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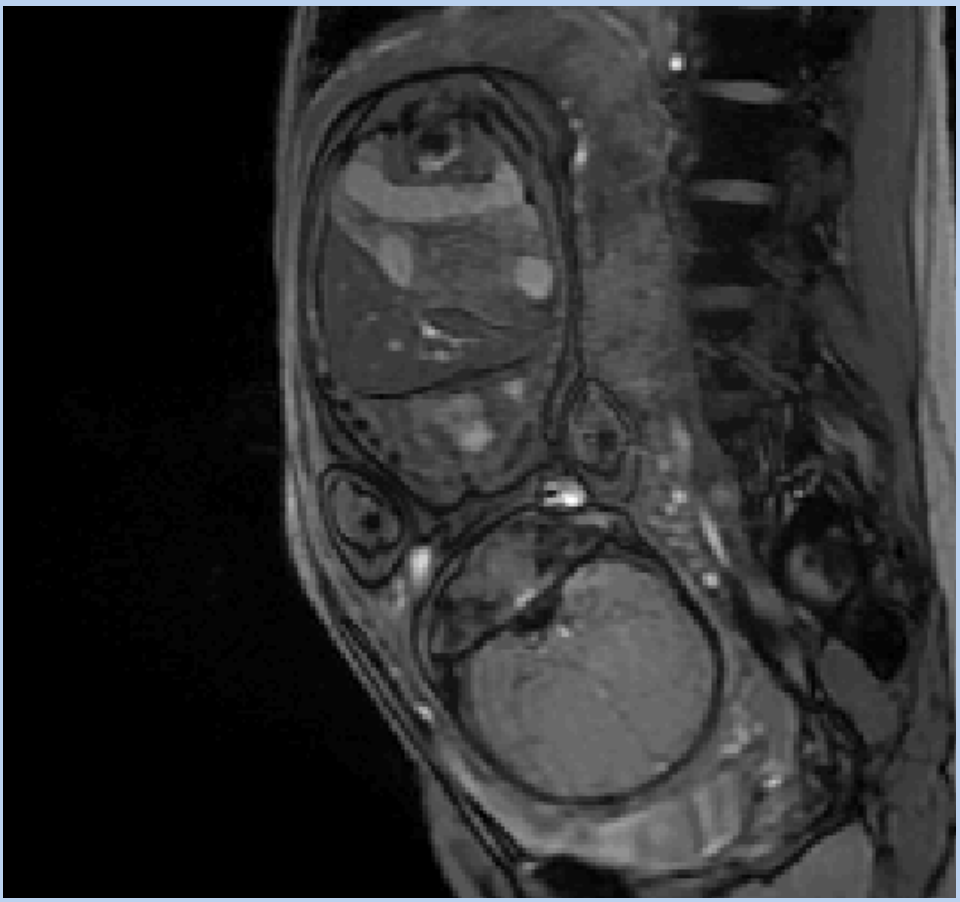

Assessment of T2* MRI in Selected Fetal Organs and the Association with Low Birth Weight

MASTER'S THESIS, 11TH SEMESTER

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MEDICINE | Aalborg University

Assessment of T2* MRI in Selected Fetal Organs and the Association with Low Birth Weight

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Dansk resumé

Baggrund:

Placentainsufficiens kan medføre utilstrækkelig ilttilførsel til fostret, hvilket kan føre til bl.a. vækstretardering inklusiv lav fødselsvægt, fosterhypoksi og irreversibel skade på fostrets organer. Fostret kan i sådanne tilfælde kompensere for iltmangel ved at redistribuere blodet, således hjernen, og andre essentielle organer, prioriteres; også kaldet *brain-sparing*. I dag findes der ikke en non-invasiv metode til vurdering af fostrets oxygenering. En non-invasiv metode til undersøgelse af fosterorganer kunne være magnetisk resonans (MR)-skanning med måling af den transverselle relaksationstid (T2*). T2* er en konstant, der afhænger af flere vævsparametre, herunder mængden af deoxyhæmoglobin og morfologi, hvorfor T2*-vægtet MR kan bruges til vurdering af vævsoxygenering. T2* værdien er velbeskrevet for moderkagen og tæt relateret til moderkagens funktion. T2* er ikke tidligere systematisk undersøgt i flere fosterorganer. Formålet med dette studie er således at undersøge T2* værdien i udvalgte fosterorganer og associationen mellem T2* i fosterorganer og lav fødselsvægt.

