

The relationship between fetal thymus volume and preterm birth in dichorionic diamniotic pregnancies

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DOI: [10.31083/j.ceog.2021.03.2340](https://doi.org/10.31083/j.ceog.2021.03.2340)

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Submitted: 28 October 2020 Revised: 25 December 2020 Accepted: 31 December 2020 Published: 15 June 2021

Background: The aim of this study was to compare fetal thymus volume in women who delivered at <36 weeks of pregnancy versus those who did not. **Methods:** A total of 32 dichorionic-diamniotic twin pregnant women were included in the prospective cohort study. The fetal thymus volumes were measured in the second trimester for each fetus using the VOCAL ultrasonography program. The data of women who experienced preterm labor (delivered at <36 weeks of pregnancy) and the control group (delivered at ≥36 weeks of pregnancy) were compared. **Results:** The mean thymus volume of each fetus was statistically significantly lower in preterm delivery cases than in the control group. Mean fetal thymus volume could be used as a marker for predicting preterm birth in the study group. The parameter of fetal thymus volume measured in twins at 18–24 weeks can be used as a predictive factor ($P < 0.001$). When the fetal thymus volume, measured 3-dimensionally by ultrasonography in conjunction with the VOCAL program, was used as a marker for predicting preterm delivery, the cut-off value was found to be 0.5245 cm^3 , with 83.3% sensitivity and 85.8% specificity (AUC 0.905, $P < 0.001$, 95% CI, 0.798–0.930). **Conclusion:** By predicting preterm delivery via measuring the fetal thymus volume in twins, physicians can suggest strategies to prevent preterm delivery at 18–24 weeks of pregnancy. In this way, fetal mortality/morbidity related to preterm delivery may be prevented.

Keywords

Dichorionic-diamniotic pregnancy; Fetal thymus volume; Preterm labor; Twin pregnancy

1. Introduction

Although twin birth rates have changed in recent years by maternal age and ethnicity, they are increasing and account for more than 3% of all live births [1, 2]. The risk of preterm birth for twins is 12 times higher than for single births. Twin pregnancies are high-risk pregnancies due to increased perinatal morbidity and mortality due to preterm delivery [3].

The two most researched methods for predicting preterm labor for multiple pregnancies are cervical length and fetal fibronectin [4]. A meta-analysis showed that in asymptomatic women with twins, a cervical length <25 mm was associated with a 25% birth risk before 28 weeks of gestation [5]. NICE does not recommend the use of fetal fibronectin in asymptomatic women with twin pregnancy; additionally, test positivity before the 34th gestational week is 33% predictive of

preterm birth risk, and test negativity before 34 weeks is 6% effective in predicting preterm birth risk [5]. Recent studies have also investigated the effects of both fetal fibronectin testing and cervical length assessment in predicting preterm delivery by women with multiple pregnancy. However, cervical length combined with fetal fibronectin did not improve prediction [6].

Chorioamnionitis is associated with a significant reduction in thymic size at birth in very-low-birth-weight preterm infants [7]. Fetal thymus measurement may allow an early diagnosis of chorioamnionitis in PPRM cases [8, 9]. A recent study speculated that small fetal thymus may be associated with early preterm birth, chorioamnionitis, neonatal sepsis, and morbidity [10]. The fetal thymus's role in preterm delivery for twin pregnancies is not well known, especially for twin pregnancies. A small thymus size may cause preterm delivery of twins.

The thymus, which is one of the primary lymphoid organs in the fetus, may undergo involution in some inflammatory processes. Whether this condition is affected by preterm labor caused by inflammation, which has a role in the etiopathogenesis of preterm labor, can be investigated. Previous studies [8] showed that fetal thymus tissue may lead to involution, which may lead to shrinkage of the thymus in chorioamnionitis. However, an exhaustive literature review failed to reveal any study investigating the role of fetal thymus size on preterm delivery rates of twins.

In this study, we aimed to evaluate dichorionic diamniotic pregnancies, a special patient group for preterm labor, in order to determine the relationship between preterm labor and thymus volume.

