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Research article

Placental MRI shows preservation of brain volume in growth-restricted fetuses who suffer substantial reduction of putative functional placenta tissue (PFPT)

D. Javor[a,b,*], C. Nasel[b], S. Dekan[c], G.M. Gruber[d], K. Chalubinski[e], D. Prayer[a]

[a] *Department of Biomedical Imaging and Image-guided Therapy, Medical University of Vienna MUW, Austria*
[b] *Department of Radiology, University Hospital Tulln, Karl Landsteiner University of Health Sciences, Tulln, Austria*
[c] *Department of Pathology, Medical University of Vienna MUW, Austria*
[d] *Department of Anatomy, Medical University of Vienna MUW, Austria*
[e] *Department of Gynecology, Medical University of Vienna MUW, Austria*

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ABSTRACT

Objective: Recently, a potentially useful diagnostic approach based on MR diffusion-tensor-imaging (DTI) was reported for the estimation of putative functional placenta tissue (PFPT), thus providing direct information about placental function. Yet, the relation between reduced PFPT and the phenomenon of brain-sparing remains unclear. This study aimed to investigate the relation between brain-sparing and reduced PFPT volume, as found in fetuses with intrauterine growth restriction (IUGR).

Methods: A total of 40 consecutive patients with a US-based diagnosis of placental IUGR were examined using fetal MRI. A control group of 78 patients who received fetal MRI, due to non-placental pathologies, was established. A somatic energy index was calculated as $I_{E=}1–(V_{brain}/V_{pfpt})$ from brain and PFPT volumes measured with DTI in both groups. I_E, V_{pfpt}, and V_{brain} were analyzed with respect to the gestational week.

Results: V_{brain} corrected for gestational weeks was no different between both groups, while V_{pfpt} was significantly reduced in IUGR patients. I_E was significantly different between both groups and indicated a higher V_{brain} at a comparable V_{pfpt}.

Conclusions: Fetuses with IUGR show preserved energetic resources necessary for brain growth. Because I_E drops in IUGR more rapidly as pregnancy progresses, depending on V_{pfpt}, I_E could prove useful for estimating fetal well-being.

1. Introduction

Management of intrauterine growth restriction (IUGR) is a major challenge in maternal healthcare, because IUGR is associated with an increased risk of perinatal mortality and morbidity [1]. The fact that antenatal detection of IUGRs is difficult is emphasized by the finding that only approximately 26% of babies at risk for IUGR are correctly recognized as such before delivery [2]. In addition to other reasons for IUGR, an insufficient uteroplacental unit may potentially restrict delivery of vital nutrients to the fetus, especially in cases with abnormal umbilical artery Doppler studies, in which differentiation of placental and non-placental causes for IUGR, especially in the early onset forms of IUGR, is of interest [3]. Although routinely used imaging modalities, such as ultrasound (US) or conventional magnetic resonance imaging (MRI), reliably depict morphological alterations of the placenta, neither of these modalities provides global, comprehensive, direct information about placental function.

Recently, the use of MR diffusion tensor imaging (DTI) of the whole placenta was suggested to enable the differentiation of non-functional and functional placenta tissue. Because DTI revealed in IUGR patients a significant reduction of the placenta volume exhibiting a high signal intensity compared to normal pregnancies, these regions were considered as presumably functional and, therefore, termed putative functional placental tissue (PFPT) [4]. In this context, also considering well-documented umbilical vascular flow alterations [3], it is conceivable that the energetic supply of the fetus declines when PFPT volume decreases, since, with decreasing PFPT volume, the active cross-section available for metabolic exchange declines as well. It is plausible that there is, consequently, a restricted delivery of vital nutrients via the placenta that might cause adaptive fetal mechanisms in which the

* Corresponding author at: Department of Radiology, Medical University Vienna, Währingergürtel 18–20, A-1090, Vienna, Austria.
E-mail address: domagoj.javor@meduniwien.ac.at (D. Javor).

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blood volume is redistributed away from the perfusion of peripheral organs and extremities toward the brain—a mechanism well known as brain-sparing as described in IUGR [5].

Therefore, in this study, we investigated the relationship between the amount of PFPT and fetal brain volume according to our hypothesis that the energetic distribution is adjunctive to the preservation of fetal cerebral volume growth, and potentially directly relates to the placental function.

2. Materials and methods

2.1. Patients

A total of 118 consecutive patients scheduled to undergo fetal MRI were differentiated prospectively into two groups according to an intention to treat basis. Patients with a previous US-based diagnosis of placental IUGR were collected in an IUGR-group (pIUGR-group: n = 40; age: 19–37 years; gestational weeks [gw]: 17–36). The, second, non-IUGR group (nonIUGR: n = 78; age: 23–39 years; GW: 18–35) contained patients who were examined for nonIUGR-related fetal pathologies suspected on previous US examinations.

The US criteria necessary for classification into the pIUGR-group were comparable to other studies on this topic and included a reduced estimated fetal weight below the 10th percentile, calculated from the abdominal circumference, and, if available, an abnormal Doppler velocimetry of the umbilical artery with a pulsatility index above the 95th percentile [6]. In the nonIUGR-group, estimated fetal weight and placental findings on US had to be reported as regular. Fetal pathologies in the nonIUGR group were mainly mild ventricular asymmetry, diaphragmatic hernia, bone malformation, heart malformation, and renal cysts.

