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Fetal thymus in growth-restricted fetuses due to placental insufficiency

Marisa Akemi Takeno[1], Roseli Mieko Yamamoto Nomura[1*]

SUMMARY

OBJECTIVE: The aim of this study was to assess fetal thymus size by ultrasound in growth-restricted fetuses due to placental insufficiency and compare to high-risk and low-risk pregnancy fetuses with normal placental function.

METHODS: This is a nested case-control study of pregnant women followed up at a university hospital (July 2012 to July 2013). In all, 30 pregnant women presenting small fetuses for gestational age (estimated fetal weight <p10) due to placental insufficiency (umbilical artery Doppler >p95) were compared to 30 high-risk and 30 low-risk pregnancies presenting normal Doppler indices. The thymus transverse diameter and perimeter were converted into zeta score according to the normal values for gestational age. Head circumference and femur length were used to calculate ratios.

RESULTS: Fetal thymus were significantly lower in pregnancies with placental insufficiency when compared to high-risk and low-risk pregnancies presenting, respectively, transverse diameter zeta score (-0.69±0.83 vs. 0.49±1.13 vs. 0.83±0.85, p<0.001) and P zeta score (-0.73±0.68 vs. 0.45±0.96 vs. 0.26±0.89, p<0.001). There was also a significant difference (p<0.05) in the ratios among the groups: pregnancies with placental insufficiency (TD/HC=0.10, P/FL=1.32, and P/HC=0.26), high-risk pregnancies (TD/HC=0.11, P/FL=1.40, and P/HC=0.30), and control group (DT/HC=0.11, P/FL=1.45, and P/HC=0.31).

CONCLUSION: Fetal thymus size is reduced in growth-restricted fetuses due to placental insufficiency, suggesting fetal response as a consequence of the adverse environment.

KEYWORDS: Thymus gland. Fetal growth restriction. Placental insufficiency.

INTRODUCTION

The relationship between nutrition and immunity is a well-known subject in the literature. It is widely recognized that malnutrition state interferes with the proper functioning of immune system, thus increasing morbidity and mortality due to infectious diseases[1]. During fetal life, chronic malnutrition state can be detected in pregnancies with placental insufficiency and fetal growth restriction (FGR). Studies in *postmortem* babies have shown that FGR is associated with a reduced weight of thymus gland[2], an important organ of immune system, and this event is attributed to atrophy of the lymphoid tissue.

Thymus atrophy seems to be part of a fetal response to intrauterine adversities. In situations such as placental insufficiency, activation of fetal hypothalamic-pituitary-adrenal axis increases glucocorticoid levels, which stimulate morphological and functional changes in a wide range of tissues to ensure fetal survival including thymus involution[3]. This process is also reported in chorioamnionitis and fetal inflammatory response syndrome, and recently, it has been investigated in preeclampsia, maternal diabetes, and COVID-19 infection[4-8]. Small thymus is associated with an increased child mortality, and its postnatal evaluation can predict the likelihood of survival in preterm infants[9,10].

Prenatal evaluation of fetal thymus has been described in the literature[11-14], along with nomograms for measurements of transverse diameter (TD) and perimeter (P), both assessed by ultrasound. This organ can be identified at the level of three-vessel and trachea views as a hypoechogenic and homogeneous element located between the vessels and the sternum. Magnetic resonance imaging (MRI) was also taken, providing an accurate representation of the structure[15]. Some authors tested the hypothesis that intrauterine growth restriction (IUGR) is associated with reduced fetal thymus size and were successful in finding that the organ was significantly smaller in growth-restricted fetuses compared to the control group[16-18].

The aim of this study was to make a sonographic evaluation of fetal thymus size in growth-restricted fetuses due to placental insufficiency and compare to high-risk and low-risk pregnancy fetuses with normal placental function. It was hypothesized that growth-restricted fetuses present reduced thymus size, as a consequence of chronic starvation and intrauterine adversity.

