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T2* weighted fetal MRI and the correlation with placental dysfunction

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ABSTRACT

Introduction: Transverse relaxation time (T2^{*}) is related to tissue oxygenation and morphology. We aimed to describe T2^{*} weighted MRI in selected fetal organs in normal pregnancies, and to investigate the correlation between fetal organ T2^{*} and placental T2^{*}, birthweight (BW) deviation, and redistribution of fetal blood flow. *Methods:* T2^{*}-weighted MRI was performed in 126 singleton pregnancies between 23+6- and 41+3-weeks' gestation. The T2^{*} value was obtained from the placenta and fetal organs (brain, lungs, heart, liver, kidneys, and spleen). In normal BW pregnancies (BW > 10th centile), the correlation between the T2^{*} value and gestational age (GA) at MRI was estimated by linear regression. The correlation between fetal organ Z-score and BW group was demonstrated by boxplots and investigated by analysis of variance (ANOVA) for each organ.

Results: In normal BW pregnancies fetal organ $T2^*$ was negatively correlated with GA. We found a significant correlation between BW group and fetal organ $T2^*$ z-score in the fetal heart, kidney, lung and spleen. A positive linear correlation was demonstrated between fetal organ $T2^*$ and outcomes related to placental function such as BW deviation and placenta $T2^*$ in all investigated fetal organs except for the fetal liver. In the fetal heart, kidneys, and spleen the $T2^*$ value showed a significant correlation with fetal redistribution of blood flow (Middle cerebral artery Pulsatility Index) before delivery.

Discussion: Fetal T2* is correlated with BW, placental function, and redistribution of fetal blood flow, suggesting that fetal organ T2* reflects fetal oxygenation and morphological changes related to placental dysfunction.

1. Introduction

In pregnancies complicated by placental dysfunction the supply of oxygen and nutrients is inadequate to meet the metabolic demand of the growing fetus. This condition may lead to fetal growth restriction, fetal hypoxia [1,2], and in severe cases irreversible ischemic organ damage and intrauterine fetal death may occur [3–5]. The fetus seeks to adapt to the hypoxic condition by redistribution of fetal blood flow towards essential fetal organs such as the myocardium, adrenal glands, and brain [6]. This finding is also known as "brain sparing" and it can be identified by ultrasound Doppler flow measurement of the middle cerebral artery (MCA) [7–9]. In the absence of direct methods to estimate fetal oxygenation in vivo, the redistribution of fetal blood such as brain sparing is a recognized clinical marker of fetal hypoxia [10]. Brain sparing is the first indicator of fetal hypoxia in a timeline of fetal circulatory changes that describes the progression of fetal deterioration

due to placental dysfunction from light hypoxia to acidosis and still birth in the absence of intervention [11]. A direct non-invasive method to assess the oxygenation of fetal organs could expand our understanding of the fetal response to placental dysfunction and thereby improve the fetal surveillance of high-risk pregnancies.

The magnetic resonance imaging (MRI) transverse relaxation time (T2*) provides direct estimates of tissue oxygenation in vivo [12,13]. The T2* relaxation time is sensitive to magnetic field inhomogeneities as created by several factors including deoxyhemoglobin, which shortens the T2* relaxation time. Thereby, T2*weighted MRI is related to tissue oxygenation [12,13]. Thus, in hypoxic tissue the amount of deoxyhemoglobin is increased and accordingly the T2* value is reduced. The T2* value is also related to tissue morphology including macromolecular deposition, water content, and accumulation of lipids [13]. Each tissue has a specific T2* value and tissue pathology may be identified by altered T2* value [13]. Over the last decades mapping of brain function by use of T2* weighted MRI and the blood oxygenation level-dependent

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Abbreviations					
BW	Birth weight				
GA	Gestational age				
MRI	Magnetic resonance imaging				
ROI	Region of interest				
T2*	Transverse relaxation time				
SGA	Small for gestational age				
MCA	Middle cerebral artery				

(BOLD) contrast have revealed new insights in brain physiology in animals and humans [14]. However, the intrauterine environment remains to be explored.

Placental function has been investigated by the use of T2* weighted MRI [15]. Placental T2* is reduced in pregnancies complicated by placental dysfunction such as fetal growth restriction [15,16], preeclampsia [17] placental T2* or histological evidence of vascular malperfusion [18], these findings are most likely related to placental hypoxia. It is generally accepted, that T2* weighted placental MRI provides non-invasive information on placental function in vivo [19].

In the fetus T2* weighted MRI is only briefly described. Experimental animal studies have demonstrated that changes in fetal oxygenation induced by maternal hyperoxia/hypoxia can be depicted by T2* weighted MRI [20,21]. However, in the human fetus, only a small number of preliminary studies are previously published. The studies focus on different fetal organs such as the fetal brain [22–24], fetal lungs [25], and selected intraabdominal organs including the fetal liver [25–28]. These studies suggest, that the T2* value can be obtained from the selected fetal organs, but the correlation with placental function and fetal oxygenation remains unexplored. Thus, the aim of this study was to describe T2* weighted MRI in selected fetal organs in normal pregnancies and the correlation with placenta related outcomes such as BW, placental T2* and Doppler flow in fetal MCA.

