Ultrasound Measurement of the Transverse Diameter of the Fetal Thymus in Pregnancies Complicated by the Preterm Prelabor Rupture of Membranes

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ABSTRACT: *Purpose.* To determine whether the measurement of the transverse diameter of the fetal thymus is of value in the identification of either histologic chorioamnionitis or funisitis in pregnancies complicated by preterm prelabor rupture of membranes (PPROM).

Methods. The transverse diameter of the fetal thymus was measured in 216 fetuses from PPROM pregnancies. A small thymus was defined as a transverse thymic diameter below the fifth percentile according to a previously published nomogram. The placenta, the fetal membranes, and the umbilical cord were assessed for the presence of inflammation.

Results. A small thymus was identified in 69% (150/216) of fetuses. A small thymus was present in 80% (106/133) and 88% (36/41) of women with histologic chorioamnionitis or funisitis, respectively. The presence of a small thymus had a sensitivity of 79%, specificity of 47%, positive predictive value of 71%, negative predictive value of 59% for the identification of chorioamnionitis ($p < 0.0001$; odds ratio 3.5) and a sensitivity of 88%, specificity of 35%, positive predictive value of 24%, and negative predictive value of 92% in the identification of funisitis ($p = 0.004$; odds ratio 4.4).

Conclusions. The sonographic finding of a small thymus is a sensitive indicator of histologic chorioamnionitis or funisitis; low specificity excludes it as a possible clinical implication in the management of PPROM pregnancies. © 2013 Wiley Periodicals, Inc. *J Clin Ultrasound* **00**:000–000, 2013; Published online in Wiley Online Library (wileyonlinelibrary.com). DOI: 10.1002/jcu.22027

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Preterm prelabor rupture of membranes (PPROM) is responsible for approximately one third of preterm deliveries.[1] Microbial invasion of the amniotic cavity has been found in approximately 30% of PPROM.[2] The presence of microorganisms in the amniotic fluid (AF) triggers a cascade of inflammatory processes, followed by the infiltration of neutrophils in the fetal membrane, the placenta and umbilical cord. This condition, which is known as histologic chorioamnionitis (HCA), has 2 parts, according to the type of host inflammatory response. It is maternal when the amnion, the chorion decidua and the chorionic plate are affected, and it is fetal (funisitis) when the umbilical cord is involved.[3] Although both HCA and especially funisitis are

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associated with a higher rate of perinatal mortality and short- and long-term neonatal morbidity, many cases remain clinically silent.[4–6]

Previous studies have indicated that the presence of HCA could stimulate the fetal hypothalamic-pituitary-adrenal gland axis with subsequent enlargement of the fetal adrenal glands and elevation of levels of fetal adrenal gland hormones.[7–9] Moreover, stress-related thymus involution has been proposed as a consequence of activation of the hypothalamic-pituitary-adrenal gland axis.[10]

The relationship between the presence of HCA and the reduction of fetal thymus was first described on a postnatal X-ray of the fetal chest. The fetuses from pregnancies complicated by HCA had smaller thymuses than those from pregnancies without HCA.[11] As prenatal sonographic (US) assessment of the fetal thymus has become feasible, the thymic alterations related to HCA or funisitis have been studied prenatally. The US evaluation of the fetal thymus has previously been used in terms of the detection of HCA or funisitis in either PPROM or spontaneous preterm delivery in relatively small studies.[12–14] The finding of the size of the fetal thymus below the fifth percentile for gestational age, called a small thymus, has been proposed as a potential tool for the prediction of both HCA or funisitis. In all these studies, the size of the fetal thymus was determined by the thymic perimeter. The identification of the thymic perimeter can be very difficult under unfavorable US conditions, especially in pregnancies with PPROM. The measurement of the transverse diameter of the fetal thymus, which is easier to define and measure than the perimeter, could be beneficial in PPROM pregnancies.[15]

Therefore, the aim of this study was to determine if the US finding of a small thymus (defined as the transverse diameter of the fetal thymus being below the fifth percentile for the gestational age) is of value for the prediction of HCA or funisitis in PPROM pregnancies.

MATERIALS AND METHODS

A prospective cohort study of pregnant women admitted between May 2008 and December 2011 to the Department of Obstetrics and Gynecology, University Hospital Hradec Kralove, Czech Republic was conducted. Inclusion criteria were a gestational age between $24^{0/7}$ and $36^{6/7}$ weeks, singleton pregnancy PPROM, maternal age $\geq$18 years. Exclusion criteria were fetal growth restriction, fetal malformation, the presence of chromosomal abnormalities, vaginal bleeding, and signs of fetal hypoxia.

