Diagn Interv Radiol 2019; 25:280–284

FETAL IMAGING

ORIGINAL ARTICLE

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

Süreyya Burcu Görkem
Abdulhakim Coşkun
Murside Eşlik
Mehmet Serdar Kütük
Ahmet Öztürk

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/mm^2). 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 cm^2; max, 200 cm^2).

RESULTS
Placental ADC values in IUGR patients (mean, 1.624±0.181 $\times10^{-3}$ mm^2/s; range, 1.35–1.96 $\times10^{-3}$ mm^2/s) were significantly reduced compared with the control group (mean, 1.827±0.191 $\times10^{-3}$ mm^2/s; range, 1.35–2.84 $\times10^{-3}$ mm^2/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 $\times10^{-3}$ mm^2/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.

Intrauterine growth restriction (IUGR) is described as an estimated fetal weight of more than 10% percentile below the mean gestational age-related reference curve with a high risk of perinatal mortality and morbidity (1). As a response to IUGR, placental perfusion decreases due to placental insufficiency and eventually fetal Doppler ultrasonography (US) and fetal biometry are affected (2–4). The main goal of the antenatal management for IUGR is the maintenance of pregnancy under close surveillance and termination of pregnancy when the intrauterine condition starts to threat the fetal viability and well-being (2). Doppler US represents the key elements of fetal assessment and guides pregnancy management in association with fetal biometrics. Doppler US including flow characteristics and resistance of fetal and placental vessels has been used for follow-up and grading the severity of IUGR (3). Fetal magnetic resonance imaging (MRI) is superior compared with the US in detecting morphologic and functional abnormalities of fetal and nonfetal tissues. Furthermore, diffusion-weighted imaging (DWI) or diffusion tensor imaging (DTI) is considered to give

From the Division of Pediatric Radiology, Departments of Radiology (S.B.G. ✉ *drburcugorkem@gmail.com*, A.C.) and Obstetrics and Gynaecology (M.E., M.S.K.) and Biostatistics (A.Ö.), Erciyes University School of Medicine, Kayseri, Turkey.

Received 5 August 2018; revision requested 16 September 2018; last revision received 11 December 2018; accepted 17 December 2018.

Published online 20 May 2019.

DOI 10.5152/dir.2019.18358

You may cite this article as: Görkem SB, Coşkun A, Eşlik M, Kütük MS, Öztürk A. Diffusion-weighted imaging of placenta in intrauterine growth restriction with worsening Doppler US findings. Diagn Interv Radiol 2019; 25:280–284.

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 principle, 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 (mean gestational week, 30 weeks 3 days ±16.2 days) and patients with normal Doppler US findings (n=13) (mean gestational week, 29 weeks 4 days±12.3 days) by using DWI (*b* value, 0–1000 s/mm^2). 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/mm^2 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 cm^2, max 200 cm^2) 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-

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.

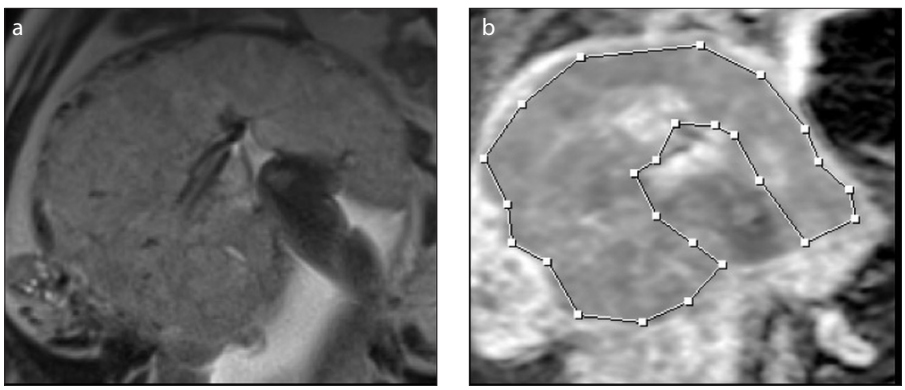

Figure 1. a, b. Coronal matched T2-weighted HASTE **(a)** and ADC (×10^{-3} mm^2/s) **(b)** images. Freehand ROI draw on placenta is demonstrated **(b)**.