2. Materials and methods

2.1 Study design

In this prospective cohort study, 40 spontaneous dichorionic diamniotic twin pregnant women admitted to our clinic for second-trimester (18–24 gestational week) anomaly screening were evaluated over a 12-month period. The Ethics Committee approved the study in 2017 (number 211), and the Scientific Research Ethics Committee of the authors' faculty approved the research on 22 January 2018.



Fig. 1. Appearance the of fetal thymus in 3 vessel sections on ultrasonography (aorta, aortic artery; pulm arter, pulmonary artery; svc, superior vena cava; thymus, fetal thymus).

2.2 Patient selection

The study group consisted of women with spontaneous dichorionic diamniotic twin pregnancies ($n = 40$), 18–35 years of age, with no complaints at 18–24 weeks of gestation with normal renal, liver, and thyroid functions.

The exclusion criteria for the research group were as follows: (i) endocrinopathies, systemic disease, collagen disorder, hypercholesterolemia (familial or chronic hypercholesterolemia), sickle cell anemia, or a history of neoplasm; (ii) patients with a history of coronary artery disease, angina, or myocardial infarction; any history of known vascular, infectious (including current urinary tract infection), or inflammatory disease; or hypertension, coronary arteritis, electrocardiographic changes, or maternal autoimmune disease; (iii) the use of any drug within 3 months before pregnancy; (iv) singleton pregnancy; (v) alcohol drinkers; (vi) abnormal renal, hepatic, and thyroid function test results; (viii) refuse to participate in the study; (ix) abnormal fetal findings in any baby (fetal anomaly, nuchal translucency increase, first-/second-trimester screening test disorder); (x) abnormal fetal estimated fetal weight (<10 th percentile and/or >90 th percentile); and (xi) abnormal fetal growth difference pattern ($>10\%$ estimated fetal weight difference) in twins. Eight cases (2 women were lost at follow-up, and 6 cases had pregnancy complications (2 women with fetal anomaly, 2 women with gestational induced hypertension, 2 women with IUGR) were excluded from the study due to the exclusion criteria.

After the participants signed the consent form, they were accepted into the study. Age, gravida, parity, body mass index (BMI), systolic and diastolic blood pressures at admission, biparietal diameter (BPD), abdominal circumference (AC), femur length (FL), estimated fetal weight (EFW), and cervical length (mm) data were recorded. Fetal thymus volumes were recorded for each fetus. Cases were followed up during preg-

nancy and the week of the delivery, and APGAR scores at the 1st and 5th minutes, neonatal weight, cord blood pH, and base excess (BE) values during delivery were recorded.

Preterm Birth Diagnosis: Although there is no definite limit for twin pregnancy, all deliveries before 36 weeks were accepted as preterm births because the mean birth week is 35 weeks in twins [11, 12]. The data of women experiencing preterm labor (delivered at <36 weeks of pregnancy) and the control group (delivered at ≥ 36 weeks of pregnancy) were compared.

2.3 Thymus volume measurement

The thymus is located superior to the fetal thorax. The thymus, fetal sternum, 3-vessel images (superior vena cava, aorta, and pulmonary artery), and fetal lungs are observable when observing the transverse section of fetal thorax (Fig. 1). In the anterior mediastinum, the thymus is observed as a hypoechoic 2-lobe structure, as compared to other tissues. Each fetus's thymus dimensions were measured using VOLUSON E-10 ultrasonography, which can perform VOCAL measurement with the 2-dimensional and 3-dimensional VOCAL program in 3-vessel trachea (3VT) sections [6, 13–16] (Fig. 1). The 3-dimensional fetal thymus volume data were assessed using spatio-temporal image correlation with a standard 10-second acquisition time and an acquisition sweep angle of 30° . Its volume was calculated using a virtual organ computer-aided analysis (VOCAL) method with 30° of rotation (6 sequential planes). The mean time required to calculate the fetal thymus volume by VOCAL was 6 minutes (range, 4–8 minutes). One author evaluated these measurements, and all of the measurements were recorded. Separate measurements were made and recorded for each fetus. In addition, the thymus volumes of both fetuses were collected, divided by 2 to predict preterm delivery, and then averaged. Mean values were used in the final analysis.

Each measurement was repeated 3 times in each fetus, and the mean size was determined. The interobserver variability and reproducibility were 3.1% and 98%, respectively [8]. The fetuses whose thymus could not be adequately visualized were not included in the final analysis.

