Ultrasound measurements of the transverse diameter of the fetal thymus in uncomplicated singleton pregnancies

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Abstract

OBJECTIVE: To determine sonographically the transverse diameter of the fetal thymus and present nomogram for the transverse diameter of the fetal thymus in uncomplicated singleton pregnancies between 19 and 38 weeks of gestation.

Setting: Department of Obstetrics and Gynecology, Charles University in Prague, Faculty of Medicine Hradec Kralove, University Hospital Hradec Kralove, Czech Republic.

METHODS: A prospective study was performed. The transverse diameter of the fetal thymus was measured by the one experienced examiner in 198 healthy fetuses between 19 and 38 weeks of gestation.

RESULTS: The transverse diameters of the fetal thymus were obtained from 183 of the 198 subjects. The regression equation was expressed as a function of gestational age: the transverse diameter of the fetal thymus (mm) = 1.001 × gestational age (week) – 0.932 or 0.143 × day – 1.34. Both the correlation coefficients, r=0.91 for weeks and r=0.92 for days were found to be highly statistically significant (p<0.0001).

CONCLUSION: This study presents normative data (mean, 5th and 95th) for the ultrasound measurements of the transverse diameter of the fetal thymus in healthy singleton pregnancies.

INTRODUCTION

The thymus is a bi-lobed, key organ of the cellular branch of the immune system which plays an important role in the differentiation, selection and maturation of T-cell lymphocytes (Ciofani & Zuniga-Pflucker 2007). The thymic organogenesis begins at the third branchial cleft and the first lymphocytes appear in the thymus during ninth week of gestation (Jeppesen et al. 2003). The thymus grows and enlarges continuously between the prenatal period and puberty. Moreover, during its prenatal development, the size of fetal thymus is in close relationship with T-cell output (Haynes & Heinly 1995).

It is a well known fact that the thymus is susceptible to involution, which can occur in two different ways (Toti et al. 2000). First, age related
involution begins in the puberty and the thymus size and its activity are dramatically reduced. Nevertheless, residual T-cells production continues throughout the adult life (Tosi et al. 1982). Second, stress involution may appear during the prenatal period in response to different forms of acute stress stimuli such as infection, trauma, sepsis, malnutrition, acute respiratory distress syndrome and physical stress (Toti et al. 2000). This type of the thymic involution is initiated by the activation of the hypothalamo-pituitary-adrenal axis which in turn causes glucocorticoids induced apoptosis of cortical thymocytes (Suster & Rosai 1990). The stress thymic involution is histopathologically described by karryorhexis of lymphocytes with phagocytosis by macrophages. This process proceeds with increasing stimulation, but appears to be reversible in contrast to age related involution (Kendall et al. 1985; Toti et al. 2000).

The main purpose of this study was to sonographically evaluate the transverse diameter of the fetal thymus as potential ultrasound screening tools for the prenatal diagnosis of the stress thymic involution. However, the assessment of the fetal thymus stress involution requires a normative data for transverse thymus diameter at each gestational age.

The patients and methods

The study population was established from healthy pregnant women referred for prenatal ultrasound examination. A total of 198 women were recruited consecutively between October 2009 and May 2010. All agreed and provided written informed consent for this study. The study was approved by the Institutional Review Board Committee (March 19, 2008; no. 200804 SO1P). All women enrolled to this study were Caucasians. Only women who fulfilled the following criteria were enrolled: maternal age more than 18 years, singleton pregnancy, certain gestational age as documented by the last menstrual period and corroborated with ultrasound dating, an ultrasound estimated weight of the fetus between the 10th and 90th percentile for gestational age, the absence of the fetal structural malformations or chromosomal abnormalities and the absence of maternal diseases. Exclusion criteria were: pregnancies resulting in newborns with birth weight below the 10th and 90th percentile for the gestational age and the presence of fetal congenital abnormalities prenatally diagnosed or after birth.

All ultrasound evaluations were performed between 19 and 38 weeks of gestation in one prenatal ultrasound centre. Each subject was examined only during routine examination in the second and the third trimester of the pregnancy using a GE Logiq P5 (GE Medical Systems, Zipf, Austria) ultrasound device with a transabdominal 2–5 MHz transducer. All women were examined by the same experienced examiner (I.M.).

As previously described (Cho et al. 2007) the fetal thymus was found in the transverse section of the fetal chest between the sternum and the great heart vessels (“the three vessels” view) and the maximum transverse diameter of the fetal thymus was measured placing a line cursor upright to junction between the sternum and the spine (Figure 1). Each measurement was repeated three times in each fetus. The mean size was determined and used for statistical analysis.