Metode:

Dette prospektive kohortestudie undersøgte T2*-vægtede MR-skanninger for 114 singleton graviditeter i gestationsalder 23+6 til 41+3. MR-skanningerne blev foretaget fra februar 2018 til november 2019 i et 1,5 Tesla MRI-system, Optima™ MR450w (GE Healthcare, Milwaukee, WI, USA). For at undgå kompression af vena cava blev kvinderne under skanningen placeret på ryggen med aflastende skråkile under højre side. De T2*-vægtede MR-skanninger blev foretaget både aksialt og koronalt på fostret. Efterfølgende blev der indtegnet en til to *regions of interest* (ROIs) for hvert foster organ og udregnet en gennemsnitsværdi af T2* værdien for de to ROIs fra hvert fosterorgan i de tilfælde, hvor det var muligt at tegne to ROIs. Lav fødselsvægt blev defineret som -22,0% eller mindre ud fra Maršáls vægtkurve. Data blev indtastet i Research Electronic Data Capture REDCap. Statistisk analyse blev foretaget i Stata®16.0 (College Station, TX, USA). Associationen mellem T2* værdien for hvert fosterorgan og gestationsalder ved MR-skanning for normalvægtige fostre blev undersøgt ved lineær regression og Pearsons korrelations koefficienter. Sammenhængen mellem T2* værdi og lav fødselsvægt blev undersøgt ved logistisk regression. *P*-værdi <0,05 blev anset som signifikant. Studiet er godkendt af Den Videnskabsetiske Komite for

Region Nordjylland, projektnummer N-20170052. Databehandling er godkendt af Datatilsynet, lokalreference-ID 2017-148.

Resultater:

Ud af 114 graviditeter havde 26,3% (n=30) lav fødselsvægt. I graviditeter med normal fødselsvægt var der negativ lineær korrelation mellem T2* værdi og gestationsalder ved MR-skanning, denne var dog kun signifikant for fosterhjerne (R^2=0,69, *P*<0,001), fosterhjerte (R^2=0,47, *P*<0.001), fosternyrer (R^2=0,67, *P*<0,001) og fostermilt (R^2=0,45, *P*<0,001), men ikke signifikant for fosterlunger (R^2=0,14, *P*=0,198) eller fosterlever (R^2=0,14, *P*=0,222). For fostre med lav fødselsvægt var T2* værdien lavere i alle undersøgte organer, dog kun signifikant i fosterhjerte (middel z-score =-3,23, *P*=0,001), fosternyrer (middel z-score =-2,84, *P*=0,005) og fostermilt (middel z-score =-2,60, *P*=0,009). Sammenhængen mellem T2* værdien og lav fødselsvægt var ikke signifikant for fosterhjerne (middel z-score =-0,62, *P*=0,538), fosterlunger (middel z-score =-1,94, *P*=0,053) eller fosterlever (middel z-score =-0,38, *P*=0,706).

Konklusion:

Ud fra vores viden er dette studie det første til at undersøge flere fosterorganer med T2*-vægtet MR. Dette studie viser en sammenhæng mellem T2* værdi i udvalgte fosterorganer og lav fødselsvægt, hvilket understøtter hypotesen om, at T2* værdien er relateret til vævsoxygenering, hvorfor denne metode potentielt kan bidrage med værdifuld non-invasiv viden om fosterfysiologi og hypoksi samt vurdering af barnets ilttilbud.

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Article manuscript

Assessment of T2* MRI in Selected Fetal Organs and the Association with Low Birth Weight

A Prospective Cohort Study

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Keywords: Transverse Relaxation; T2*; Magnetic Resonance imaging; MRI; Fetal Hypoxia; Fetal Growth Restriction

ABSTRACT

Objective: The transversal relaxation time (T2*) is related to tissue oxygenation and morphology. It is well described in relation to in vivo oxygenation in the placenta, but this method is yet unexplored in fetal organs. The objective of this study was to investigate the T2* value of selected fetal organs and the association with low birth weight (BW).

