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Three-dimensional volumetric study with VOCAL in normal and abnormal posterior fossa fetuses

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ABSTRACT

Purpose: The aim of this study was to compare volumetric parameters in the abnormal and normal posterior fossa using the Virtual Organ Computer-aided AnaLysis (VOCAL™) technique to determine whether fetuses with an abnormal posterior fossa have different volumes.

Methods: A prospective study was conducted on 17 fetuses with an abnormal posterior fossa including, Dandy Walker malformation (DWM) (n = 6), vermian hypoplasia (VH) (n = 3), mega cisterna magna (MCM) (n = 8), and 99 healthy control fetuses from 20 to 34 weeks’ gestation. Measurement of the fetal cisterna magna and cerebellar volume was performed in the standard transcerebellar plane through the VOCAL™ method. To establish the correlation of volumes with gestational age, polynomial regression analysis was performed. For comparison between groups, univariate ANCOVA was performed using gestational age as a covariate. The reliability was analyzed by the intraclass correlation coefficient (ICC).

Results: Cerebellar volume and cisterna magna volume were correlated with gestational age. Posterior fossa volume was significantly larger in DWM (p < .0001) and MCM (p < .0001) in comparison to the control group. In VH group, cisterna magna volume does not seem to expand (p = .298). Cerebellar volume does not seem to change in subgroups when the influence of gestational age is discarded (p = .09). The ratio of cerebellar volume to the cisterna magna volume decreases significantly in abnormal fetuses (p < .0001). Good intraobserver and interobserver reliabilities were found for both cerebellum and cisterna magna measurements.

Conclusions: Volume analysis may have a role in discrimination of different posterior fossa pathologies.

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Dandy Walker malformation; mega cisterna magna; posterior fossa; prenatal diagnosis; three dimensional ultrasonography; vermian hypoplasia; vocal

Introduction

In early embryonic development, fourth ventricular roof is separated into the anterior and posterior membranous areas, divided by the plica choroidea [1]. At approximately fifth week of gestation, the alar laminae along the lateral margins of the anterior membranous areas thicken to form the rhombic lips. Cerebellum originates from these structures as they enlarge and fuse in the median plane. Foramen of Magendie that perforates around 10th week derives from posterior membranous area [2]. If an insult involves the plica choroidea and anterior membranous area, there will be varying degrees of agenesis of the fourth ventricular choroid, vermis, and cerebellar hemispheres [3].

The evaluation of the posterior fossa is an important part of obstetric ultrasound that targets detection of prenatal malformations of the fetal central nervous system (CNS). The cerebellar hemispheres appear hypoechoic with intermittent echogenic stripes, which represent the folia, while the cerebellar vermis appears uniformly echogenic in the midline [4]. The cisterna magna is an anechoic space behind the cerebellum. Thin septae in the paramedian location extend from the junction of the cerebellum and vermis to the inner table of the occiput, these are appreciable in the axial plane as echogenic lines through the otherwise anechoic cisterna magna. Estimations of cerebellum and cisterna magna size are routinely carried out by ultrasonography.

Morphological and morphometric analyses of the posterior fossa structures can reveal abnormalities in a wide clinical spectrum. Accurate determination of the type of posterior fossa malformation is essential for management issues and counseling. Standard axial plane can be insufficient for discrimination of the cerebellar and posterior fossa abnormalities. It may lead to a false-positive diagnosis of vermian abnormalities, as the rotated or displaced vermis may be incompletely imaged.

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Recent advances in three-dimensional (3D) ultrasound have enabled us to measure volumes of organs with irregular borders. The Virtual Organ Computer-aided Analyis (VOCAL™) method measures a structure around an axis, with each rotation delimiting an area; at the end of the rotational process, the program automatically provides the volume.

The objective of this study was to compare volumetric parameters in the abnormal and normal posterior fossa using VOCAL™ technique to determine whether fetuses with an abnormal posterior fossa have different volumes.

