The criterion value of fetal cerebral lateral ventricular atrium width for diagnosis of ventriculomegaly

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Summary

Aim: To determine the distribution of cerebral lateral ventricular atrium width (LVAW) as established according to gestational weeks, and calculate the criterion value of LVAW that differentiates normal fetuses from abnormal fetuses. *Materials and Methods:* A total of 832 patients meeting the study's criteria were included in the control group. An additional 43 fetuses with LVAW > ten mm formed the case group. *Results:* The criterion value of LVAW was 9.7 mm. It did not change significantly throughout gestation. In the case group, 23 fetuses were terminated for fetal abnormalities, two fetuses died in utero, and 18 infants were born alive. Most of the abnormal development coincided with LVAW values greater than 12 mm. *Conclusion:* The authors suggest 9.7 mm as the criterion value, based on receiver operating characteristic (ROC) curve analysis. When the LVAW is between 9.8 and 12 mm without other fetal abnormalities, it may be regarded as a variation of the normal.

Key words: Ventriculomegaly; Criterion value; Ultrasonography; Prenatal diagnosis.

Introduction

Ventriculomegaly is one of the most common sonographically detected fetal abnormalities. The diagnosis of ventriculomegaly leads to a more intensive management that includes ultrasound examinations, screening for infections, eventual magnetic resonance imaging (MRI), potentially dangerous procedures (amniocentesis), and patient anxiety. It is not surprising that many different approaches to the diagnosis of fetal ventriculomegaly have been suggested; however, the most sensitive value for cerebral lateral ventricular atrium width (LVAW) to detect ventriculomegaly remains undetermined. This difficulty in critical assessment of the LVAW introduces borderline ventriculomegaly, which is a poorly defined but frequent condition that poses a problem for patient counseling. This condition is defined by LVAW values that range between ten and 15 mm [1]. Recently, borderline ventriculomegaly has been divided into mild (10-12 mm) and moderate (12.1-14.9 mm) cases, and it is suggested to be a benign finding [2]. However, chromosomal abnormalities and neurological squeal have been reported in infants with borderline ventriculomegaly, raising the question of whether the ten-mm criterion value is appropriate or not [3]. There is also a question of whether or not this criterion, defined by old ultrasound equipment, is suitable for the measurements in tenths of millimeters that are possible with the new ultrasound equipment.

The aim of this study was to determine the distribution of LVAW values as established according to gestational weeks, and to calculate the criterion value of LVAW that differentiates normal fetuses from abnormal fetuses.

Materials and Methods

Measurements of fetal LVAWs of consecutive pregnant women at 16-24 weeks' gestation over a period of four years were collected as part of a routine antenatal ultrasound examination. The informed consent of each patient was obtained and the prospective cross-sectional study was approved by the local ethics committee. Patients were divided into two groups. Fetuses with LVAW < ten mm and pregnancies with known normal outcomes were placed in the control group. The inclusion criteria were a singleton pregnancy and a fetus whose estimated fetal weight was between the 10th and 90th percentiles. In patients with regular menstrual periods lasting 28-32 days, the gestational age was determined by the last menstrual period (LMP). Otherwise, the earliest sonographic examination or measurements of crown-rump length (CRL) in the first trimester or biparietal diameter (BPD) in the second trimester were used to determine gestational age. Patients with fetal chromosomal or structural anomalies, multiple gestations, fetal death, preterm labor, premature membrane ruptures, and intrauterine growth restriction, oligohydramnios, and polyhydramnios, birth weights below the 10th percentile or above the 90th percentile, or maternal disease, and patients who missed their routine visits were excluded from the control group. Based on these exclusion criteria, 36 patients were excluded from the study. A total of 832 patients fulfilling the criteria were included in the control group. Aside from the control group, 43 fetuses with known karyotype analyses and with LVAW > ten mm formed the case group. These patients were ultrasonographically evaluated, as well, and a detailed inspection for other structural anomalies was also performed. Additional investigations such as karyotype and maternal serum toxoplasmosis, rubella, cytomegalovirus, and herpes simplex virus (TORCH) tests were performed in all cases with ventriculomegaly.