2. Materials and methods

2.1. Subjects

A total of 126 singleton pregnancies were included in the cohort. Fetal MRI was performed at Aalborg University Hospital from February 2018 to November 2019. MRI was performed between 23 + 6 and 41 + 3weeks' gestation. The MRI was dedicated to fetal and placental research. All pregnancies were dated by ultrasound measurements of crownrump-length in the first trimester by Fetal Medicine Foundation certified sonographers [29,30]. Small for gestational age (SGA) was defines as BW below or equal to the 10th centile for expected gestational age (GA). Furthermore, the study population was divided in three BW groups defined according to the reference curve by Maršál et al. [31]. Normal BW = BW deviation between 10th centile and 90th centile, SGA1 = BW deviation between 10th centile and 2.3rd centile, and SGA2 = BW deviation <2.3rd centile. No BWs were above 90th centile. All participants gave written informed consent. The study was approved by the North Denmark Region Committee on Health Research Ethics (Journal number N-20170052). Data storage and handling were approved by a regional notification to the Danish Data Protection Agency (local reference-ID 2017-148) using Research Electronic Data Capture (REDCap) hosted at Aalborg University Hospital, North Denmark Region [32].

2.2. Ultrasound

Ultrasound examination was performed in a Voluson E10 ultrasound system (GE Healthcare, Kretz Ultrasound, Zipf. Austria). Ultrasound examination was performed at the time of MRI. Fetal weight was estimated by Hadlock's formula [33] and weight deviation was calculated using the reference curve by Maršál et al. [31] Doppler measurements of the blood flow in the Umbilical artery (UA) and the MCA was assessed and the deviation of the pulsatility index (PI) was estimated using the reference by Parra-Cordero et al. [34].

2.3. MRI

MRI was performed in a 1.5 T MRI system, OptimaTM MR450w (GE Healthcare, Milwaukee, WI, USA). The pregnant woman was placed in a left lateral tilt position to avoid compression of the inferior vena cava, and the total scan time did not exceed 30 min. An anterior array body coil was located over the maternal abdomen covering the entire uterus. Initially, a T2-weighted localizer scan was performed to obtain information about the anatomical orientation of placenta and the fetus. Five axial slices were placed covering the upper fetal abdomen and lower thorax and five coronal slices were placed in the central part of the fetus. The orientation of the slices is illustrated in Fig. 1. The T2* weighted MRI scan was performed using gradient recalled echo with the following protocol: TR = 71.2 ms; TE (16):3.0–67.5 ms; field of view 380 × 380 mm; flip-angle 30°; matrix 256 × 128 mm, slice thickness 5 mm, and slice gap 3 mm. Each slice was acquired in a single 12-s breath-hold.

2.4. MRI analysis

MRI data were processed using an in-house developed software; RoiTool 3.95 written in MATLAB (The MathWorks Inc, Natick, MA USA). Regions of interest (ROIs) covering the entire placenta and selected fetal organs were drawn manually by a single examiner (KB) as presented in Fig. 2. The T2* value was obtained by fitting the average signal within each ROI as a function of echo times using a monoexponentially decaying function with the equilibrium magnetization (M_0) and T2* as free parameters using a non-linear least-squares fitting algorithm [35]. For the spleen, which has a very short T2* relaxation time, a third free parameter was added to account for the signal not approaching zero but instead approaching the average noise value. In each fetal organ, the T2* value was reported as the mean of two slices, and the placental T2* value was reported as the mean of 3 slices. The process of ROI drawing and calculating the T2* value was blinded to all clinical data.

2.5. Statistical analysis

In normal BW pregnancies the correlation between fetal organ T2* values and GA at the time of MRI was investigated by simple linear regression. In the total cohort, the fetal organ T2* value was converted into Z-scores adjusted for GA at MRI using the T2* values of the normal BW pregnancies as a reference. The correlation between fetal organ Z-score and the three BW groups was demonstrated by boxplots and investigated by analysis of variance (ANOVA) for each organ. The correlations between fetal organ T2* Z-score and each of the following outcomes; placental T2* Z-score, BW Z-score and MCA pulsatility index Z-score at MRI and just before delivery were estimated by Pearson correlation analysis. A p–value <0.05 was considered statistically significant. Analyses were performed using Stata®16.0 (College Station, TX, USA).

3. Results

The median GA at the time of MRI was 34.2 week's gestation (range: 30.6–37.3) and the median time between MRI and delivery was 4.0 weeks (range: 1.4–7.7) (see Table 1).

In normal BW pregnancies (n = 58), the T2* value of each fetal organ showed a significant negative linear correlation with GA at the time of MRI (Table 2 and Fig. 3). The normal T2* value at 30 week's gestation



Fig. 1. Illustration of the orientation of the five axial (A) and five coronal (B) slices at the fetal MRI scan are demonstrated.