Materials and methods

This prospective study was conducted from January 2014 through December 2016 in Kocaeli University, Obstetrics and Gynaecology Department, Maternal Fetal Medicine Unit, Turkey. The study group was composed of 17 fetuses with abnormalities of the posterior fossa before 34 weeks of pregnancy that were detected during a routine scan for abnormalities or referred from other institutions for suspicious ultrasound findings. In all cases, the diagnosis was confirmed by prenatal magnetic resonance imaging (MRI) and postnatal MRI or autopsy.

The control group was composed of 99 healthy fetuses from 20 to 34 weeks of gestation. The gestational age was confirmed by sonographic examination during the first trimester. Singleton pregnancies of healthy individuals were included in the control group. Participants were excluded from the control group if the exact gestational age could not be confirmed, a fetal abnormality was found, intrauterine growth retardation was detected or maternal disease or complications of pregnancy were present. Increased body mass index >30 kg/m² was an exclusion criteria due to reduced image quality. This study was approved by the Ethics Committee and pregnant women who consented to participate voluntarily signed consent forms.

After standard 2D examinations, 3D volumes were acquired. All patients were scanned with Voluson E6 systems (GE Healthcare, Kretz Ultrasound, Zipf, Austria) using a 4- to 8-MHz transabdominal probe. The 3D image was acquired during fetal rest and the absence of fetal movements and maternal apnea, and the standard volume sweep angle was 55°. The starting image was in the axial plane at the level of the transverse cerebellar diameter and the images were stored. The offline analysis and processing workup were performed by a single operator (YD), who used 4D View version 6 software and VOCAL™. The image was displayed in the multiplanar mode, in the form of three orthogonal planes perpendicular to each other: axial (A), sagittal (B) and coronal (C). Plan A was selected as a reference, which is rotated around the outside axis “z” until the interhemispheric line stand at 0°. Visualization with static volume contrast imaging was preferred in order to delineate structures better, with the slice thickness set to 2 mm. The reference point was the center of the fetal cisterna magna, and the measuring gauges positioned on the upper and lower poles while measuring cisterna magna volume. The reference point was the center of cerebellum and measuring gauges were positioned on the lateral edges while measuring cerebellar volume. The posterior fossa region was magnified to occupy almost 40% of the screen. The VOCAL key was activated with a rotation angle of 30° and manual mode of delimitation. The program calculated the volume automatically after reconstruction of the planes and provided a 3D image. Volumes were expressed in mm³.

Dandy Walker malformation (DWM) is defined as complete or partial agenesis of the cerebellar vermis, cystic dilatation of the fourth ventricle and enlarged posterior fossa with upward displacement of the tentorium, Torcula and transverse sinuses, mega cisterna magna (MCM) is defined as a cisterna magna measuring >10 mm and a normal vermis; isolated vermian hypoplasia (VH) is defined as a normally formed vermis but of smaller size, with an otherwise normal size and anatomy of the posterior fossa [5].

Statistical analysis was performed using Statistical Package for the Social Sciences version 23.0 (IBM, Armonk, NY). Data were first assessed for normality using the Kolmogorov–Smirnov goodness-of-fit test and Q–Q plots. Polynomial regression analysis was run on all measurements to find the correlation between gestational age and 3D volumetry. For comparing volumes of normal and abnormal groups, univariate ANCOVA was performed using gestational age as a covariate. Cerebellum to cisterna magna volume ratios of different groups were compared using the Kruskal–Wallis test.

For calculations of reliability and agreement, the same investigator performed a second random measurement of 10 volumes with an interval of at least 30 days after the first (intraobserver), while a second examiner (GY), held a third measurement (interobserver) of the same 10 volumes. To assess interobserver and intraobserver reliabilities, a two-way mixed model was used and single-measure intraclass
correlation coefficients (ICCs) for absolute agreement were calculated.

