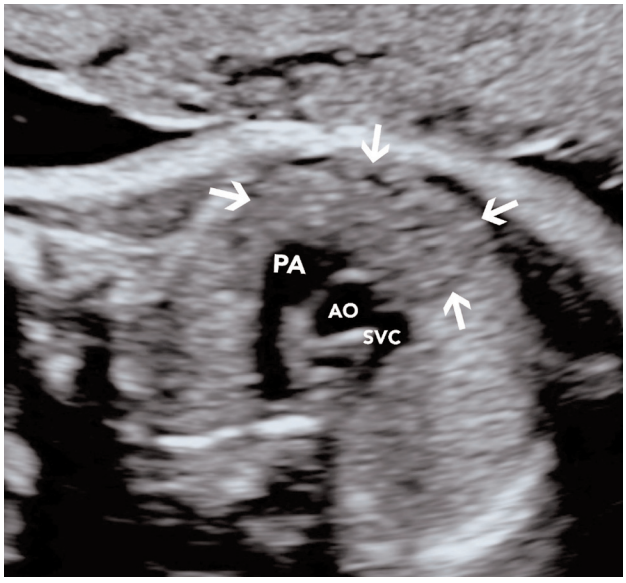

Fig. 1. Ultrasonographic view of the fetal thymus at 27 weeks of gestation, showing the thymus (**AO:** ascending aorta; **PA:** main pulmonary artery; **VCS:** superior vena cava; →: thymus).

thoracal anteroposterior diameter (thymus-thoracic ratio) and the ratio of thymus perimeter to thoracic circumference (thymus perimeter/thoracic circumference) was calculated. To create a nomogram for thymus size, a linear regression relationship between fetal thymus diameter and gestational age was calculated. The 5th, 50th, and 95th percentiles of thymic diameter for each gestational age were calculated from the regression equation.

Our study was planned by the Declaration of Helsinki. This study was approved by Başkent University Review Board (project number= KA19/410, approval date= 09.01.2020). Informed consent was obtained from all patients participating in the study.

Statistical analyses

Assistance was received from Başkent University Statistics Unit to establish the sample size. "Sonographic Measurement of Fetal Thymus Size in Uncomplicated Singleton Pregnancies (2016 Wiley Periodicals, Inc; VOL. 00, NO. 00, Month 2016)" study is utilized.[9] Based on the sample calculation results of this study, in which predicted mean and SD of maximal diameter, perimeter, and thymus/thoracic ratio, based on weeks of gestation and BPD were calculated by the regression model, a total of 210 patients with 95% CI and 90% power were determined to be included in the study. G-Power 3.1 program was used for sample size calculation. Statistical Package for the Social Sciences (SPSS) 21.0 package program (IBM Corp., Armonk, NY, USA) was used for statistical analysis of the data. Categorical measurements were summarized as numbers and percentages, while continuous measurements were defined as mean and standard deviation (median and range where necessary). Descriptive statistics were performed. The strength of association between fetal thymus transverse diameter, thymus antero-posterior diameter, thymus perimeter and biparietal diameter of the fetus was calculated by using Spearman's coefficient correlation. Linear regression analysis was performed by matching the gestational age with the fetal thymus measurements.

Results

In this study, in which fetal thymus measurements of 210 patients were performed over one year, delivery information of 16 patients could not be reached. Owing to newborn birth weight below 2500 g in five patients and above 4500 g in one patient, preterm delivery in two patients (24 and 26 weeks), preeclampsia (1 eclampsia) in two patients, and insulin-dependent diabetes mellitus in one patient, these patients were excluded from the study. Fetal thymus measurement could not be performed due to fetal position (n=7), maternal obesity (n=5), or oligohydramnios (n=2) in 14 patients who were in the last trimester and were initially planned to be included in the study (14/226, 6.25%). As a result, 184 pregnant patients, who had fetal thymus measurement after 19 weeks of gestation and who had a healthy delivery at term, were included in the study. There were 40 patients in the 19–22 weeks group, 56 patients in the 23–26 weeks group, 35 patients in the 27–30 weeks group, 26 patients in the 31–34 weeks group, and 27 patients in 35–38 weeks group. Obstetric histories of the study group were presented in **Table 1**.