2.4 Statistical methods

All of the data were entered and coded in the SPSS 13.0 software package. A Kolmogorov-Smirnov test was used to test the normality assumption. Our data failed to pass this test, so Mann-Whitney U tests and Pearson correlation analyses were used for the computer statistical analysis. The data of the cases with preterm birth (<36 weeks) were compared with those without preterm birth (≥ 36 weeks). The ability of thymus volume to predict preterm labor complications was tested using binary logistic regression analysis. $P < 0.05$ was considered statistically significant. Data were expressed as mean \pm SD.

Table 1. Comparison of the study group in terms of some demographic and sonographic factors in cases with and without preterm labor/delivery.

Demographic and sonographic factors	The group with preterm birth (n = 18)	The group without preterm birth (n = 14)	P
Age (years)	31.83 ± 5.82	31.21 ± 4.49	>0.05
Gravida (no)	2.00 ± 1.03	2.07 ± 1.27	>0.05
Parity (no.)	0.61 ± 0.70	0.71 ± 0.83	>0.05
Body mass index (kg/m ²)	31.01 ± 5.88	29.98 ± 4.22	>0.05
Pregnancy week at the time of measurement (week)	20.59 ± 1.02	21.48 ± 1.79	>0.05
Gestational week at birth (week)	33.01 ± 2.69	36.66 ± 0.71	>0.05
Cervical length at first admission (mm)	34.22 ± 6.58	37.50 ± 4.40	>0.05
1. fetus EFW (g)	308.78 ± 91.23	318.64 ± 113.49	>0.05
1. fetus thymus volume (cm ³)	0.312 ± 0.205	0.893 ± 0.440	<0.001
2. fetus EFW (g)	308.22 ± 95.63	320.71 ± 103.45	>0.05
2. fetus thymus volume (cm ³)	0.318 ± 0.176	0.939 ± 0.510	<0.001
Average fetal thymus volume (cm ³)	0.315 ± 0.177	0.916 ± 0.416	<0.001
Cesarean section (%)	%100	%100	—
1st fetus birth weight (gr.)	1888.61 ± 611.93	2628.93 ± 333.41	<0.001
1. fetus fetal PH (no.)	7.32 ± 0.06	7.33 ± 0.04	>0.05
1. fetus BE (mmol/L)	-2.24 ± 3.78	-1.47 ± 1.72	>0.05
2. fetus birth weight (gr.)	1792.78 ± 606.67	2465.71 ± 286.27	<0.001
2. fetus fetal PH (no.)	7.31 ± 0.08	7.33 ± 0.03	>0.05
2. fetus BE (mmol/L)	-2.53 ± 3.23	-1.20 ± 2.78	>0.05

Data are given as mean ± standard deviation. Mann-Whitney U test was used for statistical comparison. The *P* value was bolded for significant comparisons.

3. Results

A total of 32 cases were evaluated for the final analysis. All of the patients were delivered spontaneously. In total, 18 women delivered at <36 weeks of pregnancy, while 14 women delivered at ≥36 weeks of pregnancy. There were no significant differences between the cases with and without preterm labor/delivery in the study group, in terms of some demographic and sonographic parameters (Table 1).

For the study group, Figs. 2,3 show the ROC analysis of the relationship between fetal thymus size and preterm labor, measured in the first and second fetuses at 18–24 weeks of gestation, within the scope of preterm labor development. When the fetal thymus volume measured in the first infant was used as a marker for the development of preterm labor, the sensitivity and specificity were 83.3% and 85.7%, respectively, for a thymus volume of 0.5245 cm³ (AUC 0.905, *P* < 0.001, 95% CI, 0.798–0.930). The sensitivity for the second fetus was 88.9%, with 78.6% specificity, for a volume of 0.5280 cm³ (AUC 0.883, *P* < 0.001, 95% CI, 0.762–0.980).

Fetal thymus size (in terms both twins and average thymus size) was significantly lower in women who developed preterm labor compared to those who did not develop preterm labor. Fig. 4 shows ROC analysis of the the relationship between mean fetal thymus size per twin and preterm labor. When the mean fetal thymus volume measured per twin was used as a marker for the development of preterm labor, the sensitivity and specificity were 88.9% and 92.9%, respectively, for a thymus volume of 0.5310 cm³ (AUC 0.921, *P* < 0.001, 95% CI, 0.823–0.960).