[1]Universidade de São Paulo, Faculty of Medicine, Department of Obstetrics and Gynecology – São Paulo (SP), Brazil.
*Corresponding author: roseli.nomura@hotmail.com
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METHODS

This is a prospective comparative study comprising 90 singleton pregnancies. The research was conducted at the University Hospital (Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo) from July 2012 to July 2013. The protocol (No. 0790/11) was approved on November 11, 2011, by the local ethics committee (Comissão de Ética para Análise de Projetos de Pesquisa – CAPPesq), and all the participants signed informed consent form.

Inclusion criteria for the study group were as follows: high-risk pregnancies presenting small fetuses with gestational age ranging from 26 to 37 weeks, singleton pregnancies, absence of fetal malformations, intact membranes, not in labor, no signs of maternal or fetal infection, and no use of corticoids before ultrasound evaluation. High-risk pregnancies were defined as those with clinical or obstetric complications or maternal morbidity. FGR was characterized by small fetuses presenting estimated fetal weight p10 for gestational age[19] and increased placental resistance characterized by abnormal umbilical artery (UA) pulsatility index (PI)[20] above the 95th centile for gestational age. This population was compared to 30 high-risk pregnancies with normal UA Doppler and normal fetal growth, which presented the following inclusion criteria: high-risk singleton pregnancies presenting adequate gestational age fetuses, with gestational age ranging from 26 to 37 weeks, absence of fetal malformations, intact membranes, not in labor, no signs of maternal or fetal infection, and no use of corticoids before ultrasound evaluation. The normal control group included 30 low-risk pregnancies without maternal or fetal morbidities, with gestational age ranging from 26 to 37 weeks, absence of fetal malformations, intact membranes, not in labor, no signs of maternal or fetal infection, and no use of corticoids before ultrasound evaluation. Gestational age was determined based on a reliable last menstrual period and early ultrasonography. The exclusion criteria for all groups were postnatal diagnosis of anomaly of the newborn and postpartum diagnosis of any maternal or fetal pathology of infectious origin.

All ultrasound evaluations were performed using a transabdominal 3.5-MHz curved-array transducer (Envisor, Philips, The Netherlands, or Voluson Expert, General Electric Medical Systems, Austria) by two examiners. The thymus was measured after its identification at the three-vessel and trachea views of fetal thorax, according to the technique described by Gamez et al.[13]. The measurements were obtained three times by the same observer, in a 3- to 5-min interval between examinations, and the mean of the values obtained was used for the analysis. Thymus TD was standardized by measurement of the diameter perpendicular to the line connecting the center of the sternum and the spine, with the calipers placed at the interface between the thymus and the lungs. P was also measured at the level of three-vessel and trachea views, using the trace function drawing the organ's boundary. All thymus parameters were transformed into z-scores (SD values from the mean) according to normative references[13]. The reproducibility of measurements of the fetal thymus by ultrasound showed an intraobserver correlation for DT of 0.97 (95%CI, 0.93–0.99) and for P of 0.97 (95%CI, 0.93–0.99) and an interobserver correlation for DT of 0.84 (95%CI, 0.68–0.99) and for P of 0.79 (95%CI, 0.55–0.90).

Ultrasound evaluation was performed weekly in placental insufficiency group, and the last assessment right before birth or antenatal corticosteroid was utilized in the analysis. Patients from high-risk and low-risk groups underwent ultrasound evaluation only once, at a similar gestational age as the study group. High-risk pregnancy group was composed of patients presenting maternal or obstetrical diseases with normal UA Doppler indices, during the same period of the study. Pregnant women without maternal or obstetrical morbidities built the control group; they were evaluated at an outpatient clinic during prenatal care appointment.

Conventional fetal biometric measurements were consistently evaluated. Ratios between thymus TD and P with femur length (FL) and head circumference (HC) were established. All Doppler recordings were done in the absence of fetal body or breathing movements. The high-pass filter was set at the minimum, and the size of the sample volume was adapted to the vessel diameter. To adjust for gestational age, all Doppler parameters were transformed into z-scores (SD values from the mean) according to reference curves[20].

Statistical analysis

Data were analyzed using the MedCalc program, version 11.5.1.0 (MedCalc Software, Belgium). The Kruskal-Wallis test was applied to compare continuous nonparametric variables between the groups. Categorical data were compared using the chi-square or Fisher's exact test. To minimize a possible influence of fetal size on the dimension of the thymus, the ratio between thymus measurements and fetal anthropometric parameters was calculated. The level of significance was set at $p<0.05$ for all tests.