Results

Average maternal age was 30 ± 4 years in the pathological posterior fossa group, 29 ± 4 years in the control group. Among the 17 cases in the study group, six fetuses had DWM, three fetuses had VH and eight fetuses had MCM (Table 1). The gestational age at the time of diagnosis of an abnormal posterior fossa ranged from 21 to 33 weeks, some cases were referred late to our clinic. Additional abnormalities were present in six cases, one fetus had VH, single umbilical artery and subaortic VSD, fetal karyotype revealed derivative chromosome 13. Anomalies associated with DWM include, partial corpus callosum agenesis (one case) and dysplastic kidneys (one case). One fetus with VH had bilateral talipes, partial corpus callosum agenesis and unilateral hydrenephrosis. One fetus with MCM had brachycephaly and ventricular discordance. To all cases of DWM, VH and MCM cases with accompanying anomalies, karyotyping was offered. Only three patients accepted chromosome analysis, two were found to be normal.

After meticulous counseling of parents by multidisciplinary team, termination of pregnancy was performed in two cases.

In all cases and control group, posterior fossa volumes were measured using VOCAL™ technique. Mean cisterna magna volume was 1544 ± 949 mm³ in control group, 5575 ± 3727 mm³ in the MCM group, 2568 ± 1793 mm³ in the VH group and 13,412 ± 8664 mm³ in the DWM group. The cisterna magna volume in the healthy control fetuses was correlated with gestational age, best represented by quadratic equation ($p < .0001, R^2 = 0.753$; Figure 1). When the gestational age effect is eliminated, the volume differences between the groups are significant ($p < .0001$). In comparison to the control group (Figure 2), cisterna magna volume is significantly larger in DWM ($p < .0001$; Figure 3) and MCM ($p < .0001$). However, in VH group retrocerebellar space volume does not seem to expand significantly ($p = .298$).

Mean cerebellar volume was 4100 ± 2720 mm³ in control group, 5083 ± 1588 mm³ in the MCM group, 4434 ± 5019 mm³ in the VH group and 6429 ± 4750 mm³ in the DWM group. Cerebellar volume measurement with VOCAL™ in a healthy fetus and DWM are shown in Figures 4 and 5, respectively. The cerebellar volume of the healthy control fetuses

Table 1. Clinical data for the 17 fetuses with an abnormal posterior fossa.

<table>
<thead>
<tr>
<th>Case</th>
<th>Diagnosis</th>
<th>Associated anomalies</th>
<th>Karyotype</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>DWM</td>
<td>None</td>
<td>–</td>
<td>Delivery at term</td>
</tr>
<tr>
<td>2</td>
<td>DWM</td>
<td>pCCA</td>
<td>–</td>
<td>Delivery at term</td>
</tr>
<tr>
<td>3</td>
<td>DWM</td>
<td>None</td>
<td>–</td>
<td>Delivery at term</td>
</tr>
<tr>
<td>4</td>
<td>DWM</td>
<td>None</td>
<td>–</td>
<td>Delivery at term</td>
</tr>
<tr>
<td>5</td>
<td>DWM</td>
<td>None</td>
<td>Normal</td>
<td>Delivery at term</td>
</tr>
<tr>
<td>6</td>
<td>DWM</td>
<td>Bilateral dysplastic kidney</td>
<td>–</td>
<td>Delivery at term</td>
</tr>
<tr>
<td>7</td>
<td>VH</td>
<td>Single umbilical artery Subaortic VSD</td>
<td>Derivative chromosome 13</td>
<td>Termination of pregnancy</td>
</tr>
<tr>
<td>8</td>
<td>VH</td>
<td>None</td>
<td>Normal</td>
<td>Termination of pregnancy</td>
</tr>
<tr>
<td>9</td>
<td>VH</td>
<td>pCCA Bilateral talipes Unilateral hydrenephrosis</td>
<td>–</td>
<td>Delivery at term</td>
</tr>
<tr>
<td>10</td>
<td>MCM</td>
<td>Brachycephaly ventricular discordance</td>
<td>–</td>
<td>Delivery at term</td>
</tr>
<tr>
<td>11</td>
<td>MCM</td>
<td>pCCA</td>
<td>–</td>
<td>Delivery at term</td>
</tr>
<tr>
<td>12</td>
<td>MCM</td>
<td>None</td>
<td>–</td>
<td>Delivery at term</td>
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<td>MCM</td>
<td>None</td>
<td>–</td>
<td>Delivery at term</td>
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<td>MCM</td>
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<td>–</td>
<td>Delivery at term</td>
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<td>MCM</td>
<td>None</td>
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<td>16</td>
<td>MCM</td>
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<td>Delivery at term</td>
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<tr>
<td>17</td>
<td>MCM</td>
<td>None</td>
<td>–</td>
<td>Ongoing pregnancy</td>
</tr>
</tbody>
</table>