In **Table 2**, 5–95th percentile values of thymus measurements according to weeks of gestation are demonstrated. The 5th percentile of thymus transverse diameter, antero-posterior diameter, perimeter, thymus anterior-posterior diameter to thoracic diameter, and thymus perimeter to thoracic circumference were 11.03 mm, 5.60 mm, 32.52 mm, 0.33, and 0.32 in Group 1; 13.53 mm, 7.66 mm, 43.67 mm, 0.34, and 0.32 in Group 2; 20.43 mm, 11.22 mm, 47.72 mm, 0.33, and 0.32 in Group 3; 27 mm, 12.98 mm, 55.88 mm, 0.32, and 0.30 in Group 4, 28 mm, 13.59 mm, 63.4 mm, 0.32, and 0.30 in Group 5, respectively. Spearman's rho correlation coefficient were 0.879, 0.869, and 0.846 for thymus transverse diameter, thymus anterior-posterior diameter, and thymus perimeter, respectively (all p-values <0.001) (**Fig. 2**). Thymus anterior-posterior diameter/thoracic anterior-posterior diameter was 0.43±0.06 and mean thymus perimeter/thoracic circumference was 0.42±0.06

Table 1. Obstetric and perinatal outcomes of the study group.

Median maternal age, years (range)	31 (19–43)
Median gravidity, range	2 (1–8)
Median parity, range	1 (1–4)
Median BMI, kg/cm^2 (range)	26.2 (16.8–50.4)
Median gestational age at admission, weeks (range)	26+3 (19+0–38+2)
Median gestational age at delivery, weeks (range)	38+5 (37+1–40+6)
Median birth weight, g (range)	3305 (2500–4260)
Fetal gender (female/male), n	91/93

Table 2. Percentiles of fetal thymus measurements according to gestational age groups.

	Gestational age group	Percentiles						
		5	10	25	50	75	90	95
Transverse diameter of the thymus (mm)	Group 1 (19–22 weeks), n=40	11.03	11.45	12.63	13.77	16.02	17.92	18.24
	Group 2 (23–26 weeks), n=56	13.53	15.15	18.24	20.98	23.81	25.81	26.94
	Group 3 (27–30 weeks), n=35	20.43	21.27	23.47	27.11	28.27	32.44	34.03
	Group 4 (31–34 weeks), n=26	27.00	27.64	29.15	32.42	33.45	34.49	35.37
	Group 5 (35–38 weeks), n=27	28.00	28.41	29.34	34.17	37.10	39.79	42.88
Antero-posterior diameter of the thymus (mm)	Group 1 (19–22 weeks), n=40	5.60	5.81	6.47	7.29	8.33	9.64	10.58
	Group 2 (23–26 weeks), n=56	7.66	7.96	9.60	11.01	12.48	13.52	14.75
	Group 3 (27–30 weeks), n=35	11.22	11.75	13.15	14.06	15.82	17.44	19.14
	Group 4 (31–34 weeks), n=26	12.98	13.04	13.36	17.29	18.85	19.84	21.21
	Group 5 (35–38 weeks), n=27	13.59	14.19	17.10	19.02	21.47	23.44	24.33
Thymus perimeter (mm)	Group 1 (19–22 weeks), n=40	32.52	33.42	37.00	40.30	44.90	51.37	55.46
	Group 2 (23–26 weeks), n=56	43.67	45.15	51.68	59.30	67.83	73.36	83.49
	Group 3 (27–30 weeks), n=35	47.72	58.76	71.50	77.60	86.30	99.24	109.18
	Group 4 (31–34 weeks), n=26	55.88	63.25	79.98	89.35	98.23	109.20	109.85
	Group 5 (35–38 weeks), n=27	63.40	66.80	80.40	99.10	114.80	130.92	144.40
Thymus antero-posterior diameter/ Thoracic diameter	Group 1 (19–22 weeks), n=40	0.33	0.33	0.38	0.41	0.43	0.44	0.45
	Group 2 (23–26 weeks), n=56	0.34	0.35	0.40	0.43	0.48	0.52	0.54
	Group 3 (27–30 weeks), n=35	0.33	0.34	0.38	0.45	0.49	0.52	0.54
	Group 4 (31–34 weeks), n=26	0.32	0.36	0.38	0.44	0.46	0.51	0.54
	Group 5 (35–38 weeks), n=27	0.34	0.37	0.41	0.45	0.48	0.55	0.58
Thymus perimeter/ Thoracic circumference	Group 1 (19–22 weeks), n=40	0.32	0.32	0.34	0.38	0.41	0.44	0.48
	Group 2 (23–26 weeks), n=56	0.32	0.34	0.38	0.42	0.46	0.49	0.52
	Group 3 (27–30 weeks), n=35	0.32	0.34	0.39	0.43	0.47	0.51	0.54
	Group 4 (31–34 weeks), n=26	0.30	0.33	0.40	0.46	0.48	0.51	0.54
	Group 5 (35–38 weeks), n=27	0.32	0.34	0.38	0.43	0.49	0.53	0.57