Each patient was examined during the study by an experienced ultrasonographer using an abdominal 2-5 MHz curvilinear transducer. Measurements of fetal biometry were taken in the standard planes and fetal anatomy was scanned routinely. According to the guidelines of the International Society of Ultrasound in Obstetrics and Gynecology (ISUOG), LVAW was measured on a transventricular axial plane at the level of the glomus of the choroid plexus. The electronic calipers were positioned perpendicular to the long

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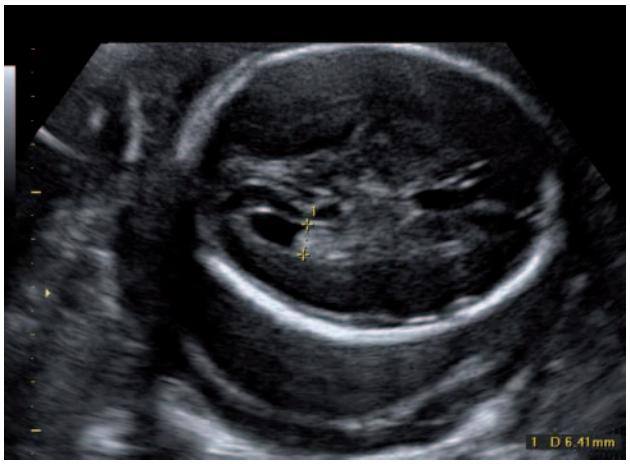

Figure 1. — The width of cerebral lateral ventricular atrium measured slightly above the level of the thalamus.

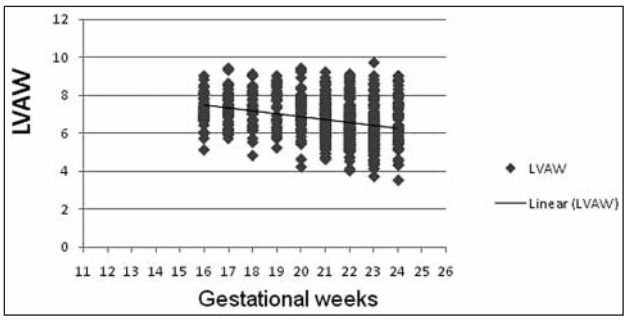

Figure 2. — LVAW according to 16-24 weeks of gestation.

Table 1. — *The sensitivity and specificity of midtrimester ultrasound in ventriculomegaly.*

Criterion value of LVAW	Sensitivity	95% Confidence interval	Specificity	95% Confidence interval
> 9.0	100.0	89.3-100.0	97.7	96.5-98.6
> 9.4	100.0	89.3-100.0	98.7	97.7-99.3
> 9.7*	100.0	89.3-100.0	98.8	97.8-99.4
> 10.0	97.0	84.2-99.5	99.4	98.6-99.8
> 10.6	93.9	79.7-99.1	99.6	99.0-99.9
> 11.0	90.9	75.6-98.0	99.8	99.1-100.0
> 12.0	75.8	57.7-88.9	99.8	99.1-100.0

*Suggested criterion value of LVAW, according to MedCalc program.

axis of the ventricle along the inner aspect of the echogenic line of the medial and lateral walls of the atrium [4] (Figure 1). Because of the typical near-field artifacts, measurements obtained in the far field were recorded in the control group. If it was not possible to obtain a correct axial view of the fetal head, the ventricles were measured on the coronal plane for a detailed evaluation of the fetal brain. If any ventricle width was greater than ten mm, the patient was included in the case group. Four of the 43 patients in the case group were detected during the routine ultrasonography scan, and the remaining were referred to the present unit. All measurements were calibrated at 0.1 mm. Each measurement was repeated twice for each fetus, and the mean size was calculated. Patients found to have ventriculomegaly were followed further, with examinations every four weeks until delivery. These families received prenatal counseling. Three cases of agenesis of the corpus callosum were confirmed via MRI. At delivery, all neonates were examined by a pediatrician. In the case group, the findings of neonatal cranial ultrasound and neurodevelopment assessment at 12 months of age were recorded.

Statistics

Statistical analysis was performed with the SPSS 13.0 program and the MedCalc program, version 10.2.0. Descriptive statistical methods (mean, standard deviation) were used in the evaluation of the study data. The criterion value of LVAW was calculated with receiver operating characteristic (ROC) curve analysis and the authors performed linear regression analysis with matching LVAW values and weeks of gestation. The relations between dependent and independent variables were assessed with Pearson correlation analysis. Results were evaluated in a 95% confidence interval (CI 95%) and at a significance level of $p < 0.05$. To calculate the intraobserver variability, the intraclass correlation coefficient (intra-CC) was used with CI 95%.