Fetuses with known genetic abnormalities were not included in any of the groups. Patients with multiple pregnancy (twins, triplets, etc.), unstable or non-compliant patients, and those with acute or chronic renal insufficiency were also not included in the study, as well as patients who presented with standard exclusion criteria for MRI (pacemakers, cochlear implants, MR-incompatible aneurysm clips, intraocular metallic foreign bodies, claustrophobia, etc.). During clinical work-up six fetuses suspected to suffer congenital heart disease (CHD) were excluded, as a postulated reduction of both, placental and brain volume, might have introduced bias into our measurements [7]. Another, six patients initally suspected to suffer pIUGR were excluded from the final evaluation because genetic abnormalities etc. became evident. Therefore, 72 patients receiving placental MRI remained in the non-IUGR group and 34 patients in the pIUGR group for the final statistical evaluation. In the collective of all 118 patients, 57 live births and eight deaths were observed, while in 53 patients who delivered their babies in other hospitals the live-birth rate remains unknown. Work up and inclusion criteria of all patients are displayed in Fig. 5

The study was approved by the local ethics committee, and written, informed consent was obtained in all cases. Terms of clinical good practice according to the declaration of Helsinki and later amendments were obeyed [8].

2.2. MRI imaging and evaluation

All fetal MRI examinations were performed on a clinical MRI scanner (1.5 T, Achieva Philips Medical Systems, Best, The Netherlands) using standard T1- and T2-weighted sequences for morphological imaging of the fetus and the placenta. PFPT volumes were derived from DTI-MRI through measurement of the placenta in six non-collinear directions, using a dual-b (b0 = 0 and b1 = 750 s/mm2) SE-EPI sequence (TE/TR: 102/1995 ms; aqu.matrix: 80 × 79 voxels; voxel size: 3 × 3 x 3 mm; scan time: app. 3:24 min). Up to 25 coronal slices covering the whole placental volume were obtained. PFPT was differentiated by its clearly higher signal intensity compared to the adjacent myometrium on the b1-DT images and was evaluated using 3D-ROIs, which were drawn manually. Semiautomatic segmentation of the PFPT volume was performed using freely available scientific assessment software [9]. PFPT was differentiated from myometric tissue using a cut-off threshold, in which PFPT had to display signal intensities of at least 60% higher than those of the adjacent myometrium. The complete method is described in detail elsewhere [4].

An estimate of the brain volume was obtained from another dual-b (b0 = 0 and b1-value 700 s/mm2), diffusion-weighted MRI sequence (TE/TR: 61/1904 ms; aqu.matrix: 124 × 100 voxels; voxel size: 3 × 3 × 5 mm; scan time: app. 1:35 min) due to the excellent stability and reproducibility of this sequence, with the advantage of an acceptable differentiation of brain parenchyma and cerebrospinal fluid. Again, 3D-ROIs of the brain were manually drawn. PFPT and brain volumetry was interpreted by two radiologists, in consensus,

From PFPT and brain volumetry, a feto-placental energy index (I_E) was calculated as:

$$I_E = 1 - \frac{V_{brain}}{V_{pfpt}} \tag{1}$$

where I_E denotes the feto-placental energy index, V_{brain} stands for the brain volume as measured on the brain b1-DT images and V_{pfpt} is the putative functional placental tissue volume derived from the b1-DT images of the corresponding placental MRI sequence.

2.3. Statistical analysis

According to earlier observations, an increase in PFPT and fetal brain volume over time was assumed to be exponential rather than linear [4]. Therefore, the relations between I_E, V_{pfpt}, V_{brain}, and the corresponding gestational week were analyzed using robust linear regression analysis that was applied to the logarithm of the responsive variables and transformed back into the original scale afterward [10]. The influence of each parameter on the respective regression model was tested using an analysis of variance (ANOVA). Comparisons between groups were performed using Dunnett's Modified Tukey-Kramer pairwise, multiple comparison test (DTK-test), with conservative correction for multiple comparisons (Bonferroni) to cope with inconsistencies of normal distribution or homoscedasticity and bias from different group sizes [11]. All statistical evaluations were performed using the software package R (version 3.2.0). If not marked differently, all demographic data are given as mean and SD.

3. Results

Ultimately, 34 pIUGR and 72 nonIUGR patients were included. The age of the mothers was not significantly different between the pIUGR and the nonIUGR group, and, as far as available, their medical history was also comparable. In addition, the gestational week in which fetal MRI was performed was not significantly different between the two groups. A summary of the demographic data is given in Table 1.

PFPT-volumes were significantly reduced in the pIUGR group (DTK, variable: PFPT-volume; groups: nonIUGR vs pIUGR, p = 0.0007). The PFPT volume in the pIUGR group was 132.1 ± 86.0 cm^3 and 320.0 ± 107.5 cm^3 in the nonIUGR group. The distribution of PFPT volumes over time (gestational week) is depicted in Fig. 1, where the excluded cases are also shown in relation to the two assessed groups. With regard to PFPT volume, the excluded cases performed comparably to the nonIUGR group.

In contrast, brain volumes for a given gestational week were not significantly different between the pIUGR and the nonIUGR group (DTK, variable: brain-volume, groups: nonIUGR vs pIUGR, p = 0.2232) (Fig. 2) the mean brain volume was 127.0 ± 69.5 cm^3 in the pIUGR group and 124.6 ± 66.9 cm^3 in the nonIUGR group, which led to a less favorable relation between PFPT and fetal brain volume in the pIUGR group (Fig. 3).