during all weeks of gestation. As the week of gestation progressed, a poor correlation of the thymus anterior-posterior/thoracic diameter and thymus perimeter/thoracic circumference with BPD was observed. Spearman's rho correlation coefficients were 0.236 and 0.267, respectively (all p-values <0.001) (**Fig. 2**).

As a result of linear regression analysis between thymus measurements and BPD, the equations for the optimal models are as follows: thymus transverse diameter= -3.49+0.4×BPD (mm) (r=0.826, R^2=0.682, p<0.001), thymus anterior-posterior diameter= -2.48+0.22×BPD (mm) (r=0.808, R^2=0.653, p<0.001), thymus perimeter= -14.37+1.21×BPD (mm) (r=0.814, R^2=0.663, p<0.001), thymus anterior-posterior diameter /thoracic diameter= 0.38+7.76E-4×BPD (r=0.213, R^2=0.045, p=0.004) and thymus perimeter/thoracic circumference= 0.35+1.02E-3×BPD (r=0.263, R^2=0.069, p<0.001) (**Fig. 3**). Thymus transverse diameter, anterior-posterior diameter, and perimeter increased linearly with increasing biparietal diameter (BPD).

Discussion

Thymus measurement is not routinely performed in the fetal ultrasonographic examination. However, knowledge of normal thymus size according to weeks of gestation will enable the evaluation of thymic aplasia/hypoplasia.[1] Therefore, we presented the normal range for fetal thymus measurements according to the weeks of gestation in healthy singleton pregnancies in this study.

Fetal thymic function and volume depend on genetic, nutritional, neural, endocrine, and immune factors.[11] Factors that cause placental implantation changes such