Methods: This prospective cohort study included 114 singleton pregnancies with Magnetic Resonance Imaging (MRI) performed between gestational week 23+6 and 41+3. T2* value was obtained from the fetal brain, lungs, heart, liver, kidneys, and spleen. The correlation between T2* value and gestational age (GA) at MRI was estimated by linear regression analysis and Pearson's correlation coefficients. The association between low BW (BW ≤-22.0%) and T2* value of selected fetal organs was investigated by logistic regression adjusted for GA at MRI.

Results: Out of 114 pregnancies 26.3% (n=30) had low BW. In normal BW pregnancies the T2* value in fetal organs showed a negative linear correlation with GA at MRI. This was significant for fetal brain (R^2=0.69, *P*<0.001), fetal heart (R^2=0.47, *P*<0.001), fetal kidneys (R^2=0.67, *P*<0.001) and fetal spleen (R^2=0.45, *P*<0.001), while statistical insignificant for fetal lungs (R^2=0.14, *P*=0.198) and fetal liver (R^2=0.14, *P*=0.222). Logistic regression demonstrated a significantly lower T2* value among fetuses with low BW. This association was significant for fetal heart (mean z-score =-3.23, *P*=0.001), fetal kidneys (mean z-score =-2.84, *P*=0.005) and fetal spleen (mean z-score =-2.60, *P*=0.009). However, insignificant in the fetal brain (mean z-score =-0.62, *P*=0.538), fetal lungs (mean z-score =-1.94, *P*=0.053) and fetal liver (mean z-score =-0.38, *P*=0.706).

Conclusion: Low T2* values of selected fetal organs in low BW pregnancies may be a result of tissue hypoxia and morphological changes related to placental insufficiency and supported by the T2* value being related to tissue oxygenation. In conclusion, this method can potentially contribute to non-invasive knowledge of fetal physiology during hypoxia and assessment of oxygenation within the fetus.

INTRODUCTION

Placental insufficiency may lead to inadequate oxygen supply to the fetus, which may lead to fetal growth restriction (FGR) and have fatal consequences for the developing fetus including brain damage and intrauterine fetal death[1–5]. The fetus has adaptive regulatory responses to fetal hypoxia, including redistribution of fetal blood prioritizing myocardium, adrenal glands, and brain, also known as 'brain sparing'[4,6–8].

Current in vivo knowledge regarding fetal hypoxia due to placental dysfunction is obtained by invasive methods, such as cordocentesis. By this invasive method, it is well established that FGR fetuses have chronic hypoxica[1]. However, cordocentesis is associated with a risk of fetal loss[9], therefore in the routine antenatal care, methods without risk such as ultrasound Doppler measurements of fetal weight based on fetal biometrics and blood flow in fetal and umbilical vessels are used as indirect estimates of fetal wellbeing[4]. Neither cordocentesis or ultrasound Doppler measurements provide direct information about tissue oxygenation in individual fetal organs, hence

a non-invasive method to assess fetal oxygenation could expand our knowledge regarding fetal physiology during placental dysfunction.

Over the last decade, functional Magnetic Resonance Imaging (MRI) has provided non-invasive estimates of tissue oxygenation in vivo. The transversal relaxation time (T2*) is sensitive to magnetic field inhomogeneities as created by the presence of deoxyhemoglobin thereby relating T2* value to tissue oxygenation[10,11]. Magnetic field inhomogeneities may also be related to tissue morphology including macromolecular surface area, water content and lipid content[11]. Each tissue has a specific T2* value and tissue pathology may be identified by altered T2* value[11].

In fetal medicine, it is well established that a low placental T2* value is associated with placental dysfunction and low birth weight (BW)[12–15]. However, the T2* value of the fetal organs remains unexplored. Therefore, the aim of this study is to investigate the T2* value of selected fetal organs and the association with low BW.

METHODS

Subjects

This prospective cohort study included 114 singleton pregnancies. Inclusions underwent placental and fetal MRI in the period from February 2018 to November 2019 at Aalborg University Hospital Denmark. Low BW was defined as BW $\leq$-22.0%, according to the reference curve by Maršál et al.[16]. All pregnancies were dated by ultrasound measurements of crown-rump-length in the first trimester by Fetal Medicine Foundation certified sonographers.