Fig. 2. T2* weighted magnetic resonance images of the selected fetal organs. The white lines indicate the Regions of interest (ROI) drawn manually according to the outline of each fetal organ.

and the decrease in T2* value per gestational week for each fetal organ are presented in Table 2.

Analysis of variance (ANOVA) demonstrated a significant correlation between BW groups and fetal organ T2* Z-score in the fetal heart (p < 0.001), fetal kidney (p = 0.001), lung (p = 0.03) and fetal spleen (p < 0.001) (Fig. 4).

In the total cohort (n = 126), a significant positive linear correlation was demonstrated between fetal organ T2* Z-scores and BW Z-score as well as placental T2* Z-score (Fig. 5). This correlation was strongest in the fetal heart, kidney, and spleen. In these three organs the T2* values showed a positive significant correlation with redistribution of fetal blood (MCA PI Z-score) at the last ultrasound before birth, but not at the time of MRI (Table 3).

4. Discussion

4.1. Principal findings

This study investigated the T2* value in selected fetal organs in normal pregnancies and those complicated by placental dysfunction. In the fetal lungs, heart, kidneys, and spleen the T2* Z-score was significant reduced n pregnancies complicated by placental dysfunction. Fetal organ T2* was correlated with outcomes related to fetal oxygenation including placental function, BW, and redistribution of blood flow. The T2* value of the fetal heart, kidneys, and spleen showed the most significant correlation with placental dysfunction. In these fetal organs, the T2* Z-score showed a significant correlation with redistribution of fetal blood as assessed by Doppler ultrasound at birth but not at the time of MRI. Thus, the fetal organ T2* value may be reduced prior to fetal

Table 1

Maternal and pregnancy characteristics of the study population.

Characteristics	Total study population (n = 126)	Normal BW pregnancies (n = 57)	SGA1 pregnancies (n = 38)	P-value	SGA2 pregnancies (n = 31)	P-value
Maternal age (years)	29.0 (26.0-34.0)	29.0 (25.4–30.8)	31.0 (27.0-34.4)	0.430	28.0 (24.0-33.0)	0.211
Maternal Body Mass Index (kg/m ²)	27.2 (24.1-30.8)	27.5 (25.4–30.8)	28.4 (24.0-30.8)	0.764	25.5 (23.4-30.0)	0.455
Nulliparous	65 (51.6)	31 (24.6)	15 (11.9)	0.112	19 (15.1)	0.0.538
Gestational Age at MRI (weeks)	34.1 (30.6–37.4)	35.1 (30.5-40.3)	33.6 (31.6–36.3)	< 0.001	33.0 (30.6–36.0)	< 0.001
Time from MRI to Birth (weeks)	4.0 (1.3–7.7)	4.0 (1.1-8.9)	4.3 (2.6–6.8)	0.388	2.9 (1.4–5.0)	0.031
Smoking	18 (14.3)	3 (2.4)	9 (7.1)	0.232	6 (4.8)	0.026
Diabetes	11 (8.7)	4 (3.2)	5 (4.0)	0.246	2 (1.6)	0.930
Preeclampsia	9 (7.1)	1 (0.8)	4 (3.2)	0.070	4 (3.2)	0.031
Cesarean section	27 (21.4)	7 (5.6)	7 (5.6)	0.456	13 (10.3)	0.001
Ultrasound at time of MRI						
Umbilical artery doppler PI ≥ 2 (z-	1 (0.8)	0 (0.0)	1 (0.8)	0.903	0 (0.0)	0.917
score) [1]						
Middle cerebral artery PI \leq -2 (z-	2 (1.6)	0 (0.0)	0 (0.0)	0.611	1 (1.6)	0.001
score) [1]						
Estimated fetal weight deviation	-22.9 (-27.018.7)	-20.1 (-22.817.0)	-23.7 (-26.419.0)	0.157	-28.4 (-33.321.0)	0.002
(%) [2]						
Last ultrasound before birth						
Time from last ultrasound to birth	1 (0.4–1.7)	1.3 (0.6–2.5)	0.8 (0-3-1.3)	0.005	0.7 (0.4–1.0)	0.006
(weeks)						
Umbilical artery doppler PI ≥ 2 (z-	4 (3.2)	0 (0.0)	0 (0.0)	0.419	4 (3.2)	0.255
score) [1]						
Middle cerebral artery PI \leq -2 (z-	8 (6.3)	2 (1.6)	0 (0.0)	0.955	6 (4.8)	0.026
score) [1]						
Estimated fetal weight deviation	-26.6 (-31.724.5)	-23.8 (-24.522.9)	-25.7 (-26.624.7)	0.064	-31.8 (-34.827.1)	0.008
(%) [2]						
Gestational Age at Birth (weeks +	39 + 4 (37+6-41.0)	40.9 (39+6-41 + 4)	38 + 6 (37+6-40.0)	< 0.001	37 + 1 (35+6-39 + 0)	< 0.001
days)						
Birthweight (g)	2860 (2460–3390)	3400 (3135–3720)	2700 (2560–2830)	< 0.001	2145 (1885–2440)	< 0.001
Birthweight deviation (z-score)	-1.3 (-1.60.6)	-0.4 (-1.0-0.1)	-1.6 (-1.71.4)	< 0.001	-2.3 (-2.81.9)	< 0.001

Data are presented as n (%) or median (interquartile range). †Relative to mean weight for gestation in normal pregnancy [2]. PI, pulsatility index, MRI, Magnetic resonance imaging. Comparison of normal BW pregnancies and respectively SGA1 and SGA2 pregnancies by students t-test.

