Diffusion-weighted imaging of placenta in intrauterine growth restriction with worsening Doppler US findings

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PURPOSE
We aimed to compare the placental diffusion difference between intrauterine growth restriction (IUGR) patients with worsening Doppler ultrasonography (US) findings and control group with normal Doppler US findings by using diffusion-weighted imaging (DWI).

METHODS
We performed a prospective study to compare the placental diffusion difference in 63 patients (gestational week, 28–34 weeks), including 50 IUGR patients (mean gestational week, 30 weeks 3 days ±16.2 days) with worsening Doppler US findings and 13 patients with normal Doppler US findings (mean gestational week, 29 weeks 4 days ±12.3 days) by using DWI (b value, 0–1000 s/mm²). We classified IUGR patients into three groups according to the reference values of the umbilical artery pulsatility index (PI) chart. Placenta apparent diffusion coefficient (ADC) calculations were performed by freehand drawn regions-of-interest (ROIs) (min, 8.04 cm²; max, 200 cm²).

RESULTS
Placental ADC values in IUGR patients (mean, 1.624±0.181 ×10⁻³ mm²/s; range, 1.35–1.96 ×10⁻³ mm²/s) were significantly reduced compared with the control group (mean, 1.827±0.191 ×10⁻³ mm²/s; range, 1.35–2.84 ×10⁻³ mm²/s) (P = 0.001). For adjusted ROI area calculation, ADC values were significantly lower in groups 3, 2 and 1, respectively, compared with the control group (P < 0.05); and there was no significant difference between groups 1 and 2 (P > 0.05). Preeclampsia significantly reduced the placental diffusion compared with patients without preeclampsia (P = 0.003). Gestational aging did not significantly affect ADC values in control patients (r=0.08, P = 0.561). The sensitivity, specificity, negative and positive predictive values of ADC to detect IUGR were 72%, 84.6%, 44%, and 94.7% with a cutoff value of 1.727 ×10⁻³ mm²/s, respectively.

CONCLUSION
The diagnostic estimation of placental ADC values to predict the severity of IUGR is comparable to that of umbilical artery PI. Considering that at the very early onset of IUGR, placental diffusion diminishes, ADC as a marker for IUGR in lieu of umbilical artery PI has the potential to determine the threshold for decreased placental diffusion. Therefore, DWI should be added to routine fetal MRI to show diffusion changes in placenta.
additional functional information regarding the placenta (5–8). The DWI with apparent diffusion coefficient (ADC) mapping shows the diffusion and perfusion changes due to diffusion motion of water molecules (6). It is known that ADC values rapidly decrease in response to acute ischemic events without reperfusion (9). Based on this fact, recent studies show that DWI as a part of fetal MRI is a complementary tool for detecting any placental ischemic changes to predict IUGR severity and to help the management of IUGR patients (9, 10).

In this study, we aimed to compare the placental diffusion difference in IUGR patients with worsening Doppler US findings and control group by using DWI.

Methods

We performed a prospective study to compare the placental diffusion difference in 63 patients (gestational week, 28–34 weeks), including 50 IUGR patients with worsening Doppler US findings (n=13) (mean gestational week, 29 weeks ±16.2 days) and patients with normal Doppler US findings (n=3) (mean gestational week, 29 weeks ±4 days±12.3 days) by using DWI (b value, 0–1000 s/mm²). Institutional review board approval was obtained for this study (approval number: 2013/734). All study participants gave written informed consent. We excluded 11 patients from IUGR (n=7) and control groups (n=4) due to positive TORCH serology (n=1), chromosomal anomaly (n=1), placental invasion and location abnormality (n=3), placental hemorrhage or infarction (n=2), renal failure/disease (n=2) and diabetes mellitus (n=2). The fetal MRI indications for control patients were unilateral borderline ventriculomegaly (n=6), neural tube defect (n=3), abdominal cyst (n=3) and vertebral segmentation anomaly (n=1), respectively.