According to the binary logistic regression analysis per-

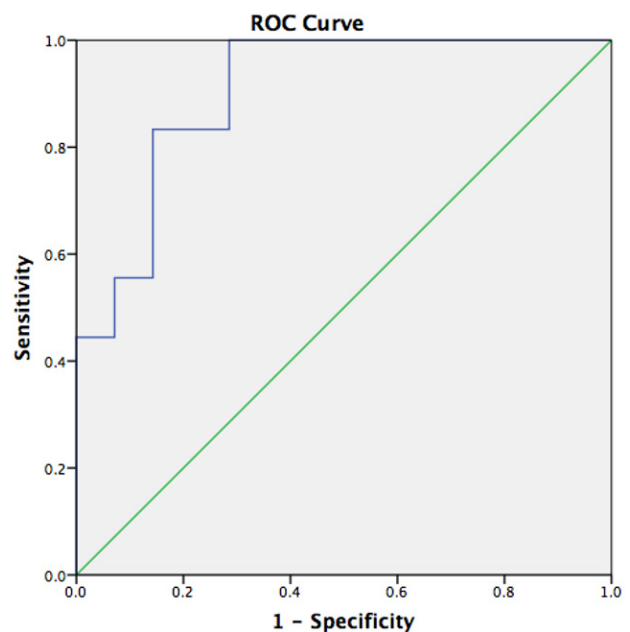


Fig. 2. ROC analysis showing the relationship between fetal thymus size and preterm labor in the first fetus for the study group.

formed to predict the development of preterm labor during pregnancy, low mean fetal thymus volume measured in both babies at 18–24 weeks can be used as a predictive factor (*P* = 0.008).

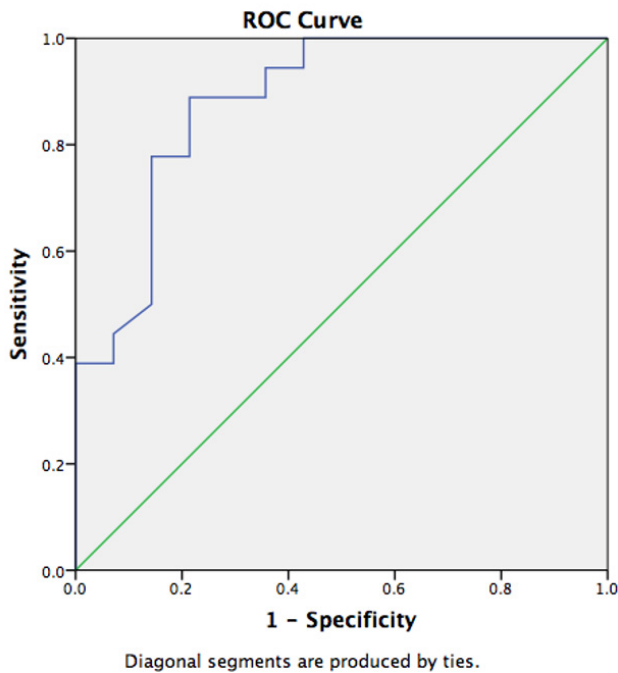


Fig. 3. ROC analysis showing the relationship between fetal thymus size and preterm labor in the second fetus for the study group.