Table 2 Normal BW pregnancies: The correlation between fetal organ T2* and gestational age.

Organ	Ν	R	P-value	Mean (±SD) decrease in T2* per week (ms/ week)	Mean (±SD) T2* at GA 30 + 0 (ms)
Brain	37	-0.871	< 0.001	-7.04 (±0.7)	170 (±16.4)
Lungs	58	-0.571	< 0.001	-2.02 (±0.4)	85 (±13.6)
Heart	57	-0.718	< 0.001	$-2.03 (\pm 0.3)$	56 (±9.3)
Liver	58	-0.414	< 0.001	-0.55 (±0.2)	31 (±5.7)
Kidneys	54	-0.871	< 0.001	-2.63 (±0.2)	65 (±7.2)
Spleen	52	-0.731	< 0.001	-1.48 (±0.2)	27 (±10.2)

For each fetal organ the linear correlation between fetal organ T2* value and gestational age at MRI is estimated by Pearson's correlations coefficient (R) and a corresponding p-value. In addition, the decrease in T2* per gestational week and the average fetal organ T2* at gestational week 30 are presented in the table. N refers to the number of normal BW pregnancies included for the analysis of the specific fetal organ.

circulatory changes identified by MCA Doppler. Our findings suggest that fetal organ $T2^*$ may be directly related to fetal oxygenation.

4.2. Results in the context of what is known

In normal BW pregnancies, we demonstrated a significant negative linear correlation between fetal organ T2* values and GA at the time of MRI for all investigated organs. This finding is in line with previous smaller studies of the fetal brain [22–24], the fetal liver [26], and placenta [15,36,37]. A recent pilot study failed to demonstrate such correlation [25], however, this finding may be related to the small study population of nine uncomplicated pregnancies. By the use of cordocentesis, Soothill et al. [38] have demonstrated a decrease in the oxygen content in the umbilical vein with increasing GA in normal pregnancies. Thus, there may be a reduction in the oxygenation of fetal organs with

increasing gestational age even in normal pregnancies, which could lead to the observed reduction in the T2* value. In addition, altered tissue morphology due to fetal organ maturation may also contribute to the decrease in the T2* value [39].

The absolute T2* value of the fetal brain is in line with the T2* values previously reported in the literature. At 30 week's gestation, the T2* value of the fetal brain is reported in the range of 150-250 msec [22-24]. Previous literature demonstrates a large variation in the T2* value in different areas of the fetal brain with the thalamic area having a markedly lower value than the white matter of the frontal and the occipital region [24]. Our MR images did not allow for a separation of different brain regions, but the white matter of the cerebral hemispheres did dominate the ROI in our analysis. This may explain why the $T2^*$ value of the fetal brain reported in our study, is in the lower range of the normal values previously published in the literature. The previous publications on the T2* value of the fetal liver report a normal value at 30 week's gestation to be 20–37 msec [25–28], which is very well in line with the fetal liver T2* value demonstrated in our study. The normal T2* values of the remaining fetal organs have only been sparsely reported in the previous literature. The T2* value of the fetal lung, kidney, and spleen was recently explored in a small pilot study of nine uncomplicated pregnancies [25], and the reported values are slightly lower than the values of this current study.

In the fetal lungs, heart, kidneys, and spleen, we found a significant correlation between the T2* Z-score and outcomes related to placental function including placental T2* Z-score and BW deviation. These findings suggest that fetal organ T2* may be related to fetal oxygenation. However, altered fetal tissue morphology due to chronic hypoxia may also contribute to the observed correlations. The correlation between placental dysfunction and fetal hypoxia has previously been demonstrated directly during pregnancy by cordocentesis [1] and immediately after delivery in elective cesarian section by blood samples from the umbilical artery and vein [40].

Among the investigated fetal organs, the fetal heart, kidneys, and



Fig. 3. Fetal organ T2* versus gestational age at MRI in the selected fetal organs. Normal BW pregnancies (BW over the 10th centile of the expected for GA) is marked with closed circles and SGA pregnancies (BW below or equal to 10th centile of the expected for GA) is marked with open squares. Linear regression (black line) with 95% prediction interval (grey lines) for normal BW pregnancies. Pearson correlation coefficients are given in Table 2.

spleen showed the strongest correlation with placental function. This may be explained by redistribution of fetal blood flow also known as "brain sparing". In pregnancies complicated by placental dysfunction, it is expected that the peripheral organs such as the fetal kidneys and spleen show a greater extent of hypoxia than the highly prioritized organs such as the fetal brain [41]. Accordingly, during hypoxia the reduction in the T2* value of the peripheral organs is expected to be more pronounced than in the fetal brain, as demonstrated by our data. Concerning the fetal heart, it is important to notice that the main content of the ROI is fetal blood within the fetal heart rather than the fetal myocardium. The high content of blood and deoxyhemoglobin in this ROI can explain the significant findings of this organ, even if the fetal heart is among the highly prioritized organs in fetal circulation. Unfortunately, it was not possible to discriminate between fetal blood and the myocardium in the current MR images.

