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Original Article

Quantitative analysis of normal fetal medulla oblongata volume and flow by three-dimensional power Doppler ultrasound

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ABSTRACT

Objective: Assessment of the fetal medulla oblongata volume (MOV) and blood flow might be important in the evaluation of fetal brain growth. We used three-dimensional power Doppler ultrasound (3DPDUS) to assess the fetal MOV and blood flow index in normal gestation. The relationships between these parameters were further analyzed.

Methods: We assessed the total volume and blood flow index of the fetal MO in normal pregnancies using a 3DPDUS (Voluson 730 Expert). The true sagittal plane over the fetal occipital area was measured by a 3D transabdominal probe to scan the fetal MO under the power Doppler mode. Then, we quantitatively assessed the total volume of the fetal MOV, mean gray area (MG), vascularization index (VI), and flow index (FI).

Results: A total of 106 fetuses, ranging from 19 weeks to 39 weeks of gestation, were involved in our study. The volume of the fetal MO was highly positively correlated with gestational age [correlation coefficient (r) = 0.686, $p < 0.0001$]. The MG was negatively correlated with gestational age [$r = -0.544$, $p < 0.0001$). VI and FI showed no significant correlation with gestational age ($p = 0.123$ and $p = 0.219$, respectively).

Conclusion: 3DPDUS can be used to assess the fetal MOV and blood flow development quantitatively. Our study indicated that fetal MOV and blood flow correlated significantly with the advancement of gestational age. This information may serve as reference data for further studies of the fetal brain and blood flow under abnormal conditions.

Introduction

The fetal brain volume and perfusion is crucial both in the evaluation of fetal growth and central nervous system (CNS) development. Deficient perfusion of the fetal brain may be related to a poor prognosis of CNS development and even to fetal well-being. A previous study thought unexplained stillbirth might be related to neuronal pathology in the arcuate nucleus of the medulla oblongata [1]. Cerebral malformations are encountered in about 1% of all births [2]. With the advent of high-resolution three-dimensional power Doppler ultrasound (3DPDUS), it is easier to assess all possible planes, views, and vascularization whenever the targeted-scanned 3D volume is obtained, including any part of fetal brain [3–6]. Recent evolution in ultrasound equipment has enabled more refined diagnosis of most congenital malformations of the brain. Through a structured analysis of the fetal CNS anatomy, even rare conditions are now being detected more often [7]. In this study, we focus on analyzing the fetal medulla oblongata (MO), which has not been studied previously.

The MO connects the higher levels of the brain to the spinal cord, and it is responsible for several functions of the autonomous nervous system, including respiration, cardiac center, vasomotor center, and reflex centers. After 28 gestational weeks, the fetal heartbeats become more variable. The maturation of the CNS, including the cerebral cortex and MO, plays an important role in controlling the fetal heart rhythm. The variability of the fetal heartbeat directly

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indicates the well-being of the fetus. The volume and vascularization of MO might be an index for evaluating fetal brain maturation.

We measured the fetal medulla oblongata volume (MOV) using 3DPDUS. We tested whether the fetal MOV vascularization and the blood flow change significantly with the increment of gestational age (GA). We conducted a prospective study to assess the fetal MOV, mean gray areas, and vascular indices [i.e., vascularization index (VI) and flow index (FI)] in normal pregnancy using 3DPDUS and quantitative 3D histogram analysis. In an Asian population, our study may be the first series to present an assessment of the fetal MOV and vascularization using 3DPDUS and quantitative 3D histogram analysis.

Methods

Patients

In this cross-sectional study, a total of 111 women with normal singleton pregnancy between 19 weeks and 39 weeks gestation were examined. Fetal age was estimated from the last menstrual period and confirmed by ultrasonographic measurement of the crown–rump length. Women with gestational diabetes, preterm labor, antepartum hemorrhage, congenital abnormalities, and maternal systemic disease; women on a regimen of tocolytic and antihypertensive agents; and women absent during patient follow