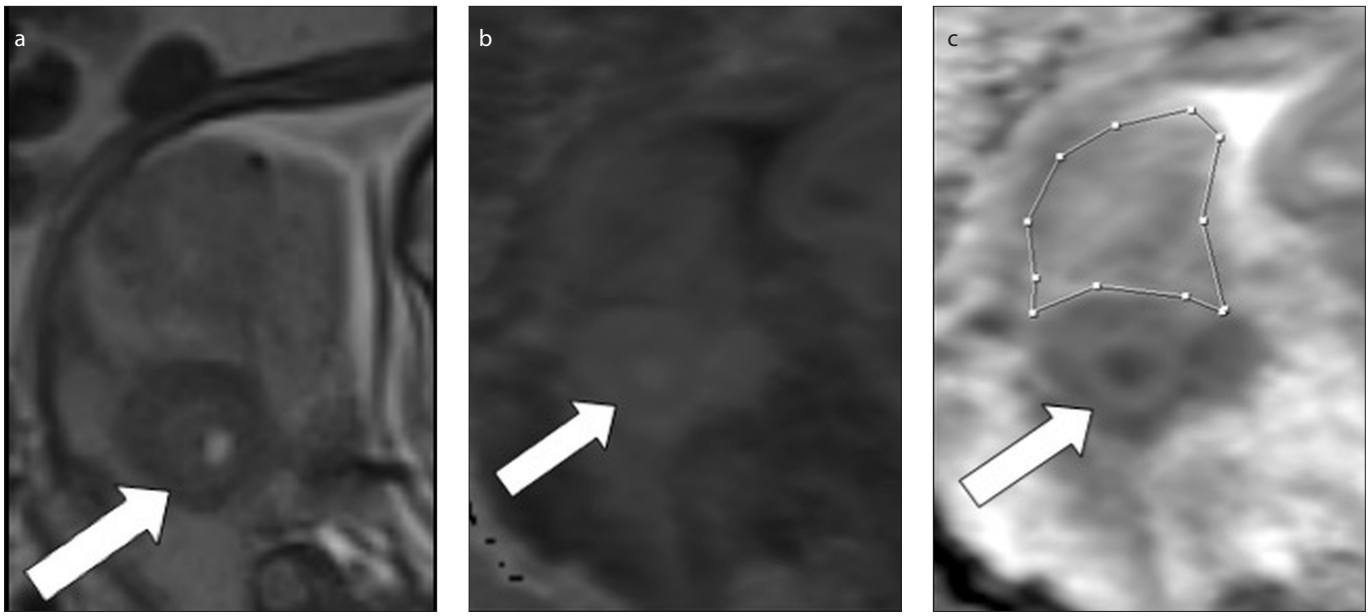

Figure 2. a–c. Coronal matched T2-weighted HASTE **(a)**, DWI **(b),** and ADC (×10^{-3} mm^2/s) **(c)** images. Infarction area is excluded from freehand ROI (cm^2) calculation *(white arrow)*.