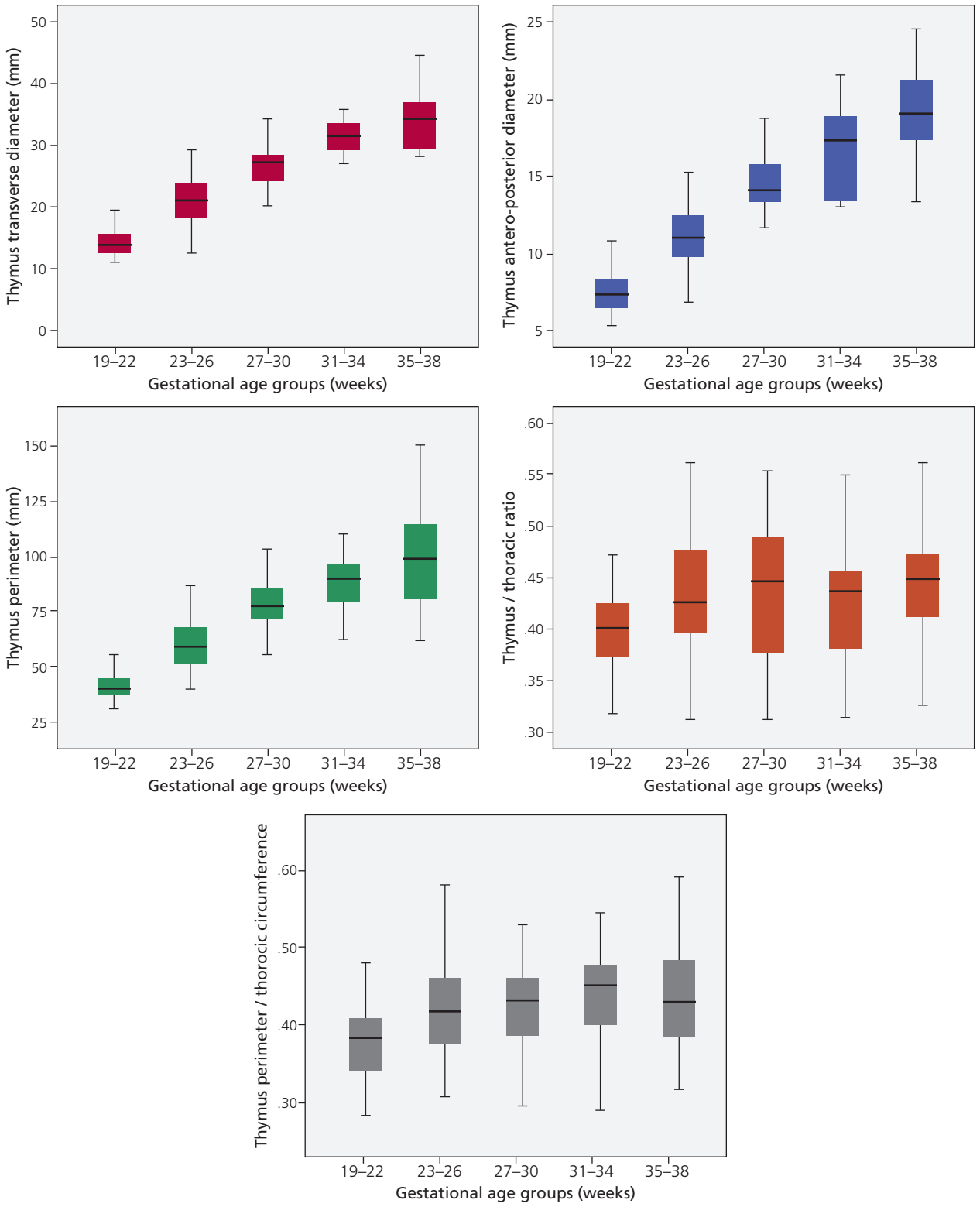

Fig. 2. Thymus measurements according to gestational age groups.