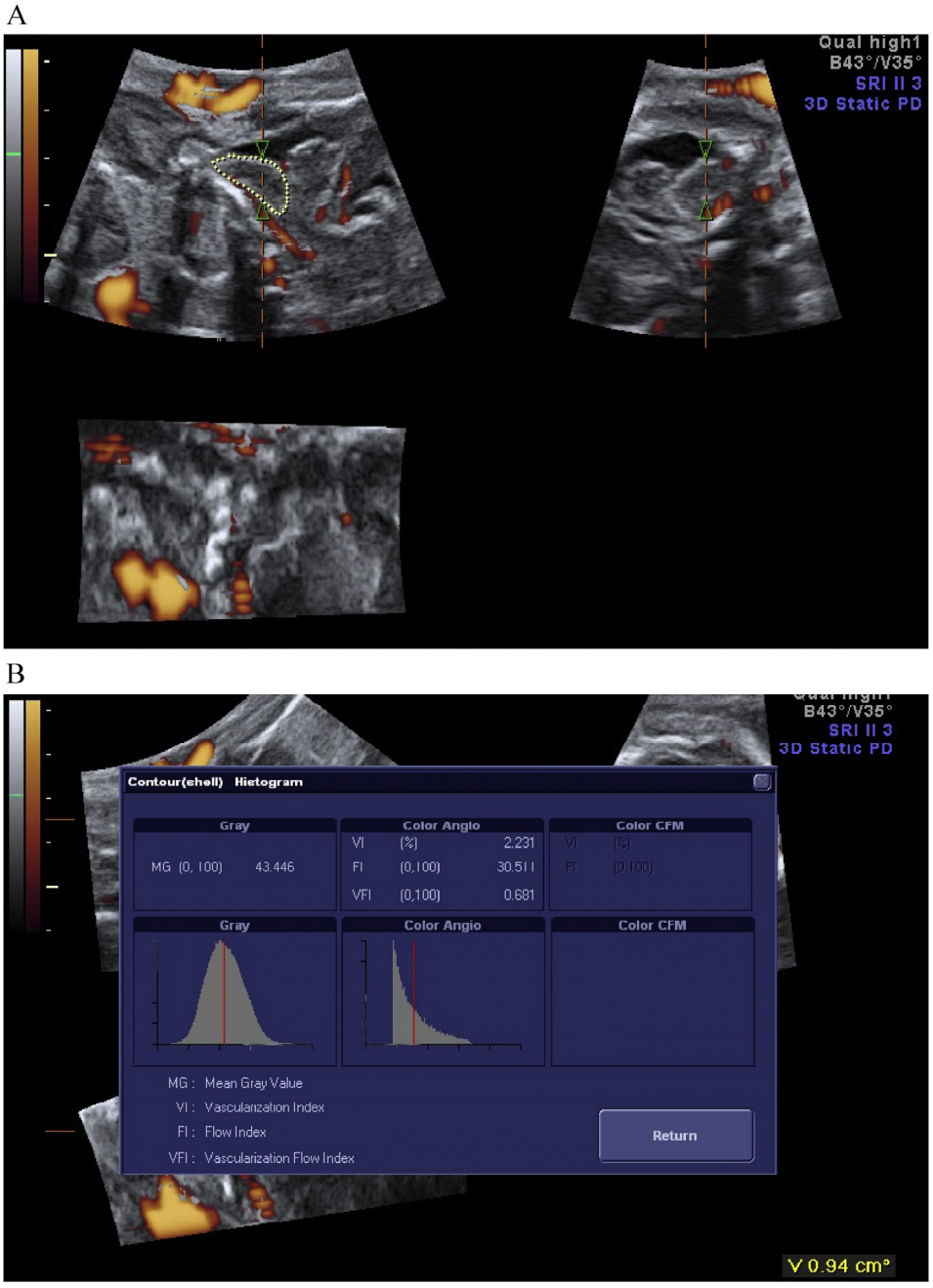

Figure 1. (A) Fetal medulla oblongata (defined by dotted line) volume at 22 weeks of gestation was calculated using the VOCAL technique in six planes. (The red arrow indicates fetal cerebellum.) (B) MG, VI, and FI of the medulla oblongata were analyzed (22 weeks of gestation). FI = flow index; MG = mean gray value; VI = vascularization index; VOCAL = Virtual Organ Computer-Aided Analysis.

up were excluded. Hospital medical records were reviewed by physicians to confirm pregnancy outcome, and newborns with abnormal karyotypes or major structural abnormalities were excluded. The study was approved by the Institutional Review Board at Taipei Veterans General Hospital (Taipei, Taiwan). Each patient participating in the study provided an oral and informed consent.