Doppler ultrasonography examination

We classified IUGR patients into three groups (groups 1–3) according to the reference values of the umbilical artery PI and absent/reverse end-diastolic flow in accordance with the definition of IUGR in the International Society of Ultrasound in Obstetrics and Gynecology practice guidelines (4). Group 1 (n=20) had high pulsatility index (PI) above 95%, group 2 (n=21) had absence of end-diastolic flow, and group 3 (n=9) had reverse flow. Preeclampsia was defined as high blood pressure (>140/90 mmHg) and proteinuria (> 2+ on a dipstick or >300 mg/24-hour urine) (3). Of 50 patients, 29 had preeclampsia (n=11 in group 1, n=13 in group 2, and n=5 in group 3).

Fetal MRI protocol

Fetal MRI (1.5 T scanner, Magnetom Aera, Siemens) with a whole-body surface coil (18 channels) was performed for each patient, after the Doppler US assessment on the same day. The protocol included: T2-weighted HASTE (Half-Fourier acquisition single-shot turbo spin-echo) (TR/TE, 1200/94; flip angle, 150°), T1-weighted FLASH (fast low angle shot magnetic resonance imaging) (TR/TE, 169/4.76; flip angle, 70°) and T2-weighted TruFISP (true fast imaging with steady-state precession) (TR/TE, 3.75/1.8; flip angle, 50°) with slice thickness 4 mm, FOV 320–400 mm, and acquisition matrix 256–448 mm in three planes. DWI through the placental surface (b value, 0–1000 s/mm²) in three orthogonal axes (x, y, z) was performed in the coronal plane without breath holding. Two phase-encoding directions were measured for each orientation (FOV 320×320 mm, matrix 256×256 mm, slice thickness 4 mm, duration 1 min 24 s). The examination was repeated if any artifact or any distortion obscuring the anatomy were detected.

Imaging evaluation of the placenta

The ADC measurements on matched coronal DWI were performed by drawing freehand region of interest (ROI) (min 8.04 cm², max 200 cm²) as large as possible within the boundaries of the placenta at the level of umbilical cord insertion on PACS (Sectra Workstation IDS7) (Fig. 1). Placental venous lakes that were hyperintense on T2-weighted images and placental infarction which showed significant diffusion restriction were excluded from the ROI measurement areas (Fig. 2).

Two pediatric radiologists (SBG and AC) with 7 and 20 years of experience, respectively, reviewed all MRI studies of each patient independently. To decrease the risk of bias, the reviewers were blinded to the results of all other clinical data, reports of fetal Doppler US studies and results of other previous imaging studies. ADC values of IUGR patients were compared within each group and the control group. The diagnostic accuracy of ADC compared with umbilical artery PI was calculated.

Statistical analysis

Pearson correlation coefficient was calculated for statistical dependence between gestational week and ADC values. Interobserver agreement was measured with the kappa coefficient. Comparisons of ADC, umbilical artery PI, birth weight between the groups were made by using a One-Way Analysis of Variance (ANOVA, Post hoc test: Tukey). Fisher’s exact test was used to ana-

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**Main points**

- Placental ADC values of intrauterine growth restriction (IUGR) patients show gradual diffusion restriction by worsening Doppler US findings.
- Preeclampsia significantly reduces placental diffusion.
- Placental diffusion decrease due to gestational aging could be underestimated within a specific week range.
- DWI is a comparable method to Doppler US to predict the severity of IUGR and it should be added to the routine fetal MRI protocol in order to notice any early placental ischemia for better patient counseling and management options in collaboration with obstetricians.

Figure 1. a, b. Coronal matched T2-weighted HASTE (a) and ADC (×10⁻³ mm²/s) (b) images. Freehand ROI draw on placenta is demonstrated (b).
analyze the categorical variables (preeclampsia and oligohydramnios). Patient groups were compared with ADC by analysis of covariance (adjustment for multiple comparisons: Bonferroni), where ROI was the covariate. The receiver operating characteristic (ROC) curves were used to evaluate the performance and the cutoff values of ADC. P values <0.05 were considered statistically significant. All analyses were done by using IBM SPSS Statistics 22 (IBM Corp.).