4.3. Clinical implications

For the fetal heart, kidneys, and spleen we found a positive correlation between fetal organ T2* and the vascular resistance in fetal cerebral circulation (MCA PI) at the last ultrasound before birth but not at the time of MRI. Decreasing resistance of the fetal cerebral circulation is part of the redistribution of fetal blood flow in response to fetal hypoxia also known as brain sparing. Accordingly, decreasing MCA PI (brain sparing) is an indirect marker of fetal hypoxia [10,42]. Thereby, the correlation between MCA Doppler and fetal organ T2* supports the hypothesis, that fetal organ T2* is associated with fetal oxygenation. Surprisingly, we found a correlation between fetal organ T2* and MCA PI assessed at the last ultrasound before birth, but not at the time at MRI. This finding indicates that fetal organ T2* starts to deviate from normal prior to Doppler flow abnormalities.

According to our data, the T2* value of the fetal liver shows a very large variation in measurements even in the normal BW fetus. The liver is a large organ that is very easily outlined when drawing the ROI in the MR image. Thus, the variation in the T2* value of the fetal liver may predominantly rely on regional oxygenation differences rather than technical issues in the process of ROI drawing. The liver receives its vascular supply from two sources with very different oxygen content. The left liver lobe is supplied by the well oxygenated umbilical vein, whereas the right liver lobe is supplied by a mixture of umbilical vein blood and the less oxygenated portal vein [43]. Because of this dual blood supply, the oxygenation of the right liver lobe tends to be markedly lower than the left lobe. During hypoxia, this difference becomes even more pronounced due to ductus venosus shunting [44], as previously demonstrated by T2* weighted MRI in a sheep model [45]. In this current study, the orientation of the MRI images did not allow for proper discrimination between the two liver lobes. Therefore, the liver ROIs contained a varying mixture of both liver lobes explaining part of the



Fig. 4. Boxplots demonstrating T2* fetal Z-scores stratified in BW groups; Normal BW (BW: 10th – 90th centile), SGA1 (BW:10th - 2.3rd centile), and SGA2 (BW < 2.3rd centile). P-value indicates analysis of variance (ANOVA).

large variation in the T2* measurements in this organ.

4.4. Research implications

Our data demonstrated that the T2* value can be obtained from selected fetal organs and suggest that fetal organ T2* is related to fetal oxygenation due to placental dysfunction. In pregnancies complicated by placental dysfunction fetal organ T2* may be reduced prior to Doppler flow changes associated with redistribution of fetal blood flow. According to our data, fetal organs such as the heart, kidneys, and spleen showed the strongest correlation with placental dysfunction. However, the timely association between changes in fetal organ T2* and changes in Doppler flow measurements as well as the association between fetal T2* and major obstetric outcomes needs to be further elucidated.

4.5. Strengths and limitations

In this cohort of pregnancies, 54% had BW below the 10th centile but only a small proportion of pregnancies showed Doppler abnormalities and the majority of pregnancies were delivered at term. Thus, this cohort of pregnancies only moderate clinical manifestations of placental dysfunction a significant correlation we demonstrated a significant correlation between fetal organ $T2^*$ and placental function and fetal oxygenation. These findings underline the strong potential of $T2^*$ weighted fetal MRI in the identification of mild fetal hypoxia in vivo.

Due to fetal movements, the orientation of the MR images in the fetal organs did vary between subjects. Accordingly, we did not achieve the T2* value of all available fetal organs in the total cohort. The ROIs were not placed in exactly the same orientation in each of the fetal organs, which may have increased the variation in T2* measurements between individuals. Because of the exploratory nature of this study, we aimed to cover the entire fetus using two separate sets of five slices. In future studies, the MRI protocol should be dedicated to one or two target fetal organs. According to our findings focus should be on the fetal heart, kidney or spleen.

A strength of this study was the large number of pregnancies included. ROI drawing was performed by a single observer blinded to all clinical outcomes, and the majority of T2* values were calculated as an average of two slices from each organ, which improves the reproducibility of the T2* values [15]. The MRI scan time was less than 30 min. The ROI drawing and the calculation of average T2* values of the placenta and six fetal organs lasted less than 15 min per pregnancy. The fact that the method is fast to obtain and easy to analyze is highly important in a clinical perspective.



Fig. 5. The correlation between fetal organ T2* and placenta T2* in selected fetal organs. Linear regression (black line) with 95% prediction interval (grey lines).

Table 3

The correlation between fetal organ T2* and Middle cerebral artery Doppler flow, placental T2* and birth weight deviation.