RESULTS

A total of 90 patients were included in the study: 30 in growth-restricted fetuses due to placental insufficiency group, 30 in high-risk group, and 30 in low-risk group. Maternal characteristics, perinatal data, and Doppler velocimetry results of all groups

are shown in Table 1. The proportion of nulliparas was similar between the groups (66.7, 43.3, and 50%, p=0.285). The same was observed for maternal age and other characteristics. In growth-restricted fetuses, UA-PI was significantly increased, and so was the corresponding z-score (4.6, -0.5, and -0.2, p<0.001). As expected, the MCA-PI z-score was significantly decreased in this group compared to the others (-2.6, 0.1, and -0.6, p<0.001).

Thymus measurements were successfully obtained in all cases. Table 2 shows that the mean fetal TD and P (z-scores) (-0.689 and -0.734, respectively) and the ratios TD/HC, P/FL, and P/HC were significantly lower in placental insufficiency group (0.096, 1.318, and 0.261, respectively), compared to high-risk and low-risk groups. The TD/FL failed to reveal significant differences among the groups. Figure 1 displays fetal thymus TD and P in placental insufficiency group, high-risk group, and low-risk group plotted on the reference ranges published by Gamez et al.[13].

DISCUSSION

The purpose of this study was to investigate if there is an association between placental insufficiency and reduced fetal thymus

Table 1. Maternal and neonatal characteristics groups with fetal growth restriction, and high-risk and low-risk pregnancies.

Characteristics	Pregnancy with FGR and abnormal Doppler (n=30)	High-risk pregnancy and normal Doppler (n=30)	Low-risk pregnancy and normal Doppler (n=30)	p-value
Maternal age, years	27.4 (7.1)	29.9 (7.4)	28.5 (6.0)	0.138
Parity 0	20 (66.7%)	13 (43.3%)	15 (50.0%)	0.285
Maternal disease				
Hypertension	7 (23.3%)	12 (40.0%)	0 (0%)	<0.001
Diabetes	3 (10.0%)	9 (30.0%)	0 (0%)	0.002
Heart disease	4 (13.3%)	4 (13.3%)	0 (0%)	0.111
Renal disease	3 (10.0%)	1 (3.3%)	0 (0%)	0.198
Lupus	1 (3.3%)	4 (13.3%)	0 (0%)	0.064
Doppler				
UA-PI (z-score)	4.6 (2.7; 28.6)	-0.5 (-2.1; 0.8)	-0.2 (-1.8; 1.2)	<0.001
GA at examination, weeks	33.7 (27.7; 36.9)	34.9 (28.7; 37.1)	31.9 (26.4; 37.0)	0.008
GA at delivery, weeks	34 (28–37)	37 (32–40)	40 (37–41)	<0.001
Birth weight, g	1375 (770–2480)	2890 (1970–4040)	3296 (2465–3900)	<0.001
Newborn gender				
Female	10 (33.3%)	15 (50.0%)	19 (63.3%)	0.067
Male	20 (66.7%)	15 (50.0%)	11 (36.7%)	

Data are expressed as n (%), mean (SD), or median (range). FGR: fetal growth restriction; UA: umbilical artery; MCA: middle cerebral artery; PI: pulsatility index; GA: gestational age.

Table 2. Transverse diameter of the fetal thymus evaluated by ultrasonography in groups with fetal growth restriction, and high-risk and low-risk pregnancies.