In total, 243 women with PPROM were recruited. The results regarding the measurement of the transverse diameter of the fetal thymus and the evaluation of the placenta were unavailable for 5 (2%) and 22 (9%) women, respectively. Therefore, 216 remaining women were included in this study. The gestational age was established on the first trimester US examination in all women.

PPROM was defined as the rupture of fetal membranes with a leakage of AF that precedes the onset of uterine contractions by at least 2 hours and that occurs at before 37 weeks gestation. This condition was diagnosed by sterile speculum examination confirming AF in the vagina in association with a positive test for the presence of insulin-like growth factor-binding protein in the vaginal fluid (ACTIM PROM test; Medix Biochemica, Kauniainen, Finland).

In the Czech Republic, women with PPROM at less than 34 weeks of gestation are treated with corticosteroids for the induction of lung maturation, tocolytics for 48 hours, and antibiotics, whereas no treatment is initiated to delay delivery after 34 weeks except antibiotics. Management of PPROM is not expectant (except for pregnancies before 28 weeks gestation); induction of labor is initiated, or elective cesarean section is performed depending on the gestational age (within 24 hours in gestational age above 34 weeks, within 48 hours between 32 and 34 weeks of gestation, and within 72 hours after rupture of the membranes at a gestational age between 28 and 31 week), the fetal status, maternal serum C-reactive protein concentrations, and cervicovaginal Group B Streptococcus colonization but not later than 72 hours after rupture of the membranes.[16]

At the time of delivery, the placenta, the fetal membranes, and the umbilical cord were fixed in 10% neutral buffered formalin. Samples were obtained from fetal membranes (minimum 2 samples), placenta (minimum 2 samples), and umbilical cord (usually 1 sample), processed according to standard protocols, and embedded in paraffin. Sections of tissue blocks were stained with hematoxylin and eosin.

This study was approved by the Institutional Review Board committee (March 19, 2008; No. 200804 SO1P), and informed consent was obtained from all participants.

US evaluation of the fetal thymus was performed at the time of admission before the

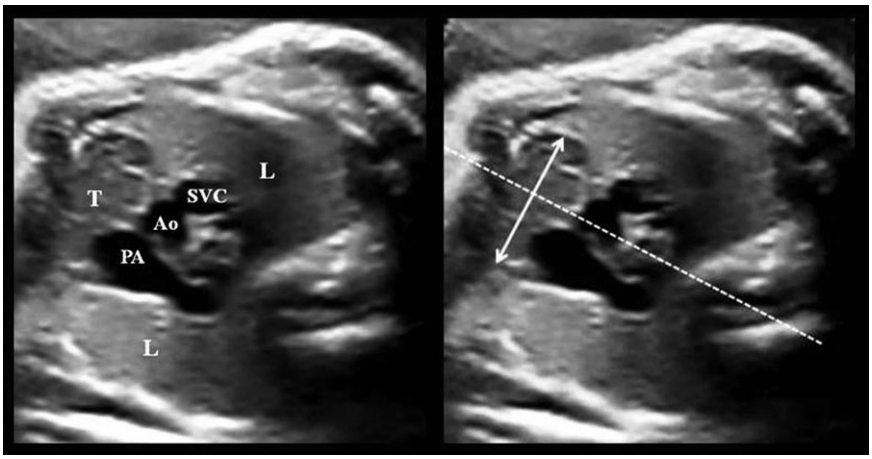

FIGURE 1. Transverse sonogram of the fetal thorax (30 weeks gestation) without (left) and with (right) the measurement of the transverse diameter of the thymus (double arrow). Abbreviations: Ao, aorta; L, lung; PA, pulmonary artery; SVC, superior vena cava; T, thymus.

administration of corticosteroids and antibiotics using an Aplio SSA-77A scanner with a 3.5–7 MHz convex transabdominal probe (Toshiba, Tokyo, Japan). The thymus was visualized in the transverse section of the fetal thorax between the sternum and great vessels ("three vessels" view). The transverse diameter was defined as a maximal diameter of the fetal thymus perpendicular to the junction between the sternum and the spine (Figure 1). The measurement was repeated 3 times on each fetus and the mean size was used for statistical analysis. A small thymus was defined as a thymic transverse diameter below the fifth percentile for gestational age, according to a previously published nomogram.[17] All measurements of the fetal thymus were performed by 2 sonographers (I.M., M.K.)