Fetal organ (T2* z-score)	MCA Doppler at MRI (MCA PI z-score)		Last MCA Doppler before birth (MCA PI z-score)		Placenta T2* (T2* z-score)		BW deviation (BW z-score)	
	R	p-value	R	p-value	R	p-value	R	p-value
Heart	0.11	0.23	0.34	< 0.001	0.65	< 0.001	0.49	< 0.001
Kidney	0.17	0.08	0.45	< 0.001	0.66	< 0.001	0.46	< 0.001
Spleen	0.02	0.12	0.31	0.004	0.43	< 0.001	0.30	0.001
Brain	0.23	0.032	0.14	0.146	0.41	< 0.001	0.27	0.01
Liver	0.10	0.299	-0.07	0.541	-0.06	0.535	-0.04	0.65
Lung	0.29	0.002	0.16	0.122	0.45	< 0.001	0.28	0.002
Placenta	0.23	0.009	0.39	< 0.001	-	-	0.46	< 0.000

Middle cerebral artery (MCA). Pulsatility index (PI). Birth weight (BW). Pearson correlation coefficient (R).

5. Conclusion

This study provided reliable T2* values from selected fetal organs. Our data demonstrates, that the fetal organ T2* value is reduced in pregnancies complicated by placental dysfunction, suggesting that fetal organ T2* may be related to fetal oxygenation. This method has a great potential to expand our knowledge on fetal physiology in response to placental dysfunction.

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Disclosure

The authors report no conflicts of interest.

Clinical trial registration

North Denmark Region Committee on Health Research Ethics (Journal number N-20170052).

Danish Data Protection Agency (local reference-ID 2017-148).

Presentations

No.

Disclaimer

No.

Declaration of competing interest

We declare no conflict of interest.

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References

- P.W. Soothill, K.H. Nicolaides, S. Campbell, Prenatal asphyxia, hyperlacticaemia, hypoglycaemia, and erythroblastosis in growth retarded fetuses, Br. Med. J. 294 (6579) (1987) 1051–1053, https://doi.org/10.1136/bmj.294.6579.1051.
- [2] K. Nicolaides, C.H. Rodeck, P.W. Soothhill, S. Cambell, Ultrasound-guided sampling of umbilical cord and placental blood to asses fetal wellbeing, Lancet (1986) 1065–1067, https://doi.org/10.1016/s0140-6736(74)92550-1.
- [3] A.A. Baschat, R.M. Viscardi, B. Hussey-Gardner, N. Hashmi, C. Harman, Infant neurodevelopment following fetal growth restriction: relationship with antepartum surveillance parameters, Ultrasound Obstet. Gynecol. 33 (1) (2009) 44–50, https:// doi.org/10.1002/uog.6286.
- [4] I.M. Bernstein, J.D. Horbar, G.J. Badger, A. Ohlsson, A. Golan, Morbidity and mortality among very-low-birth-weight neonates with intrauterine growth restriction, Am. J. Obstet. Gynecol. 182 (2000) 198–206, https://doi.org/10.1016/ S0002-9378(00)70513-8.
- [5] C. Lees, N. Marlow, B. Arabin, et al., Perinatal morbidity and mortality in earlyonset fetal growth restriction: cohort outcomes of the trial of randomized umbilical and fetal flow in Europe (TRUFFLE), Ultrasound Obstet. Gynecol. 42 (4) (2013) 400–408, https://doi.org/10.1002/uog.13190.
- [6] D.A. Giussani, The fetal brain sparing response to hypoxia: physiological mechanisms, J. Physiol. 594 (5) (2016) 1215–1230, https://doi.org/10.1113/ JP271099.
- [7] M.Y. Zhu, N. Milligan, S. Keating, et al., The hemodynamics of late-onset intrauterine growth restriction by MRI, Am. J. Obstet. Gynecol. 214 (3) (2016) 367.e1-367.e17, https://doi.org/10.1016/j.ajog.2015.10.004.