Results

The study population consisted of Caucasian patients. The median age of the pregnant women in the control and the case group was 30.68 ± 4.41 (range: 19-45) and 28.73 ± 6.65 (range: 17-41) years, respectively. The median gestational age in the control and the case group was 20.95 ± 2.23 and 20.26 ± 2.23 weeks, respectively. The mean LVAW in the control and the case group was 6.69 ± 1.10 and 13.52 ± 2.92 mm, respectively. Two measurements were performed for each patient. The intraobserver variability for the LVAW measurement (intra-CC: 0.93) was considered to be very good.

In the control group, LVAW values did not change significantly over the course of gestation (Figure 2). The criterion value of LVAW was found to be 9.7 mm with 100% sensitivity and 99% specificity using ROC curve analysis (Figure 3, Table 1).

In the case group, TORCH infections were not detected in any of the patients. In addition to ventricular dilatation, there were findings of associated central nervous system (CNS) abnormalities in 18 cases, while 14 fetuses had additional non-CNS abnormalities. The LVAW measurements and concomitant abnormalities in the case group are summarized in Figure 4 (Figure 4). In the fetuses with LVAWs between 9.8 and 12 mm, the authors observed the regression of LVAW values in three of the eight fetuses. Of the 32 fetuses with LVAWs greater than 12 mm, 14 fetuses had LVAWs greater than 15 mm. Ten of those 14 fetuses already had LVAWs greater than 15 mm upon presentation to this department. In the remaining four cases, there was an interval of up to 12 weeks between the initial detection of ventriculomegaly and the progression to severe ventriculomegaly.

Of the 43 pregnancies in the case group, 23 were terminated for fetal abnormalities, while two fetuses died in

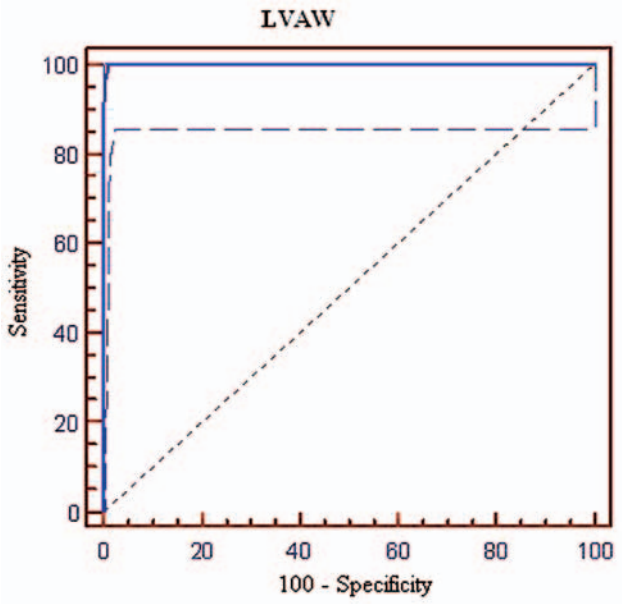

Figure 3. — The receiver operating characteristic (ROC) curve of LVAW.

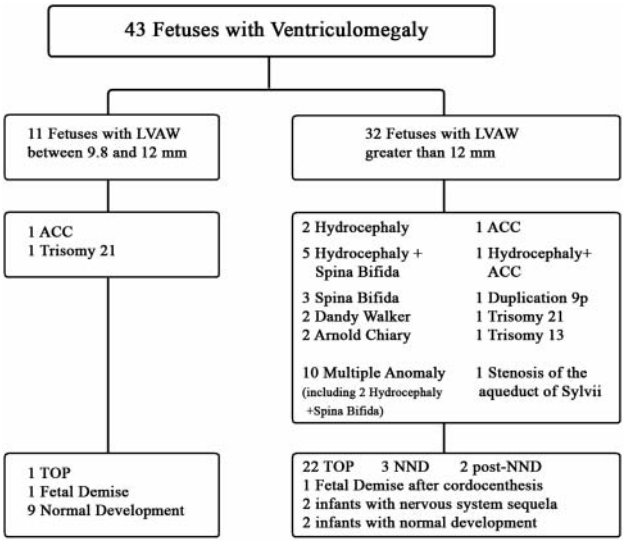

Figure 4. — Summary of prenatal findings and postnatal outcome in 43 fetuses with ventriculomegaly. NND: neonatal death; post-NND: post neonatal death; ACC: agenesis of corpus callosum; TOP: termination of pregnancy.