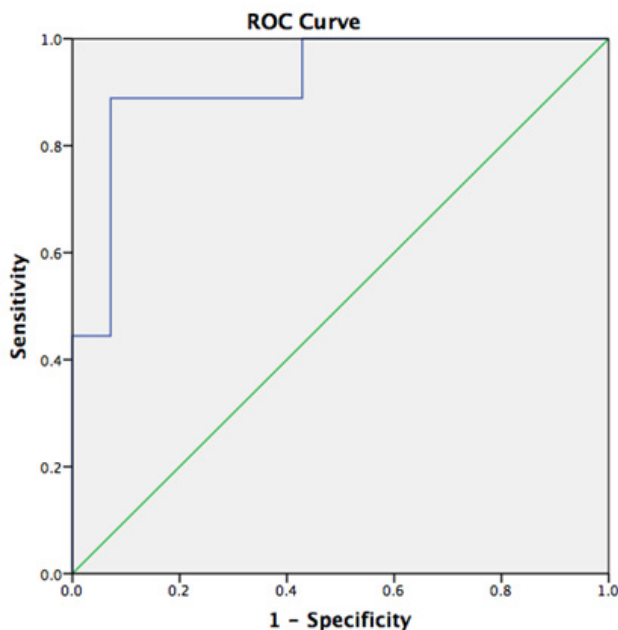


Fig. 4. ROC analysis showing the relationship between mean fetal thymus size per twin and preterm labor for the study group.

4. Discussion

Given that twin pregnancies have a higher risk for preterm delivery, identifying these cases would enable the development of effective interventions and a better understanding of the disease mechanisms leading to spontaneous preterm labor so as to prevent the associated negative perinatal outcomes [17]. The current study may suggest the use

of the fetal thymus for preventing complications associated with preterm delivery in twins.

The relationship between preterm birth and fetal thymus volume has been unknown [18]. One advantage of risk assessment with non-invasive markers such as fetal thymus volume may be the prevention of unnecessary and sometimes costly interventions for at-risk patients. In this study, fetal thymus volume was evaluated as a noninvasive marker that does not require additional cost. In dichorionic-diamniotic pregnancies, fetal thymus volume can be considered a marker for predicting preterm labor for each fetus in the second trimester.

Many markers have been used to predict preterm birth. Yet, the effectiveness of these markers in predicting preterm delivery is still controversial [17]. The evaluations needed for predicting preterm delivery should be conducted prior to 24 weeks of gestation. Although preterm labor appears at the end of second trimester and during the third trimester period, the first pathophysiological changes may occur earlier. In particular, maternal and fetal diseases that affect the fetus's immunity can initiate preterm delivery [19]. Therefore, in the current study, the fetal thymus volume was measured to evaluate the fetuses' immune adaptation and predict preterm delivery before viability in the physiology of preterm labor. The results showed that a small fetal thymus size may be a marker for preterm delivery before other reported fetomaternal findings (cervical opening, engagement, cervical remodeling, uterine contraction) appear in preterm delivery. When the thymus volume is evaluated as a marker in predicting preterm delivery, the cutoff value of 0.5280 cm^3 may be used as a valuable limit.

The fetal thymus produces thymosin alpha-1, which can be detected in maternal serum during pregnancy [19]. The thymus is the most important organ of the immune system and is responsible for immunity during the neonatal and infant periods. The idea that preterm delivery may be due to the weak immunity of the fetus was first introduced in 2007 in a chorioamnionitis study, in which the authors reported that thymus size decreased in patients who had preterm birth with chorioamnionitis [8]. As a result, they reported that the measurement of the fetal thymus might predict an early diagnosis of chorioamnionitis in PPROM cases [8]. Intrauterine infection and PPROM lead to fetal thymic involution [20]. An animal study reported that intrauterine inflammation on fetal thymus tissue decreased the number of CD8 T cells and altered the development and/or activation of CD4 T cells. Thus, the effects of chorioamnionitis in the thymus were also elucidated [21].

The fetal thymus responds sensitively to many systemic factors such as fetal chorioamnionitis. Fetal corticosteroids being released against systemic factors is the main factor of reduction in the thymus's size. These processes increase the lymphocyte release from the fetal thymus cortex. According to pathology and necropsy studies, in case of fetal infection, the fetal thymus's corticomedullary ratio changes, and

the thymus shrinks [22]. Fetal thymus shrinkage, which has been well defined during fetal infections, may also be possible in fetal latent inflammation. This inflammation may be associated with preterm birth in women with twin pregnancies. Furthermore, this situation may be predicted by measuring the fetal thymus's volume in the second trimester of pregnancy.

A small fetal thymus may initiate or be the result of a fetal systemic inflammatory process that initiates preterm labor. The fetal thymus's volume may not be large enough in response to the fetus's systemic inflammatory condition, so the low number of required protective cells (T lymphocytes) may be unable to prevent preterm delivery. Thus, future molecular and biochemical studies are needed to evaluate the relationship among fetal systemic inflammatory response, fetal thymus, and preterm labor.