- [8] J.W. Wladimiroff, Jagwyd Wijngaard, S. Degani, M.J. Noordam, J.V. Eyck, H. M. Tonge, Cerebral and umbilical arterial blood flow velocity waveforms in normal and growth-retarded pregnancies, Obstet. Gynecol. 69 (5) (1987) 705–709.
- [9] A.A. Baschat, Pathophysiology of fetal growth restriction: implications for diagnosis and surveillance, Obstet. Gynecol. Surv. 59 (8) (2004) 617–627, https:// doi.org/10.1097/01.OGX.0000133943.54530.76.
- [10] S. Vyas, K.H. Nicolaides, S. Bower, S. Campell, Middle cerebral artery flow velocity waveforms in fetal hypoxaemia, Eur. J. Obstet. Gynecol. Reprod. Biol. 75 (1997) 51–53.
- [11] A.A. Baschat, Planning management and delivery of the growth-restricted fetus, Best Pract. Res. Clin. Obstet. Gynaecol. 49 (2018) 53–65, https://doi.org/10.1016/ j.bpobgyn.2018.02.009.
- [12] M.D.G.B. Chavhan, M.D.P.S. Babyn, M.D.B. Thomas, M.D.M.M. Shroff, E. M. Haacke PhD, Principles, techniques, and applications of T2* based MR imaging and its special applications, Radiographics 29 (2009) 1433–1449.
- [13] I.L. Cameron, V.A. Ord, G.D. Fullerton, Characterization of proton NMR relaxation times in normal and pathological tissues by correlation with other tissue parameters, Magn. Reson. Imaging 2 (1984) 97–106, https://doi.org/10.1016/ 0730-725X(84)90063-8.
- [14] S.G. Kim, S. Ogawa, Biophysical and physiological origins of blood oxygenation level-dependent fMRI signals, J. Cerebr. Blood Flow Metabol. 32 (7) (2012) 1188–1206, https://doi.org/10.1038/jcbfm.2012.23.
- [15] M. Sinding, D.A. Peters, J.B. Frøkjær, et al., Placental magnetic resonance imaging T2* measurements in normal pregnancies and in those complicated by fetal growth restriction, Ultrasound Obstet. Gynecol. 47 (6) (2016) 748–754, https://doi.org/ 10.1002/uog.14917.
- [16] M. Sinding, D.A. Peters, J.B. Frøkjær, et al., Prediction of low birth weight: comparison of placental T2* estimated by MRI and uterine artery pulsatility index, Placenta 49 (2017) 48–54, https://doi.org/10.1016/j.placenta.2016.11.009.
- [17] A.E.P. Ho, J. Hutter, L.H. Jackson, et al., T2* placental magnetic resonance imaging in preterm preeclampsia: an observational cohort study, Hypertension 75 (6) (2020) 1523–1531, https://doi.org/10.1161/HYPERTENSIONAHA.120.14701.
- [18] M. Sinding, A. Sørensen, D.N. Hansen, D.A. Peters, J.B. Frøkjær, A.C. Petersen, T2* weighted placental MRI in relation to placental histology and birth weight, Placenta 114 (June) (2021) 52–55, https://doi.org/10.1016/j.
- placenta.2021.07.304.
 [19] A. Sørensen, J. Hutter, M. Seed, P.E. Grant, P. Gowland, T2* weighted placental MRI: basic research tool or an emerging clinical test of placental dysfunction? Ultrasound Obstet. Gynecol. (2019) https://doi.org/10.1002/uog.20855.
- [20] U. Wedegärtner, H. Kooijman, T. Andreas, N. Beindorff, K. Hecher, G. Adam, T2 and T2*measurements of fetal brain oxygenation during hypoxia with MRI at 3T: correlation with fetal arterial blood oxygen saturation, Eur. Radiol. 20 (1) (2010) 121–127, https://doi.org/10.1007/s00330-009-1513-4.
- [21] A. Sørensen, M. Pedersen, A. Tietze, L. Ottosen, L. Duus, N. Uldbjerg, BOLD MRI in sheep fetuses: a non-invasive method for measuring changes in tissue oxygenation, Ultrasound Obstet. Gynecol. 34 (6) (2009) 687–692, https://doi.org/10.1002/ uog.7322.

