Association of placental T2 relaxation times and uterine artery Doppler ultrasound measures of placental blood flow

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ABSTRACT

Purpose: To investigate whether, in the second trimester of pregnancy, placental T2 relaxation time (determined using magnetic resonance imaging (MRI)) is related to impedance to flow in the uterine arteries.

Methods: In 40 singleton pregnancies at 24–29 weeks’ gestation, uterine artery pulsatility index (PI) was measured by Doppler ultrasound and T2 relaxation time was measured by echo planar MRI at 1.5 T. The significance of the associations between T2 relaxation time, uterine artery PI and birth weight were examined.

Results: In 25 pregnancies that delivered small for gestational age (SGA) neonates with birth weight below the 10th percentile, compared to those with appropriate for gestational age (AGA) birth weight, the T2 relaxation time was significantly decreased (88 ms vs. 149 ms, p < 0.0001) and uterine artery PI increased (1.96 vs. 1.00, p < 0.0001). There were significant associations between placental T2 relaxation time and log10 uterine artery PI (r = −0.749, p < 0.0001), and between T2 relaxation and birth weight percentile (r = 0.693, p < 0.0001).

Conclusion: The T2 relaxation time during the second trimester is shorter in pregnancies that subsequently deliver SGA neonates and the measurement is strongly correlated with impedance to flow in the uterine arteries.

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1. Introduction

During pregnancy, non-invasive assessment of placental perfusion can be achieved by the use of Doppler ultrasound to measure uterine artery pulsatility index (PI) [1]. PI is one type of Doppler index measures, which is used to describe the shape of the flow waveform in a blood vessel. It is a measure of the variability of blood velocity in a vessel, equal to the difference between the peak systolic and minimum diastolic velocities divided by the mean velocity during the cardiac cycle [2]. Increased uterine artery PI reflects increased impedance to blood flow in the uterine arteries and it is associated with an increased risk of subsequent development of preeclampsia and/or delivery of small for gestational age (SGA) neonates [1]. The increased PI is thought to reflect the failure of the trophoblastic invasion of the spiral arteries and their conversion into low-resistance vessels, with consequent impairment in uteroplacental perfusion [1].

Assessment of placental structure can be provided by a combination of structural magnetic resonance imaging (MRI) and measurement of relaxation times [3]. Fetal MRI is considered to be safe [4–7] and ultrafast MRI sequences, such as echo-planar imaging, are almost completely insensitive to the artefacts caused by fetal motion and therefore avoid the need for sedation [8,9]. To date only one MRI study has examined placental transverse relaxation time (T2); it did so in 50 singleton pregnancies at 20–42 weeks’ gestation and reported that the values were significantly reduced in 14 pregnancies complicated by SGA fetuses and/or preeclampsia [3]. The reduced relaxation time was attributed to the pathological changes of placental necrosis and fibrosis which are commonly observed in these pregnancy complications.

1 These authors contributed equally to the preparation of this manuscript.
The aim of the current study was to extend the previous work by investigating whether placental T2 relaxation is related to uterine artery PI during the second trimester of pregnancy and whether alterations in T2 relaxation times precede the clinical onset of preeclampsia and SGA.

2. Methods

This study was a pilot study carried out at the Harris Birthright Research Centre (HBRC) at King's College Hospital, London, on 43 singleton pregnancies attending for routine and/or specialised antenatal care between February 2006 and May 2008. It was approved by the local NHS Research Committee. In our unit, all women are routinely offered their anomaly ultrasound scan at 22–24 weeks' gestation to detect any fetal abnormalities and to assess fetal growth. The fetal weight is estimated from the measurements of head circumference, abdominal circumference and femur length.

In addition, we routinely assess uterine artery blood flow by transvaginal sonography to assess the women's risk of developing preeclampsia and/or an SGA fetus. In the third group, the estimated fetal weight was below the 95th percentile of the reference range (Normal group; n = 23). These fetuses were known SGA at the time of the MRI, with most (n = 17) having abnormal fetal Dopplers.

All the pregnancies had been dated by a first trimester ultrasound. Consecutive women attending for the scan at 22–24 weeks and those referred to our unit with a known SGA fetus or a minor congenital abnormality were invited to participate in this research study by a single research fellow (ID). The study involved the use of MRI to calculate the T2 relaxation times of the placenta. Other MRI measurements were made during this study but are not reported here. All the women required serial ultrasound scans for fetal wellbeing. Women who agreed to take part gave written informed consent. All the women had an ultrasound scan (performed by ID) on the same day as the MRI to firstly, measure fetal growth and amniotic fluid volume; and secondly, to assess fetal oxygenation by Doppler measurements of impedance to flow in the maternal uterine arteries, umbilical arteries and fetal cerebral vessels and ductus venosus.