In a study on sheep, Yang *et al.* [23] reported that COX-2 and AKR1B1 dimer expression was upregulated in the maternal thymus in early pregnancy, and they concluded that the thymus was involved in immunomodulation during early pregnancy. The current results also suggest that a small fetal thymus volume affects maternal-fetal preterm delivery.

Compared to other commercially available preterm-prediction factors, fetal thymus measurement is cheap, easy to use. This is the first study to report on the role of fetal thymus measurement for predicting pre-term delivery of twins.

The strengths of the study were that a single physician made the measurements and that the method is easily applicable, with no additional costs, visits (it may be measured during routine screening), and additional time loss for the patient, as well as the prospective design of the study. In addition, the investigation of twin pregnancies—a specific group in which preterm labor is frequently seen—as well as the evaluation of two fetuses according to single-fetus pregnancies and the evaluation of the fetuses' average thymus volume also make the research strong.

The limitations of the study included the margin of error of the VOCAL program, which is integrated with ultrasonography. Larger case series studies are needed to support this hypothesis due to the limited number of cases used in our study. In this prospective study, the thymuses were measured in the second trimester, but delivery was often months later. Missed intrauterine infections also may have caused small thymus volume. No placental histology was taken to confirm the presence of this condition. Further histopathologic studies are needed to exclude missed diagnoses of intrauterine infection.

5. Conclusions

In dichorionic-diamniotic twin pregnancies, fetal thymus volume measurement was found to be a marker predicting the development of spontaneous preterm labor. Small fetal thymus volume was a significant parameter in predicting preterm labor. When the fetal thymus volume, measured 3-dimensionally by ultrasonography in conjunction

with the VOCAL program, was used as a marker for predicting preterm delivery, the cut-off value was 0.5310 cm³, with high sensitivity and specificity. By predicting preterm delivery via measuring the fetal thymus volumes in twins at 18–24 weeks of pregnancy, physicians may be able to suggest strategies to prevent preterm delivery. Thus, fetal mortality/morbidity related to preterm delivery may be prevented.

Author contributions

All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript. HS and ESGG conceived, designed and performed the experiment; SG. analyzed the data.

Ethics approval and consent to participate

Clinical Trials Identifier Number: NCT04055701. All patients gave consent to participate the study.

Acknowledgment

We thank the numerous individuals who participated in this study.

Funding

This research received no external funding.

Conflict of interest

The authors declare no conflict of interest.

References

- [1] Chauhan SP, Scardo JA, Hayes E, Abuhamad AZ, Berghella V. Twins: prevalence, problems, and preterm births. *American Journal of Obstetrics and Gynecology*. 2010; 203: 305–315.
- [2] Martin JA, Hamilton BE, Osterman MJ, Curtin SC, Matthews TJ. Births: final data for 2013. *National Vital Statistics Reports*. 2015; 64: 1–65.
- [3] Fuchs F, Senat M. Multiple gestations and preterm birth. *Seminars in Fetal and Neonatal Medicine*. 2016; 21: 113–120.
- [4] Murray SR, Stock SJ, Cowan S, Cooper ES, Norman JE. Spontaneous preterm birth prevention in multiple pregnancy. *Obstetrician & Gynaecologist*. 2018; 20: 57–63.
- [5] Conde-Agudelo A, Romero R, Hassan SS, Yeo L. Transvaginal sonographic cervical length for the prediction of spontaneous preterm birth in twin pregnancies: a systematic review and meta-analysis. *American Journal of Obstetrics and Gynecology*. 2010; 203: 128.e1–128.e12.
- [6] Suff N, Story L, Shennan A. The prediction of preterm delivery: what is new? *Seminars in Fetal & Neonatal Medicine*. 2019; 24: 27–32.
- [7] De Felice C, Toti P, Santopietro R, Stumpo M, Pecciarini L, Bag-noli F. Small thymus in very low birth weight infants born to mothers with subclinical chorioamnionitis. *Journal of Pediatrics*. 1999; 135: 384–386.
- [8] Yinon Y, Zalel Y, Weisz B, Mazaki-Tovi S, Sivan E, Schiff E, *et al.* Fetal thymus size as a predictor of chorioamnionitis in women with preterm premature rupture of membranes. *Ultrasound in Obstetrics and Gynecology*. 2007; 29: 639–643.
- [9] Asghar A, Asad MR, Naaz S, Rani M. Screening of the growth of thymus of human fetuses. *Anatomy & Cell Biology*. 2019; 52: 478.
- [10] Caissutti C, Familiari A, Khalil A, Flacco ME, Manzoli L, Scambia G, *et al.* Small fetal thymus and adverse obstetrical outcome: a

systematic review and a meta-analysis. *Acta Obstetrica et Gynecologica Scandinavica*. 2018; 97: 111–121.