- [22] A.I. Blazejewska, S. Seshamani, S.K. McKown, et al., 3D in utero quantification of T2* relaxation times in human fetal brain tissues for age optimized structural and functional MRI, Magn. Reson. Med. 78 (3) (2017) 909–916, https://doi.org/ 10.1002/mrm.26471.
- [23] M.H. Lauridsen, N. Uldbjerg, T.B. Henriksen, et al., Cerebral oxygenation measurements by magnetic resonance imaging in fetuses with and without heart defects, Circ Cardiovasc Imaging 10 (11) (2017), e006459, https://doi.org/ 10.1161/CIRCIMAGING.117.006459.
- [24] S. Vasylechko, C. Malamateniou, R.G. Nunes, et al., T2* relaxometry of fetal brain at 1.5 Tesla using a motion tolerant method, Magn. Reson. Med. 73 (5) (2015) 1795–1802, https://doi.org/10.1002/mrm.25299.
- [25] S. Sethi, S.A. Giza, E. Goldberg, et al., Quantification of 1.5 T T1 and T2* relaxation times of fetal tissues in uncomplicated pregnancies, J. Magn. Reson. Imag. (2021) 1–9, https://doi.org/10.1002/jmri.27547.
- [26] D.M. Morris, J.A.S. Ross, A. McVicar, et al., Changes in foetal liver T2* measurements by MRI in response to maternal oxygen breathing: application to diagnosing foetal growth restriction, Physiol. Meas. 31 (9) (2010) 1137–1146, https://doi.org/10.1088/0967-3334/31/9/005.
- [27] O. Goitein, Y. Eshet, C. Hoffmann, et al., Fetal liver T2* values: defining a standardized scale, J. Magn. Reson. Imag. 38 (6) (2013) 1342–1345, https://doi. org/10.1002/jmri.24132.
- [28] S.I.K. Semple, F. Wallis, P. Haggarty, et al., The measurement of fetal liver T2* in utero before and after maternal oxygen breathing: progress towards a non-invasive measurement of fetal oxygenation and placental function, Magn. Reson. Imaging 19 (7) (2001) 921–928, https://doi.org/10.1016/S0730-725X(01)00421-0.
- [29] Ö. Kilavuz, K. Vetter, T. Kiserud, P. Vetter, The left portal vein is the watershed of the fetal venous system, J. Perinat. Med. 31 (2) (2003) 184–187, https://doi.org/ 10.1515/JPM.2003.025.
- [30] H. Robinson, J. Flemming, A critical evaluation of sonar "crown-rump length" measurements, Br. J. Obstet. Gynaecol. (82) (1975) 702–710.
- [31] K. Maršál, P.H. Persson, T. Larsen, H. Lilja, A. Selbing, B. Sultan, Intrauterine growth curves based on ultrasonically estimated foetal weights, Acta Paediatr. Int. J. Paediatr. 85 (7) (1996) 843–848, https://doi.org/10.1111/j.1651-2227.1996. tb14164.x.
- [32] P.A. Harris, R. Taylor, B.L. Minor, et al., The REDCap consortium: building an international community of software platform partners, J. Biomed. Inf. 95 (December 2018) (2019), 103208, https://doi.org/10.1016/j.jbi.2019.103208.
- [33] F.P. Hadlock, R.B. Harrist, R.S. Sharman, R.L. Deter, S.K. Park, Estimation of fetal weight with the use of head, body, and femur measurements-A prospective study, Am. J. Obstet. Gynecol. 151 (3) (1985) 333–337, https://doi.org/10.1016/0002-9378(85)90298-4.
- [34] M. Parra-Cordero, C. Lees, H. Missfelder-Lobos, P. Seed, C. Harris, Fetal arterial and venous Doppler pulsatility index and time averaged velocity ranges, Prenat. Diagn. 27 (13) (2007) 1251–1257, https://doi.org/10.1002/pd.1868.
- [35] D.W. Marquardt, An algorithm for least-squares estimation of nonlinear parameters, J. Soc. Ind. Appl. Math. 11 (No 2) (1968) 431–441. https://epubs. siam.org/doi/10.1137/0111030.
- [36] P.A. Gowland, A. Freeman, B. Issa, et al., In vivo relaxation time measurements in the human placenta using echo planar imaging at 0.5 T, Magn. Reson. Imaging 16 (3) (1998) 241–247, https://doi.org/10.1016/S0730-725X(97)00308-1.
- [37] C. Wright, D.M. Morris, P.N. Baker, et al., Magnetic resonance imaging relaxation time measurements of the placenta at 1.5 T, Placenta 32 (12) (2011) 1010–1015, https://doi.org/10.1016/j.placenta.2011.07.008.
- [38] P.W. Soothhill, K.H. Nicolaides, C. Rodeck, S. Campbell, Effect of gestational age on fetal and intervillous blood gas and acid-base values in human pregnancy, Fetal Ther. 1 (4) (1986) 168–175.
- [39] P. Gowland, Placental MRI, Semin. Fetal Neonatal Med. 10 (5) (2005) 485–490, https://doi.org/10.1016/j.siny.2005.05.001.
- [40] I. Cetin, B. Barberis, V. Brusati, et al., Lactate detection in the brain of growthrestricted fetuses with magnetic resonance spectroscopy, Am. J. Obstet. Gynecol. 205 (4) (2011) 350.e1–350.e7, https://doi.org/10.1016/j.ajog.2011.06.020.
- [41] T. Kiserud, G. Acharya, The fetal circulation, Prenat. Diagn. 24 (2004) 1049–1059, https://doi.org/10.1093/bjaceaccp/mki030.
- [42] A.A. Baschat, U. Gembruch, I. Reiss, L. Gortner, C.P. Weiner, C.R. Harman, Relationship between arterial and venous Doppler and perinatal outcome in fetal growth restriction, Ultrasound Obstet. Gynecol. 16 (5) (2000) 407–413, https:// doi.org/10.1046/j.1469-0705.2000.00284.x.
- [43] J. Kessler, S. Rasmussen, K. Godfrey, M. Hanson, T. Kiserud, Longitudinal study of umbilical and portal venous blood flow to the fetal liver: low pregnancy weight gain is associated with preferential supply to the fetal left liver lobe, Pediatr. Res. 63 (3) (2008) 315–320, https://doi.org/10.1203/PDR.0b013e318163a1de.
- [44] J. Kessler, S. Rasmussen, K. Godfrey, M. Hanson, T. Kiserud, Fetal growth restriction is associated with prioritization of umbilical blood flow to the left hepatic lobe at the expense of the right lobe, Pediatr. Res. 66 (1) (2009) 113–117, https://doi.org/10.1203/PDR.0b013e3181a29077.
- [45] A. Sørensen, D. Holm, M. Pedersen, et al., Left-right difference in fetal liver oxygenation during hypoxia estimated by BOLD MRI in a fetal sheep model, Ultrasound Obstet. Gynecol. 38 (6) (2011) 665–672, https://doi.org/10.1002/ uog.9044.