Original Contribution

TRANSGAVINAL 3-D POWER DOPPLER ULTRASOUND EVALUATION OF THE FETAL BRAIN AT 10–13 WEEKS’ GESTATION

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Abstract—The objective of this study was to measure the fetal brain volume (FBV) and vascularization and blood flow using transvaginal 3-D power Doppler (3DPD) ultrasound late in the first trimester of pregnancy. 3DPD ultrasound examinations with the VOCAL imaging analysis program were performed on 36 normal fetuses from 10–13 weeks’ gestation. FBV and 3DPD indices related to the fetal brain vascularization (vascularization index [VI], flow index [FI] and vascularization flow index [VFI]) were calculated in each fetus. Intra- and interclass correlation coefficients and intra- and interobserver agreements of measurements were assessed. FBV was curvilinearly correlated well with the gestational age (R² = 0.861, p < 0.0001). All 3-D power Doppler indices (VI, FI and VFI) showed no change at 10–13 weeks’ gestation. FBV and all 3-D power Doppler indices (VI, FI and VFI) showed a correlation >0.82, with good intra- and interobserver agreement. Our findings suggest that 3-D ultrasound is a superior means of evaluating the FBV in utero, and that 3-D power Doppler ultrasound histogram analysis may provide new information on the assessment of fetal brain perfusion. (E-mail: toshi28@med.kagawa-u.ac.jp) © 2012 World Federation for Ultrasound in Medicine & Biology.

Key Words: Three-dimensional power Doppler ultrasound, Transvaginal scanning, Normal fetus, Brain volume, Cerebral vascularization, First trimester.

INTRODUCTION

There have been only three reports on 3-D sonographic volume measurements of the fetal brain during normal pregnancy (Chang et al. 2003a; Endres and Cohen 2001; Roelfsema et al. 2004). Two investigations (Chang et al. 2003a; Endres and Cohen 2001) used the parallel slice technique (or multiplanar technique) for fetal brain volume (FBV) measurement, and one investigation (Roelfsema et al. 2004) used the rotational technique with VOCAL (Virtual Organ Computer-Aided Analysis, GE Healthcare, Milwaukee, WI, USA). Moreover, all three studies were conducted in the second and third trimesters of pregnancy.

Three-dimensional power Doppler (3DPD) indices, e.g., the vascularization index (VI), flow index (FI) and vascularization flow index (VFI), have been used to assess fetal organ and placental perfusions, and it has been accepted that these indices potentially reflect fetal organ blood flow and both utero-placental and feto-placental blood flow (Chang et al. 2003b, 2003c; Hata et al. 2011; Noguchi et al. 2009; Ruano et al. 2006). There have been only two investigations on the assessment of vascular indices of the fetal brain in normal pregnancies using 3DPD histogram analysis (Chang et al. 2003d; Nardozza et al. 2009). However, both investigations measured vascular indices in only regional or partial territories of the fetal brain, and not of the whole brain. Moreover, those studies were carried out in the late second and third trimesters of pregnancy. To the best of our knowledge, there has been no report on FBV measurement using 3D sonography and assessment of vascular indices of the fetal brain using 3DPD histogram analysis late in the first trimester of pregnancy.

We undertook the present study to measure the FBV using transvaginal 3D sonography and to assess fetal brain vascularization and blood flow using 3DPD histogram analysis late in the first trimester of pregnancy.

MATERIALS AND METHODS

Subjects

Transvaginal 3DPD sonographic examinations were performed in 36 pregnant women from 10–13 weeks’
gestation in this cross-sectional study. The 36 pregnant women enrolled in the study were healthy nonsmokers, and there was no evidence of maternal complications or substance abuse. The fetal age was estimated from the first day of the last menstrual period and confirmed by first-trimester ultrasound examinations. At the time of measurement, there were no medical or obstetric complications such as threatened abortion, preeclampsia, diabetes or maternal vascular disease. No neonate was found to have congenital malformations or genetic disorders. Informed consent was obtained from all women after a full explanation of the objectives of the study. The research protocol was approved by the Ethics Committee of Kagawa University School of Medicine.