Table 2. — *Lateral ventricular atrium width in fetuses without abnormalities according to different series.*

Authors	n	Mean	SD*	3 SDs > Mean	4 SDs > Mean
Alagappan *et al.*[7]	500	6.6	1.4	10.8	12.2
Hilpert *et al.*[8]	608	6.5	1.5	11.0	12.5
Almong *et al.*[10]	427	6.2	1.2	9.8	11.0
Heiserman *et al.*[13]	652	6.5	1.3	10.4	11.7
Cardoza *et al.*[14]	100	7.6	0.6	9.4	10.0
Patel *et al.*[15]	219	6.1	1.3	10.0	11.3
Farrell *et al.*[16]	739	5.4	1.2	9.0	10.2
This study	832	6.7	1.1	10.0	11.1
Average	4077	6.5	1.2	10.1	11.3

* Standard deviation.

utero and 18 infants were born alive. There were three neonatal deaths and two postneonatal deaths. Two infants underwent neurosurgical intervention for progressive postnatal ventriculomegaly and spina bifida. One of these had features of cerebral palsy; the other suffered from motor dysfunction in the lower extremities and autonomic dysfunction. One infant with a prenatal LVAW of 10.3 mm and MRI-confirmed agenesis of the corpus callosum developed normally by one year of age. The remaining ten fetuses were completely normal at birth and at the first year of life.

Discussion

The term "borderline ventriculomegaly" is commonly used to indicate cases of a LVAW of ten to 15 mm. It is possibly associated with other abnormalities, which may worsen the condition and the clinical follow-up later [5, 6]. Therefore, counseling parents following a diagnosis of isolated ventriculomegaly is difficult for obstetricians.

In a study by Alagappan *et al.*, the mean value for LVAW was 6.6 ± 1.4 mm, and they used ten mm, 2.5 standard deviations (SDs) above the mean, as the upper limit of normal LVAW values [7]. Hilbert *et al.* proposed that 12 mm, a value approximately four SDs above the mean, would be a reasonable upper limit for normal values [8]. Senat *et al.* suggested that ten mm was approximately four SDs above the mean and would therefore be an acceptable upper limit, although this limit has not been universally applied to investigate ventricular abnormalities [9]. In light of the current and previous studies, there is agreement that the upper criterion value for LVAW should be ten mm [4,10]. This criterion value represents a range of approximately three SDs above the pooled mean (CI 99.74%). If measured with old ultrasound equipment, it would correspond to a range of 9.6-10.5 mm as measured with newer equipment [11]. The present authors conducted this study to obtain data on the normal upper limit of LVAWs in fetuses without abnormalities and, thus, to reanalyze the upper limit of these measurements in the literature. The mean value of LVAW was 6.69 ± 1.10 mm, and a range of 3 SDs above this mean corresponds to ten mm. The LVAW did not show significant change over the course of gestation, as has been previously observed [12]. The mean LVAWs and SDs of this study and seven previous studies are presented in Table 2 (Table 2). The calculated average mean of these eight studies (6.5 mm) ± three SDs corresponds to 10.1 mm. the authors thus suggest 9.7 mm as the criterion value of LVAW with 100% sensitivity and 99% specificity using ROC

curve analysis, since it is approximately three SDs above the mean (CI 95%). This criterion value is in correlation with the current literature. However, it should also be validated by the clinical outcomes of borderline dilatation.

The lateral walls of the atrium are typically perpendicular to the ultrasound beam in the axial plane and these can be identified in virtually 100% of fetuses [17]. However, the identification of these walls may be troublesome in the second trimester due to large and echogenic choroid plexuses. In addition, they fill the entire lateral ventricle posterior to the foramen of Monro, tending to mask the ipsilateral ventricle walls. This artifact disappears when coronal, sagittal, and parasagittal images are obtained, as in this study, to visualize the area near the ventricle and to evaluate the fetal brain thoroughly. In this study, the LVAW was measured at the level of the glomus of the choroid plexus. Heiserman *et al.* showed that placement of the anterior and posterior calipers on the long axis of the ventricles is not significant for the accuracy of measurement, while the assistance of the internal parieto-occipital sulcus is useful in ventriculomegaly follow-up [13, 18].