MRI

MRI was performed using a 1.5 Tesla MRI system, Optima™ MR450w (GE Healthcare, Milwaukee, WI, USA). During the MRI scan, the woman was in a left lateral tilt position to avoid compression of the inferior vena cava, and with an anterior array body coil located over the maternal abdomen covering the entire uterus. Initially, a T2-weighted localizer scan was performed to obtain information about the anatomic orientation of the fetus. T2* weighted coronal and axial sequences were performed using gradient recalled echo with repetition time 71.2 ms; 16 echoes from 3.0 to 67.5 ms in steps of 4.3 ms; field of view 380x380 mm; flip-angle 30°; and matrix 256 x 128 mm. Five slices with a gap of 3 mm and a thickness of 5 mm were obtained both in the axial and coronal plane

of the fetus. Each slice was acquired in a single 12-second breath-hold. The scan time did not exceed 30 minutes.

MRI analysis

MRI data were processed using an in-house developed software; RoiTool 3.95 written in MATLAB (The MathWorks Inc, Natick, MA USA). The T2* value of the fetal spleen was very short, so a noise term in the T2* fit was included. Regions of interest (ROIs) covering the entire fetal organs were drawn manually by a single examiner (KB). If the organ was present on two different slices, the T2* value was calculated as an average of T2* value on these two slices. The T2* values of each fetal organ were calculated by a fitting model, using a non-linear least-square fitting algorithm[17]. Figure 1 illustrates a T2* weighted MRI with ROIs of each of the fetal organs of interest. The process of drawing and examining the T2* value was blinded to all clinical data. Data was stored using Research Electronic Data Capture "REDCap" hosted at Aalborg University Hospital, North Denmark Region[18].