Ultrasound examination

Two experienced observers performed all 3-D ultrasound scans using a Voluson E-8 (General Electric Medical Systems, Kretztechnik, Zipf, Austria) with a mechanical transvaginal 3.7–17.5-MHz transducer. A routine 2-D sonographic examination provided data on the fetal biometry. All fetuses showed biometric parameters within the normal range. Conventional 2-D sonographic examinations did not reveal any structural abnormalities of the fetuses.

First, the fetal head was imaged in 2-D power Doppler mode. After switching to 3DPD mode, the region-of-interest was scanned and stored on the hard drive of the ultrasound machine for subsequent analysis and calculation. 3DPD was used to obtain a representative fetal brain vascular tree volume. The signal was detected when the blood velocity was higher than the threshold value, which depends on the pulse repetition frequency (PRF) and high-pass filter of the machine. Therefore, maximal sensitivity was ensured by setting the PRF to 0.6 kHz and the wall motion filter to “low 1.” The following constant default instrument settings (corresponding to the manufacturer’s Doppler power setting) were used throughout the examinations: frequency = low; dynamic = set 3; balance >225; smooth = 4/5; ensemble = 15; line density = 8; power Doppler map = 5; artifact suppression = on; power Doppler line filter = 2; quality = high. The power Doppler window was placed over the fetal head. The 3DPD volume box was placed over the fetal head at a fixed 60–80° angle. Volume acquisition was done during a time interval varying from 8–11 seconds in the absence of fetal movements and with the mother staying as still as possible. The stored volumes were further analyzed using the VOCAL program included in the 4DView 2000 version 2.1 computer software (General Electric Medical Systems). Each volume was retrieved from the hard drive and processed using a multiplanar system. The VOCAL switch was activated using a 30° rotation angle and the manual setting. Using plane “A” as a work pattern, the limits of a virtual reference axis were placed between the upper and lower internal borders of the head, and then the volume of the brain was obtained and measured automatically while rotating around that fixed axis (Fig. 1).

The VOCAL program automatically calculates grayscale and color values from the acquired FBV (Fig. 2). The 3-D volume is composed of voxels (smallest functional units of volume). Voxel contains all the information on

Fig. 1. Measurement of FBV using transvaginal 3-D sonography at 12 weeks’ and 3 days’ gestation.
gray-scale and color voxels. “Intensity-weighted color” voxels contain information on the detected signal amplitude. According to these values, this system calculates three power Doppler indices to evaluate vessels and blood flows: (i) VI (0–100) means the proportion of the volume showing a flow signal in the fetal brain; (ii) FI (0–100) is the average flow signal intensity inside the fetal brain; and (iii) VFI (0–100) is a combination of the information concerning vessel presence and the amount of flow obtained by multiplying VI and FI (Pairleitner et al. 1999; Yu et al. 2003). It took less than 5 min to measure each FBV and its vascular indices.

Statistical analysis

All statistical analyses were performed using SPSS statistical software, version 15.0 for Windows (SPSS Inc., Chicago, IL, USA). For each parameter dataset, regression analysis was carried out, testing the regression of the measurement value on the gestational age, using polynomials of the first through the third degree (Dunn and Clark 1974; Rohatgi 1976; Bertagnoli et al. 1983). Different models were tested, and independent variable deletion carried out by analysis of variance applied to the regression was followed by calculation of the step-down method coefficients (Snedecor and Cochran 1967). The choice of the optimal model was based on the following criteria: Largest R², all coefficients different from 0 and low standard deviation of regression (SDR) (Rohatgi 1976). A p-value < 0.05 was considered statistically significant.

Intra- and interclass correlation coefficients were defined as the correlation between any two measurements from the same subject. Their values ranged from 0–1; the latter indicates the maximum reliability. Intra- (between first and second measurements) and interclass correlation coefficients (between first measurements) were calculated in 20 of 36 subjects in this study. Intraobserver and interobserver variabilities were also calculated according to the Bland-Altman procedure (Bland and Altman 1986) in 20 of 36 subjects. Intraobserver variation was examined between first and second measurements, and interobserver variation was assessed between first measurements. This analysis consisted of a graph in which the difference between the measurements (y-axis) was plotted against their mean value (x-axis). The 95% limits of individual agreement between the two measurements were calculated as the mean difference between two measurements ± 2.0 standard deviations. Moreover, the difference between the mean difference and zero was assessed using a two-sample t-test. A p-value < 0.05 was considered significant.