Thymus measurements	Pregnancy with FGR and abnormal Doppler (n=30)	High-risk pregnancy and normal Doppler (n=30)	Low-risk pregnancy and normal Doppler (n=30)	p-value
TD (z-score)	-0.689 (0.832)	0.487 (1.125)	0.830 (0.853)	<0.001*
TD/FL ratio	0.485 (0.073)	0.501 (0.073)	0.509 (0.054)	0.392
TD/HC ratio	0.096 (0.011)	0.107 (0.017)	0.109 (0.011)	0.001*
P (z-score)	-0.734 (0.680)	0.447 (0.958)	0.258 (0.885)	<0.001*
P/FL ratio	1.318 (0.198)	1.404 (0.197)	1.448 (0.184)	0.035*
P/HC ratio	0.261 (0.031)	0.299 (0.044)	0.310 (0.035)	<0.001*

Data are expressed as mean (SD). FGR: fetal growth restriction; TD: transverse diameter; P: perimeter; FL: femur length; HC: head circumference. *FGR vs. HR: p<0.05; FGR vs. LR: p<0.05; HR vs. LR: p<0.05.

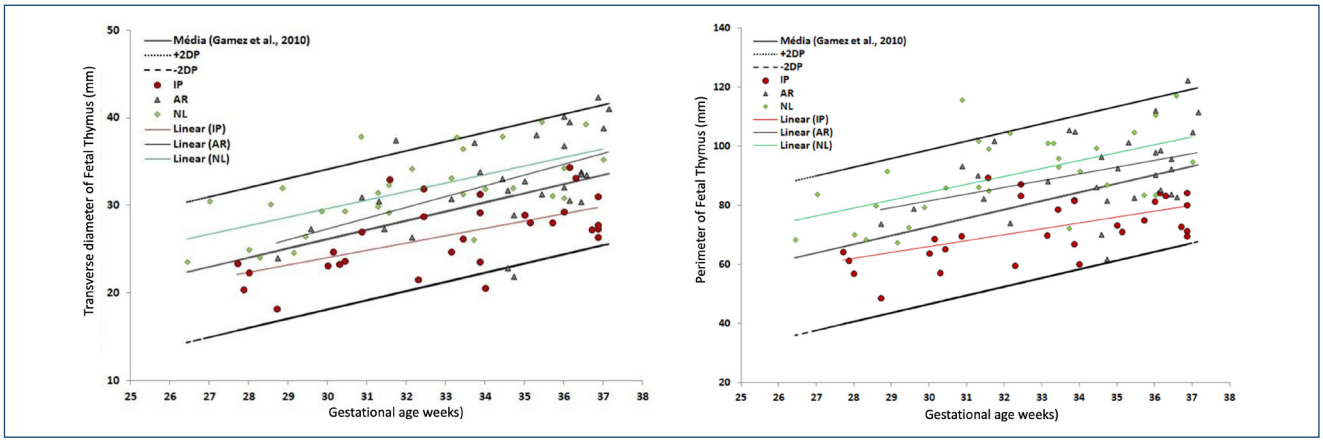

Figure 1. Transverse diameter and perimeter of fetal thymus plotted on reference ranges of Gamez et al. (media, +2DP, -2DP) in patients of placental insufficiency group (●), high-risk group (▲), and low-risk group (◆). The red, green, and blue lines represent the tendencies of placental insufficiency, high-risk, and low-risk groups, respectively.

size, suggesting the process of atrophy under hostile conditions. Our results confirmed that fetal thymus was smaller in growth-restricted fetuses due to placental insufficiency, compared to other groups without this condition. Other studies in the literature also presented similar findings[16-18]. Both high-risk and FGR groups were composed of patients with similar diseases, so they could not be considered confounding factors. The gestational age of inclusion of the cases presented a wide variation, and this may have caused the inclusion of early and late cases of FGR.

To correct the influence of fetal size, we analyzed the ratios of thymus dimensions/biometric parameters, similar to Cromi et al.[3]. We were successful in finding lower values in the ratios TD/HC, P/HC, and P/FL in FGR group, demonstrating that the structure was disproportionately reduced in this group. The only parameter that failed to show significant difference was ratio TD/FL. Cromi et al.[3] studied only thymus P, using reference range of Zalel et al.[11]. However, since the organ presents an irregular shape, in our study, TD was also measured, as a complement evaluation. We used the study of Gamez et al.[13] as a reference because it included the largest number of patients (678 fetuses), compared to other published references for normal ultrasound measurements of fetal thymus, and they assessed both TD and P.