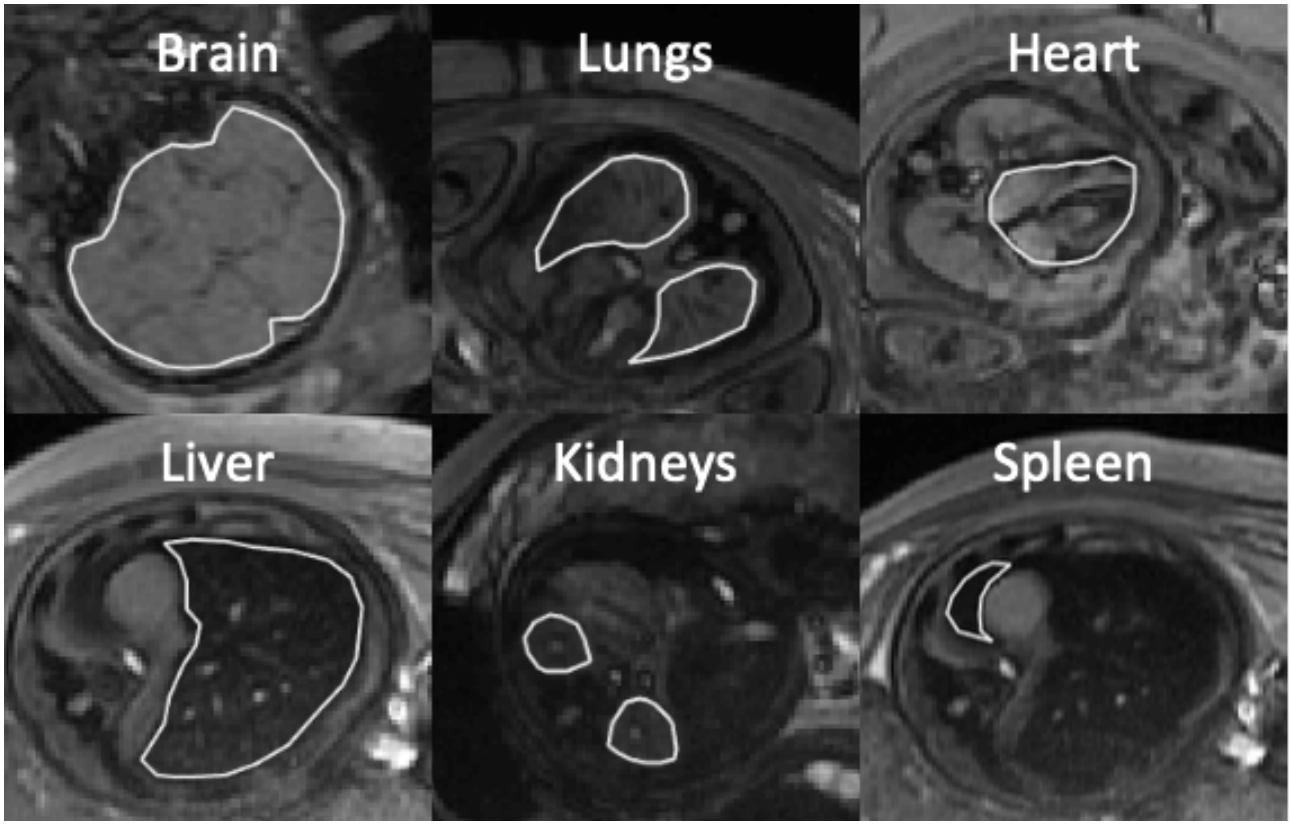

***Figure 1**. T2* weighted magnetic resonance images of fetal organs. Regions of interest for the fetal brain (coronal plane), lungs (axial plane), heart (axial plane), liver (axial plane), kidneys (axial plane) and spleen (axial plane) are marked with white lines.*

Statistical analysis

Analyses were performed using Stata®16.0 (College Station, TX, USA). In pregnancies with normal BW, the correlation between gestational age (GA) at MRI and T2* value of each fetal organ was estimated using linear regression analysis and Pearson's correlations coefficients. The association between T2* value and low BW was estimated by logistic regression adjusted for GA at MRI. A *P*-value <0.05 was considered statistically significant.

Ethical approval:

All participating women gave written informed consent. This 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).

RESULTS

Of the 114 singleton pregnancies, 26.3% (n=30) neonates were born with low BW. Maternal and pregnancy characteristics in the study population are summarized in Table 1.

In pregnancies with a normal BW, the T2* value of fetal organs showed a negative linear correlation with GA at MRI. The correlation was significant for the fetal brain (R^2=069, *P*<0.001), fetal heart (R^2=0.47, *P*<0.001), fetal kidneys (R^2=0.67, *P*<0.001) and fetal spleen (R^2=0.45, *P*<0.001), but not significant for the fetal lungs (R^2=0.14, *P*=0.198) and fetal liver (R^2=0.14, *P*=0.222). The correlation between the T2* value and GA at MRI for each fetal organ including Pearson R and P-values are shown in Figure 2 and Table 2.

Table 1. Maternal and pregnancy characteristics of the study population

Characteristics	Normal Birth weight (n=84)	Low Birth weight (n=30)
Maternal Age (years)	29.0 (27.0-34.0)	28.0 (24.0-33.0)
Maternal Body Mass Index (kg/m^2)	28.3 (24.8-30.9)	25.5 (23.4-30.0)
Nulliparous	42 (50.0%)	15 (50.0%)
Gestational Age at MRI (weeks)	34.3 (30.5-37.9)	33.0 (30.6-36.0)
Gestational Age at Birth (weeks)	30.0 (38.6-41.0)	37.1 (35.6-39.0)
Time from MRI to Birth (weeks)	4.2 (1.4-8.3)	2.9 (1.4-5.0)
Smoking	20 (17.9%)	45 (40%)
Diabetes	15 (13.1%)	6 (5%)
Preeclampsia	4 (3.6%)	14 (10%)
Birth weight (g)	2020 (2700 - 3440)	2145 (1885 - 2440)
Birth weight deviation (%) (ref. Maršál)	-14.3 (-19.7 - -3.2)	-28.6 (-35.2 - -23.6)

Data are presented as n (%) or median (interquartile range).

Table 2. Linear correlation between T2* values and gestational age at MRI for each organ of interest for fetuses with normal birth weight.

Organ	R^2	*P*-value
Brain	0.69	<0.001
Lungs	0.14	0.198
Heart	0.47	<0.001
Liver	0.14	0.222
Kidneys	0.67	<0.001
Spleen	0.45	<0.001

Table 3. The difference in fetal organ T2* value between normal birth weight and low birth weight fetuses investigated by logistic regression adjusted for gestational age at MRI.