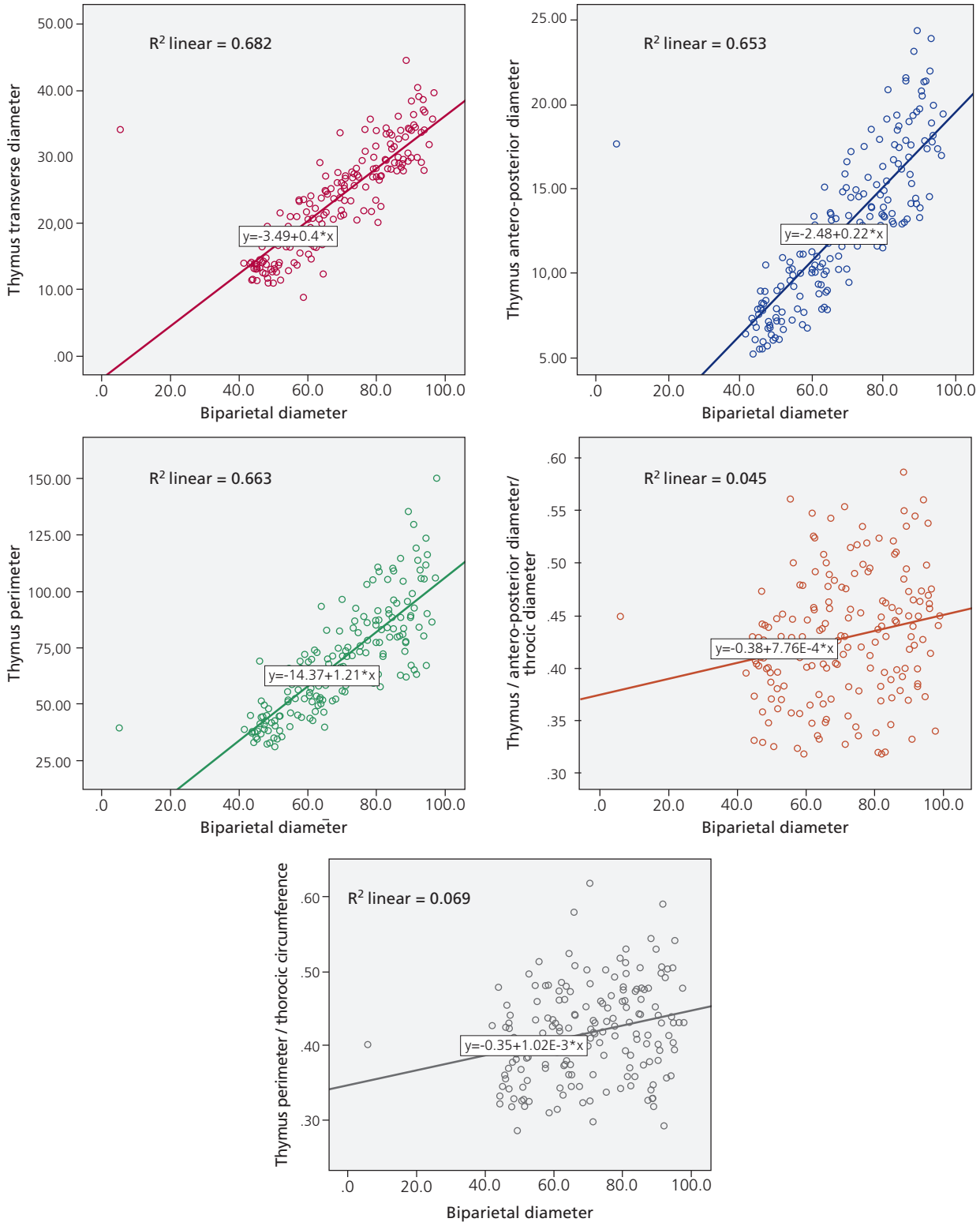

Fig. 3. Linear regression analyses of fetal thymus measurements and biparietal diameter.

as hypoxia, maternal diabetes, preeclampsia, and intrauterine growth retardation may induce fetal stress, leading to thymocyte depletion, and consequently, reduction in thymus size.[12] Since the detection of a small thymus in pregnancies with growth retardation may be an early indicator of adverse perinatal outcomes, it will enable clinicians to manage these pregnant patients more carefully, with necessary preventive measurements.[13]

Therefore, to detect abnormal fetal thymus measurements in pregnancy follow-ups in this study, we determined the reference ranges of thymus size starting from the 5th month in fetal ultrasonographic evaluation in healthy pregnancies. This can be easily used in daily practice and is suitable for monthly follow-ups.