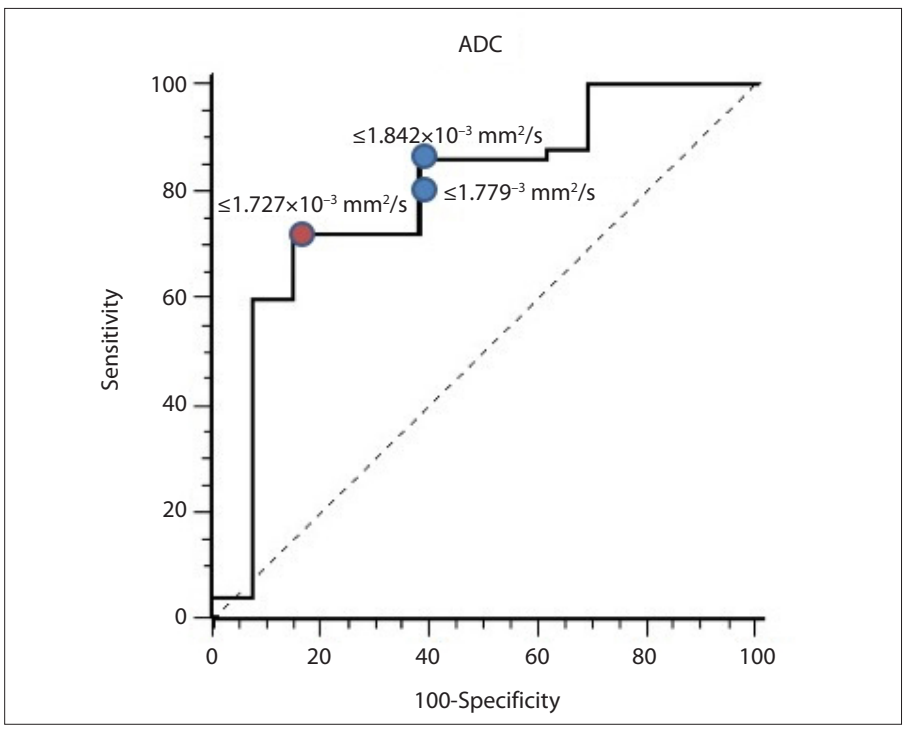

Figure 3. ROC curve of ADC (×10^{-3} mm^2/s) versus umbilical artery pulsatility index. ADC value ≤1.727 ×10^{-3} mm^2/s; AUC, 0.789; 95%CI, 0.668–0.882, $P < 0.001$ *(red dot)*. *Blue dots* are mentioned as the values above the ROC curve (also see Table 2).

lyze 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} mm^2/s; range, 1.35–1.96 ×10^{-3} mm^2/s) were significantly reduced compared with the control group (mean, 1.827±0.191 ×10^{-3} mm^2/s; range, 1.35–2.84 ×10^{-3} mm^2/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} mm^2/s) were significantly lower than in IUGR patients without preeclampsia and the control group (mean, 1.778±0.159×10^{-3} mm^2/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} mm^2/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

Table 1. Findings in patient groups

	IUGR patients				*P*
Continuous variables*	Group 1	Group 2	Group 3	Control patients	Control vs. IUGR
ADC ($\times10^{-3}$ mm^2/s)	1.684±0.16	1.652±0.13	1.593±0.25	1.827±0.19	0.012
ADC ($\times10^{-3}$ mm^2/s) covariate for ROI	1.594±0.47	1.481±0.46	1.336±0.70	1.851±0.61	<0.001
Umbilical artery PI	1.5±0.30	2.8±0.82	5.9±1.82	1.02±1.11	<0.001
Birth weight (g)	1586±750	1113±357	723±309	2835±937	<0.001
ROI (cm^2)	13432.2±6230.9	13172.3±6104.2	16015.3±7871.1	19771.9±5121.7	0.020
Categorical variables					
Preeclampsia					
+	11 (55.0)	13 (61.9)	5 (55.5)	0(0)	<0.001
-	9 (45.0)	8 (38.1)	4 (44.4)	13 (100)	
Oligohydramnios					
+	3 (15.0)	3 (14.2)	7 (77.7)	0 (0)	0.053
-	17 (85.0)	18 (85.7)	2 (22.2)	13 (100)	

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

ADC cutoff values ($\times10^{-3}$ mm^2/s)	Sensitivity (%)	Specificity (%)	PPV	NPV
≤1.727	72.00	84.62	94.7	44.0
≤1.779	80.00	61.54	88.9	44.4
≤1.842	86.00	61.54	89.6	53.3

ROC, receiver operating characteristic; ADC, apparent diffusion coefficient; PPV, positive predictive value; NPV, negative predictive value.

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, pneumothorax, 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 placenta 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. Placental ADC declination starting from

1.727 $\times 10^{-3}$ mm^2/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 placentation than late onset disease. Regardless of different pathophysiology of early and late preeclampsia in opposite directions, preeclampsia considerably reduces the placental perfusion (17). Our results are concordant with the literature.

The signal intensity and diffusivity of the placenta are affected by gestational aging (19). Manganaro et al. (20) found a negative correlation between ADC values and gestational aging (20–40 weeks), but they described that DWI with ADC maps could not be considered markers for placental aging due to perfusion and circulatory motion changes (20). Bonel et al. (9) and Sohlberg et al. (12) found no significant correlation between placenta ADC values with gestational age (22–40 weeks; 21–40 weeks) in their control groups, whereas Sohlberg et al. (17) found that perfusion fraction showed decrease by gestational aging in another study. We found that gestational aging did not significantly reduce placental diffusion. Our control patients had a gestational week range of 28–34 weeks which was earlier and shorter compared with the literature. Therefore, placental ischemia due to gestational aging could be underestimated within a specific week range according to our study.

We acknowledge our limitations. First, we did not follow up each patient by DWI so we do not know about placental diffusion changes during pregnancy. Second, our study subgroups consisted of a small number of patients from our own population. Thus, our ADC values may not be reproducible for other populations. Further prospective studies including larger populations and follow-up procedure by DWI for individual outcomes that can confirm our results would be useful.

In 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 the routine fetal MRI to show diffusion changes in placenta.

Funding disclosure

This was a TUBITAK project (The Scientific and Technological Research Council of Turkey) entitled "Assessment of correlation between uteroplacental Doppler US findings and cerebral perfusion in intrauterine growth-restricted fetuses by diffusion magnetic resonance imaging" (number: 114S082, project 3001) successfully completed in August 2016.