RESULTS

Intraobserver agreement

The mean difference between measurements and the limits of agreement for each of the parameters studied are shown in Table 1. The mean difference and 95% limits of intraobserver agreements for FBV, VI, FI and VFI were 0.074 mL (0.207, −0.059), −1.202% (0.187, −2.592), −0.439 (0.578, −1.456) and −0.431 (−0.027, −0.835), respectively. The difference between the mean difference and zero was not significant for FBV, VI, FI and VFI,
Fetal brain blood flow in the late first trimester

Moreover, 3-D FBV measurements showed excellent intra- and interobserver reliability. Chang et al. (2003a) also showed that FBV is highly correlated with the gestational age and fetal biometric parameters. Roelfsema et al. (2004) reported that 3-D sonographic measurement of FBV demonstrates an acceptable intraobserver variability and a nearly tenfold increase during the second half of gestation. However, those investigations were conducted using transabdominal 3-D sonography in the second and third trimesters of pregnancy. In the present study, we measured FBV using transvaginal 3-D sonography late in the first trimester of pregnancy. Consequently, FBV was curvilinearly correlated well with gestational age. Moreover, good intra- and interclass correlation coefficients and intra- and interobserver agreements were obtained for 3-D sonographic FBV measurements. To the best of our knowledge, there has been no report on transvaginal FBV measurement late in the first trimester, and this is the first report on transvaginal 3-D sonographic volume measurement of the fetal brain in utero.

There have been only two studies on 3DPD indices of the fetal brain in normal pregnancies (Chang et al. 2003d; Nardozza et al. 2009). Chang et al. (2003d) measured fetal brain vascularization and blood flow in normal pregnancies using 3DPD sonography between 21 and 40 weeks’ gestation. All the fetal brain VI, FL and VFI increased significantly with the gestational age and fetal biometric parameters. Nardozza et al. (2009) calculated 3DPD vascular indices in the anterior territory of the middle cerebral artery of the fetal brain in normal pregnancies between 24 and 35 weeks. However, the 3DPD vascular indices showed a low correlation with the gestational age. The reason for these differences in the correlation of 3DPD vascular indices of the fetal brain with advancing gestation between those two investigations is currently unknown. One possible explanation is

<Table 1. Intraclass correlation coefficient and intraobserver agreement for FBV and VI>

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Mean difference</th>
<th>95% CI</th>
<th>Limits of agreement</th>
<th>P value</th>
<th>ICC</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>BV</td>
<td>0.074</td>
<td>0.207 to −0.059</td>
<td>0.684 to −0.536</td>
<td>0.295</td>
<td>0.991</td>
<td>0.0001</td>
</tr>
<tr>
<td>VI</td>
<td>−1.202</td>
<td>0.187 to −2.592</td>
<td>5.152 to −7.554</td>
<td>0.107</td>
<td>0.828</td>
<td>0.0001</td>
</tr>
<tr>
<td>FI</td>
<td>−0.439</td>
<td>0.578 to −1.456</td>
<td>4.204 to −5.083</td>
<td>0.408</td>
<td>0.901</td>
<td>0.0001</td>
</tr>
<tr>
<td>VFI</td>
<td>−0.431</td>
<td>−0.027 to −0.835</td>
<td>1.417 to −2.279</td>
<td>0.051</td>
<td>0.852</td>
<td>0.0001</td>
</tr>
</tbody>
</table>

ICC = Intraclass correlation coefficient.

respectively. Intraclass correlation coefficients for each of the parameters studied are also shown in Table 1. FBV, VI, FI and VFI had intraclass correlation coefficients of 0.991, 0.828, 0.901 and 0.852, respectively (p = 0.0001).