Mercier *et al.* retrospectively examined 26 cases with borderline ventriculomegaly (10-15 mm) [19]. The LVAW regressed in ten fetuses and stayed constant in ten fetuses. Among the remaining cases, one had Down syndrome, one had porencephaly, and four had growth retardation. Senat *et al.* followed 14 fetuses that had unilateral ventriculomegaly [9]. They found that the LVAW was constant within the range of 11-13 mm in ten fetuses, and it reached 20-25 mm in four fetuses. They identified atresia of the foramen of Monro, Weaver syndrome, congenital toxoplasmosis, and cerebral atrophy in these fetuses. Three of the pregnancies were terminated, and postmortem examinations confirmed the diagnoses. In this study, during the antenatal period, the authors observed regression of the LVAW in three fetuses with LVAW values between 9.8 and 12 mm. However, LVAW increased in four cases with LVAW values greater than 12 mm. In these cases, the pregnancies were terminated.

Two studies reported abnormal neurological outcomes in 13% of fetuses with LVAW values greater than 12 mm, while this rate was only four percent in fetuses with LVAW values between ten and 12 mm [6, 20]. Similarly, the rates of abnormal neurological outcomes in this study were 12.5% in fetuses with LVAWs greater than 12 mm and nine percent in fetuses with LVAWs between ten and 12 mm. It has also been reported that the incidence of karyotype abnormalities observed in borderline ventriculomegaly is higher than in patients with severe ventriculomegaly [21]. Signorelli *et al.* examined 62 fetuses with LVAWs between ten and 12 mm [22]. They diagnosed one fetus with trisomy 21. Gaglioti *et al.* reported that aneuploidy is observed in 5% (3/57) of borderline ventriculomegaly cases [5]. In this present study, the authors diagnosed one case of trisomy 21 in the fetuses with LVAWs between 9.8 and 12 mm. The LVAW value of the other fetus diagnosed with trisomy 21 in this study was between 12.1 and 14.9 mm, while the LVAWs in the other two cases of karyotype abnormalities in this study were above 15 mm.

Breeze *et al.* examined the etiology and prognosis of 20 fetuses with severe ventriculomegaly (> 15 mm) [23]. Ten of the pregnancies were terminated and diagnoses were confirmed after delivery. Two infants died in the fourth month postpartum. Of the remaining eight infants, seven had abnormal neurodevelopment. In the present study, 14 fetuses with LVAWs greater than 15 mm were identified, and 12 of the pregnancies were terminated. One fetus died after cordocentesis. Only one of the 14 fetuses was born alive, but died within two months.

The present study had a few handicaps. First of all, there were few cases of ventriculomegaly. Following the patients in the postnatal period for a longer period of time would be more informative. Fetal MRI has been recently employed to diagnose subtle cerebral maldevelopment in fetuses with mild ventriculomegaly [24]. Since the authors' experience in this field was limited, they did not use MRI in the evaluation of fetal mild ventriculomegaly cases, except to confirm diagnosis of agenesis of the corpus callosum. They could not obtain autopsy findings for the terminated pregnancies or postnatal deaths. Another difference between this study and others is that ROC curves were used here to analyze the criterion value of LVAW.

In conclusion, the authors suggest 9.7 mm as the criterion value with 100% sensitivity and 99% specificity using ROC curve analysis, because it is approximately three SDs above the mean. In order to avoid undue anxiety in parents, correct measurements should be obtained. When the LVAW is found to be between 9.8 and 12 mm and no other fetal abnormality is detected, this finding might be considered as a variation of the normal.

References

[1] Bloom S.L., Bloom D.D.: "Clinical outcome of mild fetal ventriculomegaly". *Am. J. Obstet. Gynecol.*, 1998, *179*, 562.

[2] Falip C., Blanc N., Maes E., Zaccaria I., Oury J.F., Sebag G. *et al.*: "Postnatal clinical and imaging follow-up of infants with prenatal isolated mild ventriculomegaly: a series of 101 cases". *Pediatr. Radiol.*, 2007, *37*, 981.

[3] Gaglioti P., Oberto M., Todros T.: "The significance of fetal ventriculomegaly: etiology, short- and long-term outcomes". *Prenat. Diagn.*, 2009, *29*, 381.

[4] International Society of Ultrasound in Obstetrics & Gynecology Education Committee. Sonographic examination of the fetal central nervous system: guidelines for performing the 'basic examination' and the 'fetal neurosonogram'. *Ultrasound Obstet. Gynecol.*, 2007, *29*, 109.

[5] Gaglioti P., Danelon D., Bontempo S., Mombro M., Cardaropoli S., Todros T.: "Fetal cerebral ventriculomegaly: outcome in 176 cases". *Ultrasound Obstet. Gynecol.*, 2005, *25*, 372.