DWM: Dandy Walker malformation; VH: vermian hypoplasia; MCM: mega cisterna magna; pCCA: partial corpus callosum agenesis; VSD: ventricular septal defect.
was correlated with gestational age that fits quadratic model \( (p < .0001, R^2 = 0.932; \text{Figure 6}) \). When the gestational age effect is discarded, cerebellar volume does not seem to change in subgroups \( (p = .09) \).

The ratio of cerebellar volume to the cisterna magna volume ranges between 1.36 and 4.86 in healthy fetuses, it does not change with gestational age \( (p = .16) \). In abnormal fetuses, this ratio decreases significantly but intersection between groups is observed \( (p < .0001; \text{Figure 7}) \).

Regarding cisterna magna measurement, both intraobserver reliability, with ICC = 0.96 (95% CI 0.88; 0.99) and interobserver reliability with ICC = 0.90 (95% CI 0.63; 0.97) were good. Cerebellar volume measurements showed a better intraobserver and interobserver reliability with ICC = 0.98 (95% CI 0.92; 0.99) and ICC = 0.96 (95% CI 0.86; 0.99), respectively.

**Discussion**

The concepts about the development of vermis and cisterna magna are evolving since the last decade. Detection of anomalies of fetal posterior fossa is a challenge but newer ultrasound equipments with different modalities shed light on the posterior fossa anatomy.

Fetal retrocerebellar fluid collections range from benign asymptomatic conditions to severe abnormalities. These anomalies include DWM, VH, MCM, and Blake’s pouch cyst. They have subtle differences in sonographic appearance but a very different prognosis [6].

Advances in prenatal imaging techniques have led to more comprehensive assessment of the fetal posterior fossa. 3D sonographic technique has many advantages in the detection of posterior fossa abnormalities. Although it is not essential for two-dimensional measurement, the 3D mode allows faster and more practical analysis of fetal CNS because of automatic capture which allows the examiner to perform offline evaluation.

Substantially, 3D volumes are used to obtain orthogonal views from an axial view of the fetal brain. Recent publications on posterior fossa include additional measurements such as the vermian cranio-caudal diameter, tentoro-clival angle, tentoro-vermian...
angle and the clivo-vermian angle, brainstem–vermis and brainstem–tentorium angles, vermian perimeter and cross-sectional area in midsagittal plane of reconstructed 3D images [7–9].

Actually, cisterna magna is not a linear structure, making it difficult to determine its dimensions precisely. Furthermore, in 2D ultrasound, if the transducer is angled in a semicoronal plane, the cisterna magna could falsely appear enlarged in approximately 40% of cases [10]. MRI has been used to enhance visualization of vermian anatomy and morphometry and assess associated anomalies but it is time consuming and expensive. Therefore, volumetric measurements may be more accurate compared to the 2D ultrasound and more feasible than MRI.

3D ultrasonographic volume assessment has gained popularity since the introduction of newer techniques. In the majority of cases, this is accomplished by manual organ segmentation, using one of the two methods: the multiple parallel or the rotational plane. VOCAL™ is a new method that sketches a structure around axis, with each rotation delimiting an area; at the end of the rotational process the program automatically converges the planes and provides the volume. This novel technique has been used for first trimester fetal volume, placental volume, fetal thigh volume, thymus volume, fetal urinary bladder volume, cardiac ventricular volume, lung volume, cerebral ventricle volume in ventriculomegaly, brain and frontal lobe volumes in growth restricted fetuses, cerebellar volume measurements [11–23].

There are no reports describing the use of 3D ultrasonography VOCAL™ technique comparing normal and abnormal fetal posterior fossa volumes during pregnancy.