Organ	Mean z-score	*P*-value
Brain	-0.62	0.538
Lungs	-1.94	0.053
Heart	-3.23	0.001
Liver	-0.38	0.706
Kidneys	-2.84	0.005
Spleen	-2.60	0.009

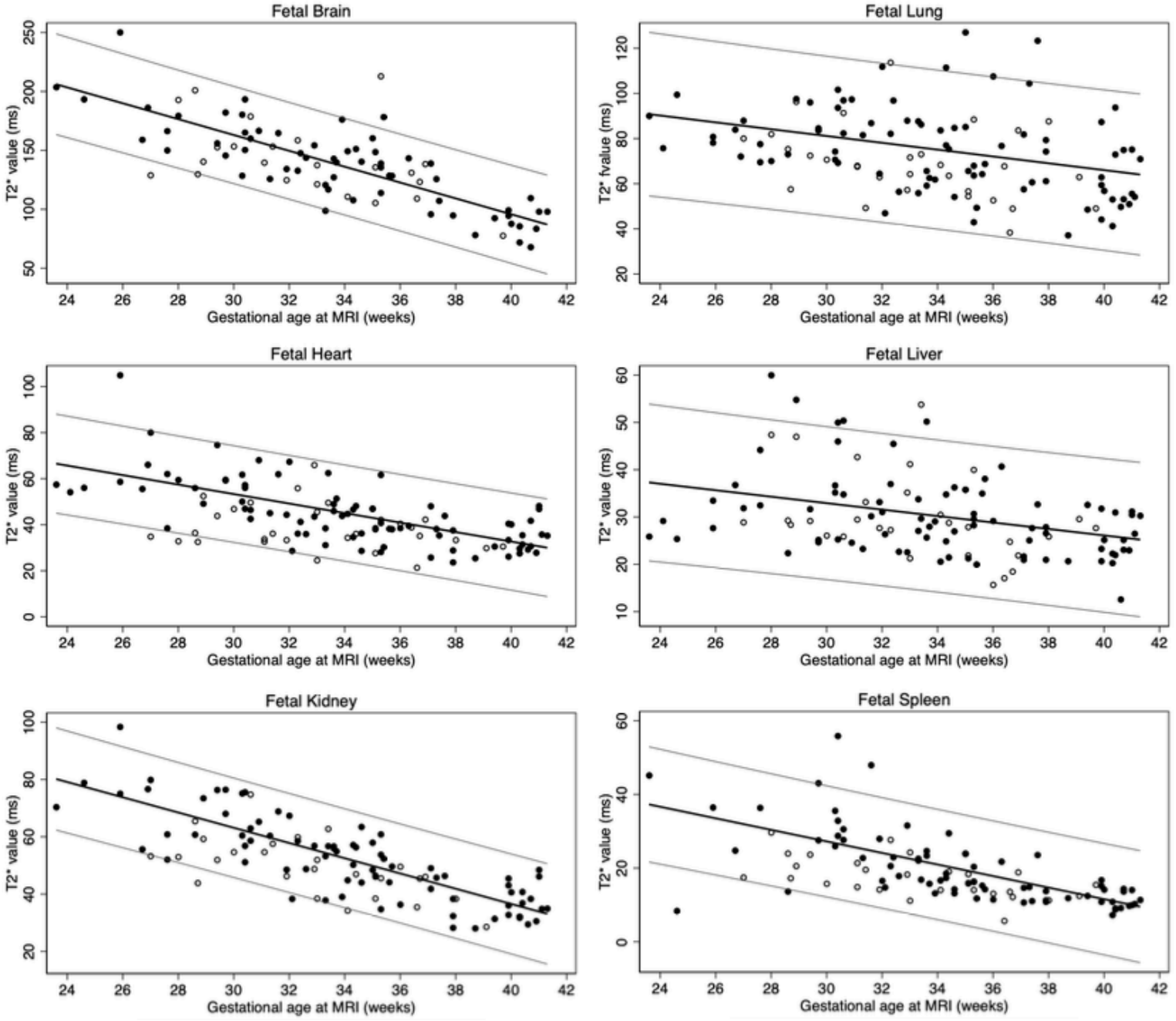

***Figure 2**. Association between T2* values in the fetal brain, lungs, heart, liver, kidneys, and spleen and gestational age at MRI. Linear regression (black line) with 95% confidence interval (grey lines) for fetuses with normal birth weight. Normal birth weight (>-22.0%) is marked with closed circles and low birth weight (≤-22.0) is marked with open circles.*