Results
Almost perfect interobserver agreement was found between the two reviewers (κ=0.95, P = 0.009). Placental ADC values of IUGR patients (mean, 1.624±0.181 ×10^{-3} mm²/s; range, 1.35–1.96 ×10^{-3} mm²/s) were significantly reduced compared with the control group (mean, 1.827±0.191 ×10^{-3} mm²/s; range, 1.35–2.84 ×10^{-3} mm²/s) (P = 0.012). There was no significant difference among IUGR subgroups (P = 0.78) and between group 1 and the control group (P = 0.10). We observed that the placental ADC values in IUGR patients with preeclampsia (mean, 1.586±0.162 ×10^{-3} mm²/s) were significantly lower than in IUGR patients without preeclampsia and the control group (mean, 1.778±0.159×10^{-3} mm²/s) (P = 0.003) (Table 1). ROC analysis of ADC versus umbilical artery PI was shown on Fig. 3. The sensitivity, specificity, negative and positive predictive value of ADC to detect IUGR were 72%, 84.6%, 44%, and 94.7% with a cutoff value of 1.727×10^{-3} mm²/s, respectively (Table 2).

There was no statistically significant correlation between gestational week and ADC values in the control group (r=0.08, P = 0.56). ROI area calculations were significantly smaller in IUGR patients compared with the control group (P = 0.020). For adjusted ROI area calculation, ADC values were significantly lower in groups 3, 2, and 1, respectively, compared with the control group (P < 0.001); and there was no significant difference between group 1 and group 2 (P = 0.10).

All IUGR patients performed preterm delivery with an APGAR score between 0–6 on the first minute of life. Twenty women (40%) with IUGR (group 1, n=5; group 2, n=10; group 3, n=5) underwent cesarean section...
due to worsening fetal distress in 72 hours. Three pregnancies from groups 1 and 3 and the control group were complicated by placental abruption and ended in one week. Among 60 births, 46 preterm babies (76%) (group 1, n=14; group 2, n=21; group 3, n=9; control group, n=2) were followed-up in intensive care unit due to worsening pediatric parameters and prematurity complications (e.g., hyperbilirubinemia, hypoglycemia, respiratory distress syndrome, sepsis, pneumonia, germinal matrix hemorrhage, necrotizing enterocolitis) and 9 babies (group 1, n=1; group 2, n=3; group 3, n=5) died during follow-up. The rest were successfully discharged after approximately 40±5 days of hospitalization. One patient from the control group had severe preeclampsia in her 29th week and underwent a cesarean section. The baby weighed 850 g, was diagnosed with hypoglycemia and hyperbilirubinemia, and was followed up in the intensive care. Nine term babies from the control group were successfully delivered without any complication.

### Discussion

Our study shows that IUGR placenta has restricted diffusion compared with similar gestational week placentas with normal Doppler US findings. Recent studies showed that placental perfusion decreased in IUGR patients by using DWI, perfusion mapping in human and animal models and contrast-enhanced placental perfusion mapping (9–18). Bonel et al. (9) evaluated morphologic findings and DWI of the placenta in patients with and without IUGR. Their patient population was from pregnancies with high-risk fetal abnormalities and they did not follow pregnancies over time individually. They found that lower ADC values could be new markers for the dysmature placenta (9). Although our study group did not have any high-risk fetal abnormality, our results were correlated with their findings. To the best of our knowledge, our study is the first to compare IUGR placentas with worsening Doppler US findings and normal placental tissue by using DWI. There was significant placental diffusion difference between IUGR subgroups and the control group except group 1 versus group 2 for adjusted ROI areas. Considering the positive correlation between the ROI areas and ADC values, we tried to ignore this effect on ADC values by calculating an adjusted ROI area. We could also acknowledge that at the early onset of IUGR in which umbilical artery PI is above 95% to the absence of end-diastolic flow (group 1), placental diffusion restriction is noted on ADC mapping. Therefore, we may consider that placental ADC values could be suggested as a valuable method with high diagnostic estimation to determine early onset IUGR.