<Table 2. Inter-class correlation coefficient and inter-observer agreement for fetal brain volume and vascularity indices>

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<table>
<thead>
<tr>
<th>Parameters</th>
<th>Mean difference</th>
<th>95% CI</th>
<th>Limits of agreement</th>
<th>P value</th>
<th>ICC</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>BV</td>
<td>0.035</td>
<td>0.158 to −0.089</td>
<td>0.603 to −0.534</td>
<td>0.594</td>
<td>0.994</td>
<td>0.0001</td>
</tr>
<tr>
<td>VI</td>
<td>0.305</td>
<td>1.28 to −0.671</td>
<td>4.745 to −4.414</td>
<td>0.548</td>
<td>0.908</td>
<td>0.0001</td>
</tr>
<tr>
<td>FI</td>
<td>0.061</td>
<td>1.095 to −0.972</td>
<td>4.789 to −4.667</td>
<td>0.090</td>
<td>0.899</td>
<td>0.0001</td>
</tr>
<tr>
<td>VFI</td>
<td>0.117</td>
<td>0.444 to −0.209</td>
<td>1.611 to −1.377</td>
<td>0.491</td>
<td>0.888</td>
<td>0.0001</td>
</tr>
</tbody>
</table>

BV = brain volume; VI = vascularization index; FI = flow index; VFI = vascularization flow index; 95% CI = 95% confidence interval; ICC = interclass correlation coefficient.

### DISCUSSION

Endres and Cohen (2001) were the first to report that FBV, measured by 3-D sonography, correlated well with the gestational age and fetal biometric parameters.
that the authors did not describe the exact placement of the sampling volume in the fetal brain. Another possible explanation for the difference between the two investigations is the different machines used. In this study, no 3DPD vascular indices of the fetal whole brain changed in normal pregnancies between 10 and 13 weeks’ gestation. Moreover, good intra- and interclass correlation coefficients and intra- and interobserver agreements for 3DPD vascular indices of fetal brain were confirmed. This is the first report on transvaginal 3DPD sonographic measurement of fetal brain vascularization and blood flow in utero. Pinter et al. (2001) found children and young adults with Down syndrome had smaller overall brain volumes assessed by high-resolution magnetic resonance imaging. Moreover, 3-D sonographic studies in chromosomally abnormal fetuses (especially fetuses with trisomy 21) at 11–13 + 6 weeks reported that the fetal head volume was smaller than in chromosomally normal fetuses (Falcon et al. 2005a, 2005b). Therefore, we may be able to know the cause and pathogenesis of these reduced FBVs in chromosomally abnormal fetuses by assessing fetal brain perfusion using 3DPD sonography in the first trimester of pregnancy. Our results may play an important role in future research on early fetal brain perfusion and in the prediction of abnormal fetal brain development.

Bioeffects and safety issues are very important in obstetrics because of the presumably more sensitive fetal tissues, particularly in early gestation (Kremkau 1995). Sheiner et al. (2007) reported that the acoustic output of clinical 2-D ultrasound machines, as expressed by TI and MI, during routine first-trimester sonographic
examinations has a negligible rise in TI. In a new International Society of Ultrasound in Obstetrics and Gynaecology statement on the use of Doppler ultrasound at 11–13 + 6 weeks (Salvesen et al. 2011a), the displayed TI should be ≤1.0 and exposure time should be kept as short as possible (usually no longer than 5 to 10 min) and should not exceed 60 min. In the present study, the TI during transvaginal 3DPD sonographic examination was <1.0, and examination time was <5 min. Moreover, the intensities in transvaginal scanning are generally lower than those in the transabdominal route because the path lengths involved are shorter, resulting in lower attenuation and thus requiring less intensity to achieve the same imaging quality (Salvesen et al. 2011b). However, it should always be borne in mind that minimizing exposure time with the lowest acoustic output possible to permit adequate diagnostic acuity is the embodiment of the as low as reasonably achievable principle (Abramowicz 2007; Kremkau 1995). Therefore, the Doppler evaluation should only be used as an investigational tool of the fetal brain at this gestation.

In conclusion, transvaginal 3-D ultrasound is a superior means of FBV measurement late in the first trimester of pregnancy, and 3DPD ultrasound histogram analysis may play an important role in the assessment of early fetal brain perfusion.

REFERENCES