The degree of neutrophil and leukocyte infiltration was assessed separately in free fetal membranes (amnion and chorion-decidua), in the chorionic plate, and in the umbilical cord, according to the criteria described by Salafia et al.[18] HCA diagnosis was made based on the presence of neutrophil infiltration in the chorion-decidua (grade 3–4), the chorionic plate (grade 3–4), the umbilical cord (grade 1–4) and/or the amnion (grade 1–4). Funisitis was diagnosed by the presence of neutrophil infiltration within the umbilical cord.[18] Histopathological examination was performed by a single pathologist (H.H.) who was blinded to the clinical status of the women.

Statistical Analyses

The normality of the data was tested using the D'Agostino and Pearson omnibus normality test and the Shapiro-Wilk test. Continuous variables were compared using the unpaired *t* test (presented as mean ± SD) and the nonparametric Mann-Whitney *U* test (presented as median [interquartile range]) as appropriate. Categorical variables were compared using the Fisher exact test and presented as number (%). Intraclass correlation coefficient (ICC) was used to assess intra- and interobserver reliability. To identify the transverse diameter of the fetal thymus as a determinant of HCA or funisitis, Spearman partial correlation was used to adjust for gestational age. Differences were considered statistically significant at $p < 0.05$. All p values were from 2-sided tests, and all statistical analyses were performed with GraphPad Prism 5.03 for Mac OS X (GraphPad Software, La Jolla, CA), the SPSS 19.0 for Mac OS X (SPSS Inc., Armonk, NY), and MedCalc 12.3.0 (MedCalc Software, Mariakerke, Belgium)

RESULTS

Demographic and clinical characteristics of the patients are presented in Table 1. HCA or funisitis were diagnosed in 62% (133/216) and 19% (41/216) of women, respectively. All women were Caucasian.

The fetal thymus was identified and its transverse diameter measured (thymus detection ratio) in 98% (238/243) women. The evaluation failed in 5 women because of anhydramnion and/or unfavorable fetal position. Ninety-three percent (222/238) of the women delivered within 96 hours of measuring the fetal thymus.

Intraobserver ICC for the measurements of transverse thymic diameter were 0.97 [95% confidence interval (CI): 0.96–0.98] and 0.92 (CI: 0.87–0.95) for examiner M.K. and I.M., respectively.

TABLE 1
Maternal and Newborn Characteristics According to the Presence or Absence of Histological Chorioamnionitis or Funisitis

	Presence of HCA (n = 133)	Absence of HCA (n = 83)	*p* value[1]	Presence of Funisitis (n = 41)	Absence of Funisitis (n = 175)	*p* value[2]
Maternal age (years)	31.5 ± 5.8	30.0 ± 4.8	0.07	30.9 ± 5.6	30.9 ± 5.4	0.98
Primiparous	56 (42%)	44 (53%)	0.13	16 (39%)	84 (48%)	0.38
Prepregnancy BMI	23.0 (16.5–40.6)	21.3 (16.3–38.6)	0.06	22.6 (17.0–36.8)	22.3 (16.3–40.6)	0.37
Gestational age on admission (weeks + days)	32 + 0 (24 + 0–36 + 4)	34 + 0 (24 + 0–36 + 5)	**< 0.0001**	28 + 1 (24 + 0–35 + 0)	33 + 3 (24 + 0–36 + 5)	**<0.0001**
Gestational age on delivery (weeks + days)	32 + 1 (24 + 1–36 + 6)	34 + 1 (24 + 1–36 + 6)	**< 0.0001**	28 + 4 (24 + 1–35 + 0)	33 + 2 (24 + 0–36 + 6)	**< 0.0001**
CRP on admission (mg/L)	9.0 (0–82.0)	4.0 (0–71.0)	**< 0.0001**	8.0 (0.5–59.0)	6.0 (0–82.0)	0.35
Antepartal corticosteroids	87 (65%)	35 (40%)	**0.001**	31 (76%)	91 (52%)	**0.008**
Spontaneous delivery	97 (73%)	63 (75%)	0.61	30 (73%)	130 (74%)	0.85
Caesarean delivery	36 (27%)	20 (25%)	0.61	11 (27%)	45 (26%)	0.85
Puerperal endomyometritis	7 (5%)	0 (0%)	**0.045**	4 (10%)	3 (2%)	**0.03**
Birth weight of newborn (grams)	1,728 ± 684	2,099 ± 613	**< 0.0001**	1,313 ± 571	1,998 ± 641	**< 0.0001**
Apgar score, 5 minutes	9 (0–10)	9 (6–10)	0.24	9 (0–10)	9 (3–10)	**0.005**
Apgar score, 10 minutes	10 (1–10)	10 (7–10)	0.06	9 (1–10)	10 (7–10)	**0.001**