Ultrasound examination

All ultrasound examinations were performed by one experienced doctor (Dr Chen) using a Voluson 730 Expert ultrasound machine (GE Healthcare, Milwaukee, WI, USA) equipped with a 4–8-MHz transducer. High-resolution 2D US was applied to scan the sagittal view of the fetal head and identify the landmark of the corpus callosum. Then, we moved the probe caudally to identify the vermis of the cerebellum, and the MO was found a few centimeters below the vermis. The MO is the lower half of the brainstem, with the upper half of the brainstem being the pons. We differentiated the pons from the MO easily because the pons is within the same level of the cerebellum and above the skull base. The MO protrudes from the foramen magnum of the skull base, after which it gives rise to the spinal cord. After identifying the MO, we used the 3D technique to measure the MOV with the normal velocity mode (which swept 90° automatically within 4 seconds). The power Doppler characteristics applied were as follows: normal color quality, Doppler gain −5.0, low wall motion filter of 1 and pulse repetition frequency of 0.6 kHz, grayscale gain 0, normal frequency and Optimal tissue image (OTI) level, and focal zone 2. All women were examined using the same sonographic presets. The analyzing software allowed the 3D volume to display simultaneously in three perpendicular orthogonal planes on the monitor. The data set was subsequently saved for further retrieval and processing, such as volume determination or 3D image reconstruction.

In this study, we used the VOCAL (Virtual Organ Computer-Aided Analysis; GE-Kretztechnik, Zipf, Austria) software with the manual mode for each rotation plane with 30° and fetal Brain volume (BV) and 3D structure constructed. The volume, mean gray value (MGV), VI, FI, and Vascularity flow index (VFI) of the fetal MO were calculated using the VOCAL software. Three-dimensional power Doppler histogram analysis software and VOCAL were used to calculate the histogram indices of the fetal MO vascularization and blood flow obtained from the quantitative 3DPDUS scanning. The VOCAL imaging program can automatically calculate grayscale and color-scale values for the defined volume (Figure 1). The stored US volume obtained using 3DPDUS was defined by voxels. Grayscale voxels contain all 3D grayscale information grades from black to white, with the lowest value (intensity) being 0 and the highest 100 (g0 to g100). Then, the MGV was calculated.

A similar scale was used for color values (c0 to c100). Pursuant to these values, two indices were calculated: VI and FI. Briefly, VI measures the number of color voxels in the region of interest representing the vessels in the tissue and is expressed as a percentage (%). FI, the mean color value in the color voxels, represents the average intensity of flow.

Statistical analysis

Data were collected and analyzed using an Excel spreadsheet (Microsoft, Redmond, WA, USA) and analyzed using the software SPSS for Windows, version 15.0 (SPSS Inc., Chicago, IL, USA). The relationships between the Doppler variables and GA were evaluated by regression analyses. Pearson's correlation coefficient was used to assess the degree of correlation between variables.

Table 1
Maternal characteristics and general data of fetal medulla oblongata.

Participants	$n = 106$ cases
Mother characteristics	
Age (y)	32.85 ± 3.96
Gestational age at study (wk)	23.51 ± 3.59
Fetal medulla oblongata volume (mL)	0.75 ± 0.44
Fetal medulla oblongata flow indices	
Mean gray value	29.59 ± 7.56
Vascularization index (%)	4.55 ± 5.73
Flow index	28.25 ± 6.80

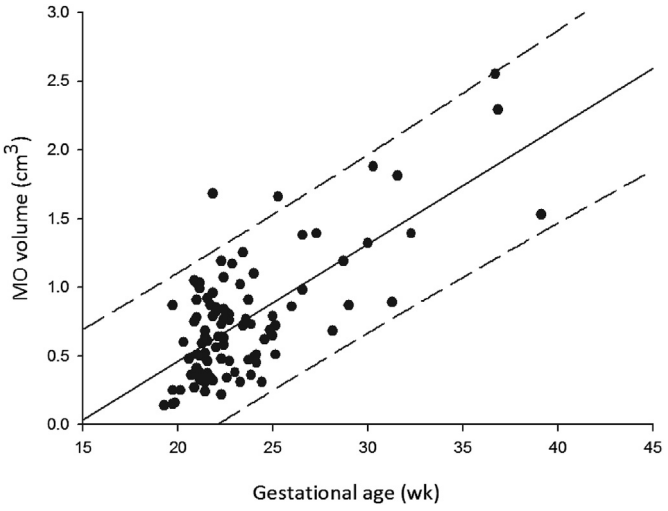

Figure 2. Fetal medulla oblongata volume (MOV) and gestational age (GA). The fetal MOV was highly positively correlated with GA [MOV = 0.084 × GA − 1.211; correlation coefficient (r) = 0.686, $p < 0.0001$].