### Table 1. Findings in patient groups

<table>
<thead>
<tr>
<th>Continuous variables*</th>
<th>IUGR patients</th>
<th>Control patients</th>
<th>Control vs. IUGR</th>
</tr>
</thead>
<tbody>
<tr>
<td>ADC (×10⁻³ mm²/s)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1.684±0.16</td>
<td>1.652±0.13</td>
<td>1.593±0.25</td>
<td>1.827±0.19</td>
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<tr>
<td>1.594±0.47</td>
<td>1.481±0.46</td>
<td>1.336±0.70</td>
<td>1.851±0.61</td>
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<tr>
<td>Umbilical artery PI</td>
<td>1.5±0.30</td>
<td>2.8±0.82</td>
<td>5.9±1.82</td>
</tr>
<tr>
<td>Birth weight (g)</td>
<td>1586±750</td>
<td>1113±357</td>
<td>723±309</td>
</tr>
<tr>
<td>ROI (cm²)</td>
<td>13432.2±6230.9</td>
<td>13172.3±6104.2</td>
<td>16015.3±7871.1</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Categorical variables</th>
<th>IUGR patients</th>
<th>Control patients</th>
<th>Control vs. IUGR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preeclampsia</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>+</td>
<td>11 (55.0)</td>
<td>13 (61.9)</td>
<td>5 (55.5)</td>
</tr>
<tr>
<td>-</td>
<td>9 (45.0)</td>
<td>8 (38.1)</td>
<td>4 (44.4)</td>
</tr>
<tr>
<td>Oligohydramnios</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>+</td>
<td>3 (15.0)</td>
<td>3 (14.2)</td>
<td>7 (77.7)</td>
</tr>
<tr>
<td>-</td>
<td>17 (85.0)</td>
<td>18 (85.7)</td>
<td>2 (22.2)</td>
</tr>
</tbody>
</table>

Continuous variables are presented as mean value ± standard deviation. Categorical variables are presented as n (%).

IUGR, intrauterine growth restriction; ADC, apparent diffusion coefficient; ROI, region of interest; Umbilical artery PI, umbilical artery pulsatility index.

### Table 2. Cutoff values and coordinates of the ROC curve of ADC versus umbilical artery pulsatility index

<table>
<thead>
<tr>
<th>ADC cutoff values (×10⁻³ mm²/s)</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
<th>PPV</th>
<th>NPV</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤1.727</td>
<td>72.00</td>
<td>84.62</td>
<td>94.7</td>
<td>44.0</td>
</tr>
<tr>
<td>≤1.779</td>
<td>80.00</td>
<td>61.54</td>
<td>88.9</td>
<td>44.4</td>
</tr>
<tr>
<td>≤1.842</td>
<td>86.00</td>
<td>61.54</td>
<td>89.6</td>
<td>53.3</td>
</tr>
</tbody>
</table>

ROC, receiver operating characteristic; ADC, apparent diffusion coefficient; PPV, positive predictive value; NPV, negative predictive value.
1.727 × 10⁻³ mm²/s was determined as the cutoff value of diffusion restriction with the highest confidence interval under the ROC curve (Fig. 3). Our study is the first to depict a cutoff ADC value to determine early onset IUGR; however, the reproducibility of ADC calculations should be considered as the main limitation which could define different cutoff values in future studies.

Preeclampsia is characterized by poor trophoblastic invasion, oxidative stress, hypoxia or endothelial dysfunction (11). Brunelli et al. (11) found that preeclampsia was altering the maternal placental blood on dynamic contrast-enhanced fetal MRI in IUGR. However, contrast-enhanced fetal MRI is still considered to be the major contradiction for fetal imaging (11, 12). Sohlberg et al. (17) studied the different causes in early and late preeclampsia by comparing the perfusion fractions and found that early preeclampsia is more closely associated with poor placentalation than late onset disease. Regardless of different pathophysiology of early and late preeclampsia in opposite directions, preeclampsia considerably reduces the placental perfusion. Thus, DWI could be added to the routine fetal MRI to show diffusion changes in placenta.

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Conflict of interest disclosure
The authors declared no conflicts of interest.

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