[6] Pilu G., Falco P., Gabrielli S., Perolo A., Sandri F., Bovicelli L.: "The clinical significance of fetal isolated cerebral borderline ventriculomegaly: report of 31 cases and review of the literature". *Ultrasound Obstet. Gynecol.*, 1999, *14*, 320.

[7] Alagappan R., Browning P.D., Laorr A., McGahan J.P.: "Distal lateral ventricular atrium: reevaluation of normal range". *Radiology*, 1994, *193*, 405.
[8] Hilpert P.L., Hall B.E., Kurtz A.B.: "The atria of the fetal lateral ventricles: a sonographic study of normal atrial size and choroid plexus volume". *Am. J. Roentgenol.*, 1995, *164*, 731.
[9] Senat M.V., Bernard J.P., Schwarzler P., Britten J., Ville Y.: "Prenatal diagnosis and follow-up of 14 cases of unilateral ventriculomegaly". *Ultrasound Obstet. Gynecol.*, 1999, *14*, 327.
[10] Almog B., Gamzu R., Achiron R., Fainaru O., Zalel Y.: "Fetal lateral ventricular width: What should be its upper limit? A prospective cohort study and reanalysis of the current and previous data". *J. Ultrasound Med.*, 2003, *22*, 39.
[11] Ogge G.P., Gaglioti P., Danelon D., Mensa M., Ciriminna V., Oberto M. *et al.*: "Mild ventricolomegaly: should the cut-off be lowered to 9.5 mm?". *Ultrasound Obstet. Gynecol.*, 2007, *30*, 388.
[12] Bronsteen R.A., Comstock C.H.: "Central nervous system anomalies". *Clin. Perinatol.*, 2000, *27*, 791.
[13] Heiserman J., Filly R.A., Goldstein R.B.: "Effect of measurement errors on sonographic evaluation of ventriculomegaly". *J. Ultrasound Med.*, 1991, *10*, 121.
[14] Cordoza J.D., Goldstein R.B., Filly R.A.: "Exclusion of fetal ventriculomegaly with a single measurement: the width of the lateral ventricular atrium". *Radiology*, 1988, *169*, 711.
[15] Patel M.D., Goldstein R.B., Tung S., Goldstein R.B.: "Fetal cerebral ventricular atrium: difference in size according to sex". *Radiology*, 1995, *194*, 713.
[16] Farrell T.A., Hertzberg B.S., Kliewer M.A., Harris L., Paine S.S.: "Fetal lateral ventricles: reassessment of normal values for atrial diameter at US". *Radiology*, 1994, *193*, 409.
[17] Chinn D.H., Callen P.W., Filly R.A.: "The lateral cerebral ventricle in early second trimester". *Radiology*, 1983, *148*, 529.
[18] Guibaud L.: "Fetal cerebral ventricular measurement and ventriculomegaly: time for procedure standardization". *Ultrasound Obstet. Gynecol.*, 2009, *34*, 127.
[19] Mercier A., Eurin D., Mercier P.Y., Verspyck E., Marpeau L., Marret S.: "Isolated mild fetal cerebral ventriculomegaly: a retrospective analysis of 26 cases". *Prenat. Diagn.*, 2001, *21*, 589.
[20] Arora A., Bannister C.M., Russell S., Rimmer S.: "Outcome and clinical course of prenatally diagnosed cerebral ventriculomegaly". *Eur. J. Pediatr. Surg.*, 1998, *8*, 63.
[21] Nicolaides K.H., Berry S., Snijders R.J., Thorpe-Beeston J.G., Gosden C.: "Fetal lateral cerebral ventriculomegaly: associated malformations and chromosomal defects". *Fetal. Diagn. Ther.*, 1990, *5*, 5.
[22] Signorelli M., Tiberti A., Valseriati D., Molin E., Cerri V., Groli C. *et al.*: "Width of the fetal lateral ventricular atrium between 10 and 12 mm: a simple variation of the norm?". *Ultrasound Obstet. Gynecol.*, 2004, *23*, 14.
[23] Breeze A.C., Alexander P.M., Murdoch E.M., Hackett G.A., Smith G.C., Murdoch E.M.: "Obstetric and neonatal outcomes in severe fetal ventriculomegaly". *Prenat. Diagn.*, 2007, *27*, 124.
[24] Greco P., Resta M., Vimercati A., Laforgia N., Mautone A., Selvaggi L.: "Antenatal diagnosis of isolated lissencephaly by ultrasound and magnetic resonance imaging". *Ultrasound Obstet. Gynecol.*, 1998, *12*, 276.

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