Abbreviations: BMI, body mass index; CRP, maternal serum C-reactive protein; HCA, histological chorioamnionitis; MIAC, microbial invasion of the amniotic cavity.
[1] Comparison between the group with HCA and that without HCA.
[2] Comparison between the group with funisitis and that without funisitis.
Continuous variables were compared using unpaired *t* tests (values are presented as mean ± SD) or nonparametric Mann-Whitney *U* test (values are presented as median [range]). Categorical variables were compared using Fisher exact test and presented as number (%).Statistically significant results are bold.

FIGURE 2. Sonogram shows the transverse diameter of the fetal thymus plotted on our reference ranges[17] in women with (●) and without (○) histologic chorioamnionitis. The lines represent 5th, 50th, and 95th percentiles for gestational age.

The interobserver ICC, assessed from the measurements of the transverse diameter of the fetal thymus of 34 uncomplicated singleton gestations, was 0.97 (CI: 0.95–0.99)

Fetuses from pregnancies complicated by HCA had smaller transverse thymic diameters than those from pregnancies without HCA [with HCA: median 23.9 mm, interquartile range (IQR) 18.5–28.8 mm versus without HCA: median 28.8 mm, IQR 24.7–32.8; $p < 0.0001$], as well as after adjusting for gestational age ($p = 0.0001$). A small thymus was present in 80% (106/133) and 53% (44/83) of women with and without HCA, respectively (Figure 2). There was a relationship between the US finding of a small thymus and the presence of HCA ($p < 0.0001$). The presence of a small thymus had a sensitivity of 79% (CI: 72–86%), specificity of 47% (CI: 36–58%), positive predictive value of 71% (CI: 63–78%), negative predictive value of 59% (CI: 46–71%), odds ratio of 3.5 (CI: 1.9–6.4), and likelihood ratio of 1.5 (CI: 1.2–1.9) for the identification of HCA.

Fetuses from pregnancies with funisitis had smaller transverse diameters of the fetal thymus

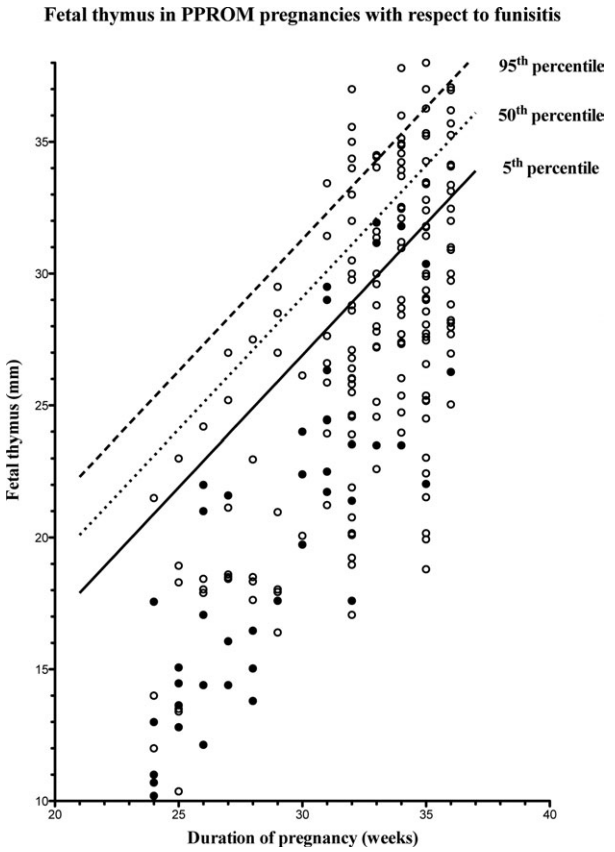

FIGURE 3. Sonogram shows the transverse diameter of the fetal thymus plotted on our reference ranges[17] in women with (●) and without (◦) funisitis. The lines represent 5th, 50th, and 95th percentiles for gestational age.

than those from pregnancies without funisitis (with funisitis: median 20.1 mm, IQR 16.2–24.6 mm versus without funisitis: median 27.5 mm, IQR 22.5–31.4 mm; $p < 0.0001$), as well as after adjusting for gestational age ($p = 0.005$). The presence of a small thymus was found in 88% (36/41) and 65% (114/175) of women with and without funisitis, respectively (Figure 3). There was a correlation between the US finding of a small thymus and the presence of funisitis ($p = 0.004$). The presence of a small thymus had a sensitivity of 88% (CI: 74–96%), specificity of 35% (CI: 28–42%), positive predictive value of 24% (CI: 18–32%), negative predictive value of 92% (CI: 83–97%), odds ratio 4.4 (CI: 1.5–10.3), and likelihood ratio of 1.5 (CI: 1.2–1.8) for the identification of funisitis.