- [11] Ballabh P, Kumari J, AlKouatly HB, Yih M, Arevalo R, Rosenwaks Z, *et al*. Neonatal outcome of triplet versus twin and singleton pregnancies: a matched case control study. *European Journal of Obstetrics, Gynecology, and Reproductive Biology*. 2003; 107: 28–36.
- [12] Jacquemyn Y, Martens G, Ruysinck G, Michiels I, Van Overmeire B. A matched cohort comparison of the outcome of twin versus singleton pregnancies in Flanders, Belgium. *Twin Research*. 2003; 6: 7–11.
- [13] Falcon O, Peralta CFA, Cavoretto P, Faiola S, Nicolaides KH. Fetal trunk and head volume measured by three-dimensional ultrasound at 11 + 0 to 13 + 6 weeks of gestation in chromosomally normal pregnancies. *Ultrasound in Obstetrics & Gynecology*. 2005; 26: 263–266.
- [14] Peralta CFA, Cavoretto P, Csapo B, Falcon O, Nicolaides KH. Lung and heart volumes by three-dimensional ultrasound in normal fetuses at 12–32 weeks' gestation. *Ultrasound in Obstetrics & Gynecology*. 2006; 27: 128–133.
- [15] Falcon O, Cavoretto P, Peralta CFA, Csapo B, Nicolaides KH. Fetal head-to-trunk volume ratio in chromosomally abnormal fetuses at 11 + 0 to 13 + 6 weeks of gestation. *Ultrasound in Obstetrics & Gynecology*. 2005; 26: 755–760.
- [16] Falcon O, Peralta CFA, Cavoretto P, Auer M, Nicolaides KH. Fetal trunk and head volume in chromosomally abnormal fetuses at 11+0 to 13+6 weeks of gestation. *Ultrasound in Obstetrics & Gynecology*. 2005; 26: 517–520.
- [17] Conde-Agudelo A, Romero R. Prediction of preterm birth in twin gestations using biophysical and biochemical tests. *American Journal of Obstetrics and Gynecology*. 2014; 211: 583–595.
- [18] El-Haieg DO, Zidan AA, El-Nemr MM. The relationship between sonographic fetal thymus size and the components of the systemic fetal inflammatory response syndrome in women with preterm prelabour rupture of membranes. *BJOG: an International Journal of Obstetrics and Gynaecology*. 2008; 115: 836–841.
- [19] Welch RA, Mutchnick MG, Weller FE, Sokol RJ. Maternal and fetal circulating levels of thymosin alpha 1 during parturition. *American Journal of Reproductive Immunology and Microbiology*. 1987; 13: 125–127.
- [20] Kacerovský M, Dosedla E. Involuče fetálního thymu v ultrazvukovém obraze. Fetal thymic involution on ultrasound. *Ceská Gynekologie*. 2008; 73: 328–331. (In Czech)
- [21] Melville JM, Bischof RJ, Meeusen EN, Westover AJ, Moss TJM. Changes in fetal thymic immune cell populations in a sheep model of intrauterine inflammation. *Reproductive Sciences*. 2012; 19: 740–747.
- [22] Toti P, De Felice C, Stumpo M, Schürfeld K, Di Leo L, Vatti R, *et al*. Acute thymic involution in fetuses and neonates with chorioamnionitis. *Human Pathology*. 2000; 31: 1121–1128.
- [23] Yang L, Lv W, Liu Y, Chen K, Xue J, Wang Q, *et al*. Effect of early pregnancy on the expression of prostaglandin synthases in the ovine thymus. *Theriogenology*. 2019; 136: 166–171.