Araujo Júnior et al. measured cisterna magna volume in 224 healthy pregnant women to determine the reference ranges and observed a good correlation between the volume of the fetal cisterna magna and gestational age [24]. Our study supports this finding, furthermore, we were able to obtain posterior fossa volume measurements in fetuses with the most

Figure 3. Cisterna magna volume measurement of a fetus with Dandy Walker malformation using VOCAL™ at 30 weeks of gestation.
common abnormalities of the posterior fossa: DWM, VH, and MCM. We demonstrated that, in DWM and MCM, retrocerebellar space volume expands significantly even when gestational age influence is removed. As expected, volumes were maximal in DWM group in our study. Whereas in VH, although retrocerebellar volumes were slightly larger than the healthy fetuses, the difference was insignificant. We assume that this condition may be due to the small number of cases that precludes reaching a statistical significance. Another explanation is that, both in DWM and MCM posterior fossa enlarges globally. However, in VH posterior fossa, size does not change by the definition, so it should not be surprising to see volumetric measurements that reflect this dimension.

Ultrasound and MR studies have proven that cerebellar volume increases with gestational age [21,25,26]. Our findings are consistent with previous studies that showed correlation. Cerebellar expansion is linked with the proliferation of the external granular layer and migration of precursor cells to the internal granular layer [27]. Growth trajectories show that the cerebellar volume increases fivefold from 24 to 40 weeks. Chang et al. stressed that cerebellar volume is correlated with fetal biometric measurements. In a volumetric study including both multiplanar technique and VOCAL™, Rutten et al. emphasized that the growth rate of cerebellum associated with gestational age [22]. Their study highlights that at 20 weeks of gestation the increment of cerebellar volume is 51% per 2 weeks whereas the growth rate decreases at late gestation. They postulated that the left fetal cerebellar hemisphere is larger than the right hemisphere. Interestingly, we found that cerebellar volume does not change significantly in fetuses with abnormal posterior fossa when gestational age effect is discarded. So, we think that the contribution of vermis on total cerebellar volume is minimal in prenatal life.

In an attempt for searching a parameter independent from gestational age, we calculated the ratio of cerebellar volume to cisterna magna volume. It is logical that this ratio decreases in posterior fossa dilations, because the denominator increases while the nominator does not change. Nevertheless, there is an overlap between groups.
Figure 5. Cerebellar volume measurement of a fetus with Dandy Walker malformation using VocaL™ at 30 weeks of gestation.

Figure 6. Scatterplot showing the relationship between the cerebellar volume and gestational age ($R^2 = 0.932$).

Figure 7. Boxplot presentation of cerebellum/cisterna magna volume ratio in healthy fetuses, Dandy Walker malformation (DWM), mega cisterna magna (MCM), and vermian hypoplasia (VH).
The results should be analyzed cautiously because the small number of pathological cases in the study may cause bias. A major drawback of our study is volumetric differences in Blake’s pouch cyst could not be evaluated because of lack of this entity during the study period.

Ultrasonography has limitations mainly related to the acoustic shadows of the bones of the skull, so it is difficult to delineate the borders of cisterna magna and cerebellum in the late third trimester during rotation in some planes which may decrease the accuracy of measurements. Anatomical landmarks have to be identified clearly, even minor aberrations during tracing a structure may create huge differences in calculations and decrease intraobserver and interobserver agreement. Both intraobserver and interobserver reliabilities were good for cerebellum and cisterna magna volumetry in our study. Another technical difficulty is that, enough room must be present between cerebellar hemispheres and the occipital bone for rotation and volume reconstruction. 3D view of the transcerebellar plane should be taken under optimal conditions for a better volume acquisition because fetal position and fetal movements affect the visualization of the structures to be measured after each rotation.

This is a preliminary study that underlines volume analysis may have a role in discrimination of different posterior fossa pathologies. Future researches with more cases and standardization of the measurements is necessary to correlate the biometric results and clinical outcome.

Disclosure statement
The authors report no declarations of interest.

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