Many authors present different ultrasonographic parameters in fetal thymus development. Thymus measurement parameters can be 2 or 3 dimensional (volume data set).[7–9,14] In Tai's study, it was stated that measurement of transverse diameter is more advantageous than thymus perimeter and thymus/thoracic ratio in thymus evaluation due to less interobserver variability.[14] On the other hand, it has also been reported that the thymic/thoracic ratio is a good predictor in the assessment of thymus in diabetic pregnant patients.[7,15] Chaoui et al. reported that the mean thymic/thoracic ratio in healthy fetuses was 0.44, independent of gestational age,[16] Also, in our study, the mean thymic/thoracic ratio was 0.43; however, no stability was found during pregnancy similar to the Iran study.[7] Therefore, in our study, we determined the reference range of 5 parameters owing to short measurement time and practicality in many cases in three-vessel cross-sections, with a non-invasive cost-free method. On the other hand, measuring only three parameters (thymus transverse diameter, anterior-posterior diameter, and perimeter) that are strongly correlated with gestational age may also be a better choice to assess thymus size.

Fetal thymus localization may always not be possible in the early and last weeks of pregnancy depending on fetal mobility, technique, and the characteristics of the ultrasound device.[17] It was stated in 1989 that the thymus gland could be seen from the 14th week of pregnancy at a rate of 74%.[18]

Despite important factors such as variability of thymic contours, the isoechoic structure of thymus and fetal position, current developments in ultrasound imaging have increased the visibility of the fetal thymus and allowed it to be visualized at earlier weeks.[18–20] It has been possible to visualize thymus 100% with the utilization of methods such as high-resolution transvaginal scan, thy-box (Doppler use), and 3D.[5,21] In the study of Tangshewinsirikul et al., thymus measurements were formulated according to weeks in healthy fetuses between 17 and 38 weeks of gestation, and an estimated reference range was determined. In this study, it was reported that 1% of the measurement could not be performed due to fetal position; however, the trimester in which the measurements could not be taken was not specified.[9] However, in our study, fetal thymus could be visualized at a rate of 93.5%, similar to the study of Cho et al.[1] All of the cases, whose measurements could not be performed, were in the last trimester and they were planned to be included in the study in terms of fetal thymus evaluation only at a glance.

As a result of our study, we observed that all thymic measurements (transverse diameter, anterior-posterior diameter, perimeter) increase linearly as the week of gestation progresses. In the study of Cho et al., the authors determined that the transverse diameter of the thymus at 33 weeks of gestation was similar in millimeters, while it was lower in earlier weeks, and it was slightly higher than the week of gestation after 33 weeks.[1] In our study, while we observed the thymus transverse diameter to be lower in millimeters compared to the week of gestation before 27 weeks, it was similar to the week of gestation after 27 weeks. It can be considered that these differences may occur due to ethnic or environmental changes as well as differences in measurement methods.

In our study, in which the reference range of all measurement parameters of the thymus was determined, we observed that thymic transverse diameter, thymus anterior-posterior diameter, and thymus perimeter nomograms were in high correlation (0.85–0.87) as the week of gestation progressed, while did not find ratio of thymic to thoracic anterior-posterior diameter and ratio of thymus perimeter to thoracic circumference nomograms useful. This ratio instability might be related to the thymus measurement skills. Research with larger series may bring about a more stable ratio of thymic to thoracic diameter and thymic

to the thoracic circumference. In some studies, thymus transverse diameter is often used as the only parameter due to its practicality and ease of measurement.[1,13,22,23] However, studies are evaluating 2 or more thymus parameters.[2,6,8,9,14,15] As a result, it is not evident which measurement methods are more sensitive and valuable in the evaluation of thymus aplasia.

Including the small number of patients for each week of gestation, being performed in a single-center, and excluding 6.5% of the patients due to lack of measurements are the main limitations of the study. Multicentric studies involving large populations from different regions and ethnic groups are needed on this subject. On the other hand, measurement of the fetal thymus by experienced specialists with standard measurement techniques in selected healthy singleton pregnancies is the strength of the study.

Conclusion

There are a limited number of studies on this subject, and the reference range for fetal thymus gland measurements in our country has not been determined yet. We consider that this study will contribute to the evaluation of abnormal thymus by determining the normal range for fetal thymus measurements according to the weeks of gestation.

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Compliance with Ethical Standards: The authors stated that the standards regarding research and publication ethics, the Personal Data Protection Law and the copyright regulations applicable to intellectual and artistic works are complied with and there is no conflict of interest.

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