Similarly, Ekin et al.[18] also studied only one parameter of fetal thymus measurement. They established a reference range of TD based on their control group and verified that the proportion of fetuses with this measurement below 5% for gestational age was higher in IUGR with abnormal Doppler group compared to IUGR with normal Doppler group. It apparently suggests that the more critical the situation of placental insufficiency is, the worse the thymus atrophy becomes[21].

In such cases of fetal chronic starvation, thymus involution seems to be mediated by activation of hypothalamic-pituitary-adrenal axis and glucocorticoid release[3]. The increased production of these steroids induces thymocyte depletion, and probably this is the mechanism responsible for thymus shrinkage[22]. Experimental studies in mice have confirmed that exposure to high concentrations of glucocorticoid leads to reduction in the total number of thymocytes, and this is due to an increased rate in cell death. On the contrary, adrenal insufficiency in humans and adrenalectomy of animals result in thymic hypertrophy[22]. The mechanism by which glucocorticoids cause thymocyte apoptosis is not totally known, but it may involve caspases, in a cell type-specific process. In 2020, Jones et al.[23] concluded that antenatal corticosteroid exposure was associated with a significant reduction in thymic size by ultrasound evaluation. Therefore, in our study, we excluded cases that received corticosteroid before assessment.

Fetal thymus can be evaluated in antenatal period either by ultrasound or by MRI[17,24]. The comparison of these two imaging modalities demonstrated good reproducibility, but the high cost of MRI made it not feasible for our study. Although 3D ultrasound assessment method seems to be promising[25], we chose not to use it, because thymus has a complex 3D shape, which could adversely affect the reproducibility of the method. In addition, the learning curve for volume measurement of the structure by 3D ultrasound is much longer and more difficult than standard 2D. Some authors preferred to use a second trimester thymus-thorax ratio, defined as the quotient of anteroposterior thymus diameter and anteroposterior thoracic diameter. However, they failed to predict preterm birth, as there is no gold standard for thymus measurements[5].

Small thymus is associated with increased neonatal adverse outcomes in very low birth weight infants, such as bronchopulmonary dysplasia, respiratory distress syndrome, patent ductus arteriosus, retinopathy of prematurity, periventricular leukomalacia, and sepsis[26], as thymic involution presumably occurs because of depletion of thymocytes. It is known that IUGR infants present low T-lymphocyte count, and this is apparently responsible for an increased susceptibility to infection. A meta-analysis that explored the association between small fetal thymus on ultrasound and adverse obstetrical outcome reported that small thymus increased the risk of neonatal sepsis and morbidity[27]. Small thymus size was also found in fetuses of diabetic mothers when compared to healthy controls[28].

This study had some limitations. There is no gold standard for validating ultrasound methods for measuring the fetal thymus. The small sample size does not allow to cause-and-effect association, and this restricted the performance of multivariate analyses and the construction of predictive curves for the parameters studied. We also did not perform a detailed assessment of factors related to the immunity or immunocompetence of neonates. The study of thymic function in prenatal life may help establish implications for later immune competence. As a limitation, we also observed a significant difference between the groups regarding hypertension. Although UA Doppler is normal in the high-risk group, placental insufficiency can be seen with altered uterine artery Doppler, but this has not been investigated in this population. So, further longitudinal studies must be conducted linking such prenatal assessment to a long-term follow-up of the infants.

CONCLUSION

Fetal thymus size is reduced in growth-restricted fetuses due to placental insufficiency, suggesting fetal response to adverse environment. Currently, we do not recommend the practical use of fetal thymus evaluation to predict perinatal outcome or to determine the timing of delivery in FGR. However, perhaps we should focus more on the fetal thymus in routine of morphological and obstetrical ultrasound. Besides, this field of study has recently started to be applied in association with other diseases during pregnancy, hence there is more to investigate. In the future, studies may combine prenatal assessment with the analysis of immune status markers and long-term follow-up of the infants and, then, establish a clear application of them in clinical practice.

AUTHORS' CONTRIBUTIONS

RMYN: Conceptualization, Data curation, Formal Analysis, Methodology, Supervision, Writing original draft, Writing – review & editing. **MAT:** Conceptualization, Data curation, Formal Analysis, Writing – original draft, Writing – review & editing.

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