The T2* value was lower in fetuses with low BW. This was significant for fetal heart (mean z-score =-3.23, *P*=0.001), fetal kidneys (mean z-score =-2.84, *P*=0.005) and fetal spleen (mean z-score =-2.60, *P*=0.009), but not for fetal brain (mean z-score =-0.62, *P*=0.538), fetal lungs (mean z-score =-1.94, *P*=0.053) or fetal liver (mean z-score =-0.38, *P*=0.706). Results of logistic regression including mean z-score and *P*-values are displayed in Table 3.

DISCUSSION

This study demonstrated a negative linear correlation in fetuses with normal BW between GA at MRI and T2* value in fetal organs. Additionally, the T2* value of fetal heart, kidneys, and spleen was significantly lower in neonates with low BW compared to normal-weighted neonates.

The Correlation Between T2* Value Gestational Age

To the best of our knowledge, this is the first study to describe the T2* value of multiple fetal organs in vivo. However, a few studies have investigated the T2* value in the fetal brain and liver and the correlation to GA at MRI[19–21]. Consistent with our study, Blazejewska et al.[20] and Lauridsen et al.[21] revealed a decline in T2* value of the fetal brain at increasing GA. The decrease in T2* values over GA is also in accordance with the decrease in placental T2* value over GA as previously reported[12,22,23]. Morris et al[19] found a significant negative linear correlation between T2* in the fetal liver and GA. Accordingly, we demonstrated a negative linear correlation, however, not significant. This may be a consequence of the rather complex blood supply of the liver. The fetal liver has two vascular sources that distribute oxygen unevenly to the two liver lobes[24,25]. Thus, the left side receives well-oxygenated blood from the umbilical vein and the right side receives blood from the less-well oxygenated portal vein[26]. They drew ROIs only in the right liver lobe, and wherefore the dual blood supply of the fetal liver did not interfere with their results. We did not differentiate between the left and the right side of the liver in this current study, as the orientation of the images did not allow us to evaluate both lobes in all fetuses.

The T2* value is influenced by magnetic field inhomogeneities of which tissue morphology and the presence of deoxyhemoglobin have a great impact[10,11]. Accordingly, the decrease in the T2* value of fetal organs at advancing GA can be due to morphological maturation[22,23] and reduced fetal oxygenation[22,27]. The extent of which maturation influences tissue morphology and thereby T2* values in fetal organs is yet to be explored. By the use of cordocentesis, Soothill et al.[27] demonstrated a decrease in oxygen content in both the umbilical vein and the umbilical artery with increasing GA. Thus, oxygen could be the substantial factor influencing the decrease in T2* values of fetal organs with advancing pregnancy in normal weighted pregnancies.

The Association Between T2* Value and Low Birth Weight

The lower T2* value in low BW fetuses compared to normal BW fetuses may reflect important physiological differences, like those described in fetal hypoxia. In previous publications, cordocentesis has demonstrated that FGR is associated with fetal hypoxia[28]. During hypoxia the presence of deoxyhemoglobin reduces the T2* value, and thereby the lower T2* value in the low BW group may reflect hypoxia in fetal organs. Furthermore, chronic hypoxia is associated with morphological changes in the fetal heart such as increased apoptosis in cardiac cells[5,29]. These changes may also influence the T2* value.

Among the fetal organs included in this study, the T2* value of the fetal heart was reduced to the greatest extent in the low BW fetuses compared to the other organs of interest. The large blood volume in this organ may explain this finding, as the amount of deoxyhemoglobin influences the T2* value[10,11]. Due to a large blood volume, this explanation may also be applied to the fetal spleen. Still, the difference in fetal spleen T2* for the two BW groups could be explained by the physiological changes of brain-sparing. The fetal kidney also shows a significant difference in T2* value between the normal and low BW fetuses. The prominent difference in the kidney is probably less due to a lower blood volume, and more due to the physiological changes of brain-sparing.