All statistical analyses were performed using GraphPad Prism 5.03 for Windows (GraphPad Software, USA). The relationships between the transverse diameters of the fetal thymus with gestational ages were determined by linear regression modeling. A Bland-Altman plot of agreement was created for the intraobserver variability. A $p$-value < 0.05 was considered statistically significant.

RESULTS

The results of the fetal thymic transverse diameter measurements were obtained in 183 subjects. Thymus detection ratio was 92% (183/198 fetuses). The linear regression equations for mean transverse diameter of fetal thymus as a function of week and day of gestation.
The relationships are presented in Table 1. The relationships are shown graphically in Figures 2 and 3, which illustrate the regression line, the 5th and 95th percentile with the measured data. The Spearman correlation coefficient r=0.96 was found to be highly statistically significant p<0.0001. Table 2 displays the calculated mean of the transverse diameter of the fetal thymus and the 5th and 95th percentile for gestational age between 19 and 38 weeks of gestation. A Bland-Altman plot of the intraobserver agreement for the transverse diameter of the fetal thymus is shown in Figure 4. Intraobserver variability in our study was 3.5%.

**DISCUSSION**

The main goal of our study was to determine the transverse diameter of the fetal thymus in uncomplicated singleton pregnancy, with a secondary aim to determine the opportunity to be measured routinely during the prenatal fetal ultrasound examination in the second and the third trimester of the pregnancy. These questions are very important because they could perform the right way for our future an ultrasound clinical examination of prenatal fetal thymic involution in pathological singleton pregnancies.

Three different approaches for ultrasound measurement of fetal thymus have been published so far: the anterior-posterior thickness, the perimeter and the transverse diameter. The measurement of the anterior-posterior thickness of fetal thymus was referred to first (Felker et al. 1989). This technique does not appear to be useful because it suffers from a key limitation due to asymmetric shape and position of the thymus which is defined by the size and arrangement of the great heart vessels (Cho et al. 2007; Zalel et al. 2002). Other authors (Cromi et al. 2009; Di Naro et al. 2006; El-Haieg et al. 2008; Yinon et al. 2007; Zalel et al. 2002) have reported measurement of the thymus perimeter, but only a few studies were published about measurement of the thymic transverse diameter (De Leon-Luis et al. 2009; Gamez et al. 2010; Cho et al. 2007). The perimeter of the thymus is difficult to define due to poor echogenic conditions and the measurement itself is rather time consuming. On the other hand, the transverse diameter of the fetal thymus can be defined more consistently, and is therefore more readily measurable, owing to the fact that the borderline between the thymus and the lung (lateral margin of the thymus) are clearly defined (Cho et al. 2007; Kacerovsky & Boudys 2009).

To obtain reliable results in our study, we did not perform the measurements if the image was not of good quality due to unfavorable fetal position or maternal acoustic conditions. In 8% of fetuses the image quality was considered as unsatisfactory. Nevertheless, most of the unsuccessful measurements in our cohort of subjects were at the beginning of the study. Therefore, the failure of the fetal thymus measurement is considered to decrease with examiner experience.

**Tab. 1.** Linear regression equations for normalizing the transverse diameter of the fetal thymus (mm).

<table>
<thead>
<tr>
<th>Variable</th>
<th>Regression equation</th>
<th>r²</th>
<th>p-value</th>
</tr>
</thead>
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<tr>
<td>Gestational age - weeks</td>
<td>1.001 \times week - 0.932</td>
<td>0.91</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Gestational age - days</td>
<td>0.143 \times day - 1.34</td>
<td>0.92</td>
<td>&lt; 0.0001</td>
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**Tab. 2.** Predicted mean and 5th and 95th percentile (mm) range for the transverse diameter of the fetal thymus at each gestational age.

<table>
<thead>
<tr>
<th>Weeks of gestation</th>
<th>n</th>
<th>Mean</th>
<th>5th percentile</th>
<th>95th percentile</th>
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Utrasound measurement of the fetal thymus uncomplicated singleton and twin pregnancies and in addition it is not affected by twin chorionicity (Gamez et al. 2010). Therefore, we suppose, that our nomogram may be used not only for singleton but also for twin pregnancies.

In summary, the present study provides a normative data for the noninvasive ultrasound measurement of the transverse diameter of the fetal thymus in healthy singleton pregnancies and confirms that the fetal thymic transverse diameter can be easily measured prenatally. Nevertheless, further studies are necessary to clarify usefulness of this nomogram for detection of thymic involution in the pathological pregnancies.

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Disclosure of interest

There is no direct or indirect commercial or financial incentive associated with publishing this article.
Details of ethics approval
The study was approved by the Institutional Review Board Committee (March 19, 2008; No. 200804 SO1P)

REFERENCES