Conflict of interest disclosure

The authors declared no conflicts of interest.

References

1. Gabbe GS. Obstetrics, normal and problem pregnancies, 6th. ed., Philadelphia, Elsevier/ Saunders, 2012; 23–41.
2. Longo LD. Respiratory gas exchange in the placenta. In Fishman AP, Farhi LE, Tenney SM, (Eds). Handbook of Physiology, section 3, The Respiratory System, Volume. IV., Gas Exchange. Washington, DC. American Physiological Society, 1987; 351.
3. Moore RJ, Ong SS, Tyler DJ, et al. Spiral artery blood volume in normal pregnancies and those compromised by pre-eclampsia. NMR Biomed 2008; 21:376–378. [CrossRef]
4. Bhide A, Acharya G, Bilardo CM, et al. ISUOG Practice Guidelines: use of Doppler ultrasonography in obstetrics. Ultrasound Obstet Gynecol 2013; 41:233–239. [CrossRef]
5. Abramowicz JS, Sheiner E. In utero imaging of the placenta: importance for diseases of pregnancy. Placenta 2007; 28:14–22. [CrossRef]
6. Morita S, Ueno E, Fujimura M, Muraoka M, Takagi K, Fujibayashi M. Feasibility of diffusion-weighted MRI for defining placental invasion. J Magn Reson Imaging 2009; 30:666–671. [CrossRef]
7. Sandrasegaran K, Lall CG, Aisen AA. Fetal magnetic resonance imaging. Curr Opin Obstet Gynecol 2006; 18: 605–612. [CrossRef]
8. Dekan S, Linduska N, Kasprian G, Prayer D. MRI of the placenta - a short review. Wien Med Wochenschr 2012; 162:225–228. [CrossRef]
9. Bonel HM, Stolz B, Diedrichsen L, et al. Diffusion-weighted MR imaging of the placenta in fetuses with placental insufficiency. Radiology 2010; 257: 810–819. [CrossRef]
10. Derwig I, Lythgoe DJ, Barker GJ, et al. Association of placental perfusion, as assessed by magnetic resonance imaging and uterine artery Doppler ultrasound, and its relationship to pregnancy outcome. Placenta 2013; 34:885–891. [CrossRef]
11. Brunelli R, Masselli G, Parasassi T, et al. Intervillous circulation in intra-uterine growth restriction. Correlation to fetal well-being. Placenta 2010; 31:1051–1056. [CrossRef]
12. Sohlberg S, Mulic-Lutvica A, Olovsson M, et al. MRI estimated placental perfusion in fetal growth assessment Ultrasound Obstet Gynecol 2015; 46: 700–705. [CrossRef]
13. Moore RJ, Strachan BK, Tyler DJ, et al. In utero perfusing fraction maps in normal and growth restricted pregnancy measured using IVIM echo-planar MRI. Placenta 2000; 21: 726–732. [CrossRef]
14. Francis ST, Duncan KR, Moore RJ, Baker PN, Johnson IR, Gowland PA. Non-invasive mapping of placental perfusion. Lancet 1998; 351:1397–1399. [CrossRef]
15. Duncan KR, Gowland P, Francis S, Moore R, Baker PN, Johnson IR. The investigation of placental relaxation and estimation of placental perfusion using echo-planar magnetic resonance imaging. Placenta 1998; 19:539–543. [CrossRef]
16. Damodaram M, Story L, Eixarch E, et al. Placental MRI in intrauterine fetal growth restriction. Placenta 2010; 31:491–498. [CrossRef]
17. Sohlberg S, Mulic-Lutvica A, Lindgren P, Ortiz-Nieto F, Wikström AK, Wikström J. Placental perfusion in normal pregnancy and early and late preeclampsia: a magnetic resonance imaging study. Placenta 2014; 35:202–206. [CrossRef]
18. Chalouhi GE, Alison M, Deloison B, et al. Fetoplacental oxygenation in an intrauterine growth restriction rat model by using blood oxygen level-dependent MR imaging at 4.7 T. Radiology 2013; 269:122–129. [CrossRef]
19. Wright C, Morris DM, Baker PN, et al. Magnetic resonance imaging relaxation time measurements of the placenta at 1.5 T. Placenta 2011; 32:1010–1015. [CrossRef]
20. Manganaro L, Fierro F, Tomei A, et al. MRI and DWI: feasibility of DWI and ADC maps in the evaluation of placental changes during gestation. Prenat Diagn 2010; 30:1178–1184. [CrossRef]