The fetal circulation is complex and in case of hypoxia brain-sparing is present, in which the fetus redistributes blood from e.g. kidneys and spleen prioritizing essential organs as the fetal brain[4,6,8]. Accordingly, in case of brain-sparing MRI would be expected to depict a decrease in T2* value in the fetal lungs, liver, kidneys, and spleen, but not in the fetal brain nor heart.

Consistent with the physiology of brain-sparing[4,6,8], we found no significant difference in T2* value of the fetal brain between fetuses with low BW when compared to normal weighted fetuses. However, the amount of blood relative to tissue can influence the T2* value since the T2* values mainly reflect inhomogeneities in the blood. Therefore, the findings of the fetal brain may be explained by both brain-sparing and blood volume relative to tissue volume.

In contrast with expected findings according to brain-sparing physiology, the fetal heart represents the most optimal organ in this study when operating with T2* MRI to differentiate fetuses with low BW from fetuses with normal BW. During brain-sparing, the fetal heart receives an increased amount of umbilical vein blood due to regulation of blood flow in ductus venosus, and thus, blood flow and blood oxygen concentration are not expected to decrease in the fetal heart to

the same extent as other fetal organs. Instead, the significantly lower fetal heart T2* value in fetuses with low BW may be a result of universal hypoxia. Furthermore, the substantial amount of blood relative to tissue in the heart, and thereby a greater amount of deoxyhemoglobin makes the heart an organ of interest in T2* MRI evaluation of fetal organs. According to the physiology of brain-sparing, a difference in fetal liver T2* values between low BW fetuses and normal BW fetuses was expected. However, this was not demonstrated in this study. In some cases, we identified a visual difference between the two liver lobes, while examining MRIs of the liver. Both may be a consequence of the complex dual-blood supply of the liver.

Our results depend on identifying and ROI drawing of the organ. All organs were easily identified, and the drawing of the fetal heart, liver, kidneys, and spleen is facilitated by clear organ contours. In some cases, the sulci of the brain and the hilum of lung complicated the process of identifying the border of the brain and lungs respectively. The difficulties in discrimination between the lung tissue and blood vessels at the pulmonary hilum may explain the variation in T2* values for the fetal lung. Thus, may accounting for the tendency to decreased T2* value at advancing GA and the association between T2* value and low BW was not significant.

Strengths and Limitations

The use of low BW as a proxy for placental insufficiency has limitations. Fetal growth and BW are influenced by various genetic and environmental factors and not placental insufficiency alone[30]. Therefore, to apply BW as an estimate of placental insufficiency exclusively is complicated by the fact that not all neonates suffering from placental insufficiency have low BW and in reverse that not all neonates with low BW suffer from placental insufficiency[13]. This limitation may be reduced by using abnormal placental histology as an outcome rather than low BW[31]. Further studies could include a comparison of T2* value in fetal organs and currently used methods to assess fetal well-being such as ultrasound Doppler flow.

In our population, 26.3% had low BW in contrast with 3.3% in the average population[32,33]. Consequently, this study population consists of substantially smaller neonates than the average population[32,33], and the difference in T2* value between the low BW group and the normal BW group is reduced accordingly. Nevertheless, we found a significant difference in T2* values between the two groups for several of the fetal organs, which supports the strength of this method.

This study has several strengths. A single observer blinded to all clinical outcomes drew ROIs, thus limiting bias in the measurement of T2* values. Moreover, the majority of T2* values were calculated as an average of two slices from each organ, which improves the reproducibility of the T2* values. Another strength of this study was limited artifacts on MRIs, so no pregnancies were excluded due to artifacts. Ultimately, the MRI analyses of each subject lasted maximum of 15 minutes. Thus, this is an accessible and time-efficient method, which may have potential as a diagnostic tool in clinical practice.

Conclusion and Clinical Implications

The T2* value of fetal organs decreases with advancing pregnancy and the T2* value of the fetal organs was reduced among fetuses with low BW. T2* weighted MRI of fetal organs provides new insight in fetal physiology in vivo, and important differences between normal BW and low BW fetuses are revealed, which may be related to differences in fetal tissue oxygenation. A clinical perspective of this study could be to identify fetal hypoxia caused by placental insufficiency among fetuses that are small for GA. Thereby; this method could be a tool to differentiate between constitutionally small fetuses and small fetuses suffering from placental insufficiency. However, this method needs further investigation.

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