DISCUSSION

The fetal thymus is an organ susceptible to either age-related or stress-related involution.[19,20] Stress-related involution is associated with conditions such as infection, sepsis, trauma, malnutrition, acute respiratory distress syndrome, and physical stress and is characterized by acute loss of CD4/CD8 double-positive cortical thymocytes with reduced output of naive T cells to the periphery.[20–26] Morphologically, karryorhexis of lymphocytes with phagocytosis by macrophages has been described in the cortex of the thymus.[27,28] Stress-related involution, which seems to be dependent on the intensity of the stress, could be partially reversible when the stimulus is removed.[29–31] However, the process of stress-related thymic involution is not completely understood; the activation of the hypothalamus-pituitary-adrenal axis with the increase of corticosteroid levels has been considered as a mechanism leading to this type of involution. Particularly, corticosteroids can induce the apoptosis of fetal thymocytes, which express the steroid receptors.[10] Moreover, it was shown that antenatal administration of synthetic corticosteroids, which are used for the induction of lung maturation, can also induce thymic involution in rats.[32] The postnatal administration of a single dose of dexamethasone induced a dramatic reduction of the thymic weight in the mice model, reaching the minimum in 2–4 days after the treatment.[31] On the other hand, other mechanisms could participate in the stress-induced thymus involution. In a recent study, the thymic involution induced by intraamniotic injection of lipopolysaccharide in a sheep model preceded the rise of fetal plasma cortisol levels. Moreover, no increase of thymocyte death or apoptosis was detected. It was suggested that the lymphocyte migration from the thymus into the blood and inflamed organs can be involved in acute thymic involution.[30]

Predicting the risk of HCA or funisitis seems crucial for improving the outcome in pregnancy management in preterm delivery. Therefore, since the evaluation of the fetal thymus has become feasible with US, the signs of stress-induced involution of the fetal thymus have been considered potential noninvasive markers of HCA or funisitis in both spontaneous preterm delivery and PPROM.[12–14] Specifically, the identification of HCA or funisitis could help clinicians select women who would benefit from active management of PPROM.

Two previous studies have evaluated the "small thymus" in PPROM pregnancies complicated by either HCA or funisitis.[13,14] Both showed an excellent sensitivity and a good specificity of a "small thymus" in the prediction of either HCA or funisitis; these promising results should be confirmed by other studies. Our study

tried to validate these results on a larger cohort with the use of a different approach for thymus measurement. Although measurements of the perimeter of the thymus were used previously in PPROM pregnancies, we preferred to use the transverse diameter of the fetal thymus, which is much easier and more precise under unfavorable acoustic conditions associated with the oligohydramnion, when PPROM is present.

Our results regarding the sensitivity of a small thymus are in accordance with previously reported findings. On the other hand, we found only a low specificity of the presence of a small thymus, when either HCA or funisitis was present. From our point of view, this finding excludes it from possible clinical use. We speculate that stress-induced thymic involution is a nonspecific process reflecting both inflammatory and noninflammatory activations of hypothalamic-pituitary-adrenal gland axis and that the other noninfectious factors, including PPROM itself, could be mirrored in the alteration of fetal thymic size.

The strength of this study is a relatively large cohort of women with a specific phenotype of preterm delivery (PPROM) and all women were recruited in the same institution. Another strength of the study is the active management of PPROM in our cohort with a short interval of latency from PPROM to delivery. Therefore, we assume that placental histopathology at birth provides similar information compared with placental histopathology at the time of the thymus measurement in most of the women.

The limitation of our study is the absence of the evaluation of white blood cell counts, and level of glucose and/or cytokines in the AF. On the other hand, it is known that the intensity of intraamniotic inflammation as determined by the AF white blood cell count strongly correlates with the presence of HCA or funisitis. Another limitation of this study is that only the measurement of the transverse diameter of the fetal thymus technique was used. Although we do not assume a difference between a measurement of the transverse diameter of a fetal thymus and a measurement of the thymus perimeter, the use of the latter might produce a more accurate result.

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