Results

One hundred and six fetuses ranging from GA 19 weeks to 39 weeks were analyzed (5 patients were excluded because they were lost to follow up). The mean maternal age was 32.85 (range 21–43) years, with a corresponding GA of 23.51 (range 19–39) weeks. The maternal characteristics and fetal MO indices are listed in Table 1.

The total volume of fetal medulla oblongata (MOV) was highly positively correlated with GA [MOV = 0.084 × GA − 1.211; correlation coefficient (r) = 0.686, $p < 0.0001$; Figure 2]. The MGV was negatively correlated with GA (MGV = −1.134 × GA + 56.288; $r = -0.544$, $p < 0.0001$; Figure 3). The VI and FI showed no significant correlation with GA ($p = 0.123$ and 0.219, respectively).

Discussion

In this study, we used 3DPDUS to assess the fetal MO, and the results also showed that the correlation between the fetal MOV and GA is highly significant ($p < 0.0001$).

Previous studies have focused on the middle cerebral artery and the circle of Willis [4,5]. Chang et al [4] examined the circle of Willis in 155 fetuses between 21 weeks and 40 weeks of gestation. They reported a strong positive correlation between all of the indices and GA, with an increase in brain vascularization and blood flow throughout gestation [3]. Their data revealed a positive correlation coefficient, indicating that the fetal brain vascularization and the blood flow increased with the advancement of GA [4]. In our study, MGV revealed a negative correlation with GA, and VI and FI showed

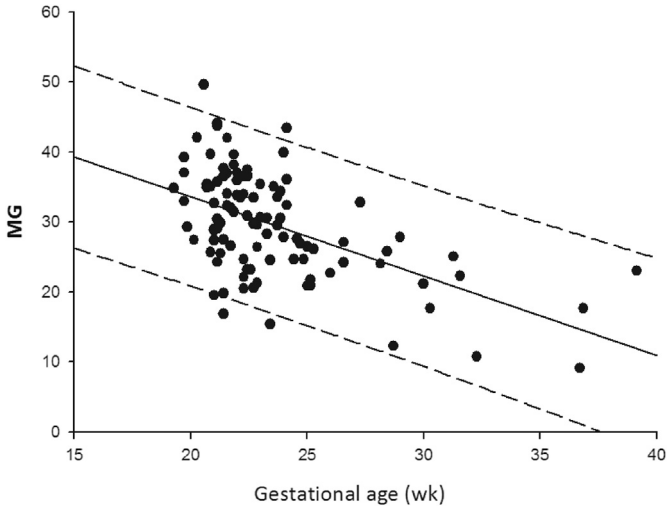

Figure 3. Mean gray value (MG) and gestational age (GA). MG was negatively correlated with GA [MG = −1.134 × GA + 56.288; correlation coefficient (r) = −0.544, $p < 0.0001$].

no correlation, although we studied a different part of the CNS. Our previous report revealed a similar result on MGV of the whole fetal brain [8]. One possible explanation is that the growth rate of MO parenchyma is much greater than the vessels but less than the flow volume. Prior to delivery, the fetal MO vascularization remains at a constant level regardless of whether the MOV increases. There were several limitations in our study. First, the number of cases was still too small to build the reference ranges of 3DPD indices of the fetal MO. Second, we only collected normal fetuses, which made it difficult to compare the differences between normal and abnormal groups.

To the best of our knowledge, this is the first research focusing on fetal MO vascularization. Nevertheless, our cases were mainly between 18 weeks' and 30 weeks' gestation, which might not represent the general pregnant population. Further studies involving a larger number of cases are ongoing to confirm the results presented here and establish the reference range in the Taiwanese population.

Conflicts of interest

The authors have no conflicts of interest relevant to this article.

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