Data on pregnancy outcome were obtained from the maternity computerised record, the estimated fetal weight, and the sex of the baby. The GROW centile calculator v5.15_UK [12] was used for this. All the women required serial ultrasound scans for fetal wellbeing. Women who agreed to take part gave written informed consent. All the women had a scan (performed by ID) on the same day as the MRI to firstly, measure fetal growth and amniotic fluid volume; and secondly, to assess fetal oxygenation by Doppler measurements of impedance to flow in the maternal uterine arteries, umbilical arteries and fetal cerebral vessels and ductus venosus.

The study population

Three groups of patients were selected. In the first group, the estimated fetal weight was above the 10th percentile of the reference range and the mean of the general medical practitioners of the women. The outcome measures were preeclampsia, as defined by the International Society for the Study of Hypertension in Pregnancy [13], and SGA, defined as the birth weight being below the 10th percentile for gestational age at delivery. Again, the GROW centile calculator v5.15_UK [12] was used for this.

2.1. Study population

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2.2. Measurement of placental T2 relaxation

All MR scanning took place on a 1.5T Signa HDx scanner (General Electric, Waukesha, USA) using the manufacturer's body coil for RF transmission and a dedicated torso array coil for signal reception. As MR scanning can be noisy, ear plugs were used to allow the mother to lie supine but with her body angled by approximately 20° to her left, which reduced the risk of aortocaval compression caused by the pregnant uterus.

A total of 621 cm² (range 743–3035); 621 cm² (range 261 cm²–1067 cm²). There were differences in the size of the areas for the ROI between the three study groups because women were scanned at different gestational ages and the women with low estimated fetal weight (LFW) pregnancies had significantly smaller placaeae. Regression analysis showed that there was no significant association with gestational age (central regression p = 0.690), and therefore it was not necessary to adjust for this.

To allow reproducibility and the intraobserver variability to be assessed, the ROI was defined twice, at different settings at least 24 h apart, resulting in two ROIs per image slice. All measurements were performed by the same observer (ID).
For each of the ROI on all eight images, the mean signal values, the standard deviation values and the area values were recorded into a database. These values were then used to construct the relaxation curves. Following Miller and Joseph [14], the signal power was calculated, and fitted to the equation

\[ S(TE) = S_0 e^{-TE/T_2} + N \]

where \( S(TE) \) is the mean signal in the ROI at echo time \( TE \), \( T_2 = T_2/2 \), \( S_0 \) is the signal for \( TE = 0 \), and \( N \) is a parameter related to the noise level. The parameters \( S_0, T_2, \) and \( N \) were fitted using the Levenberg Marquardt non-linear least squares method as implemented in the GNU Scientific Library. From these, \( S_0 \), \( T_2 \), and the noise level were calculated. In total there were two curves for each of the three contiguous slices and each curve was examined in turn (Fig. 3). It is from these curves that the \( T_2 \) values were generated. The mean areas and \( T_2 \) values were calculated for each of the three contiguous slices. The three slices were then combined to produce a final averaged \( T_2 \) value.

2.3. Statistical analysis

The intraobserver variability of the ROI area and the \( T_2 \) values were calculated using Bland Altman Plots [15]. Comparison between variables was done by \( \chi^2 \)-test or Fisher’s exact test for categorical variables and Mann–Whitney \( U \)-test for continuous variables.

The distributions of placental \( T_2 \) relaxation times and uterine artery PI were examined for Gaussian normality using probability plots and the Shapiro–Wilk test. Placental \( T_2 \) relaxation had a normal distribution, and uterine artery PI was loga-rhythmically transformed which achieved normality. Multiple regression analysis was then used to determine which of the factors amongst the maternal characteristics and gestation and outcome were significant predictors of placental \( T_2 \) relaxation and \( \log_{10} \) uterine artery PI. Regression analysis was used to examine the significance of the association between placental \( T_2 \) relaxation, \( \log_{10} \) uterine artery PI and birth weight percentile.

The statistical software package SPSS 17.0 (SPSS Inc., Chicago, IL) was used for data analyses.

3. Results

The maternal and pregnancy characteristics in the study population are described in Table 1.

In the Bland Altman Plots, the difference of two measurements of the ROI area and the \( T_2 \) relaxation times was less than 7% in 95% of cases.

All 10 cases of group 1, with normal prenatal findings, had no pregnancy complications and delivered phenotypically normal

Fig. 2. \( T_2 \)-weighted images of slice 1 showing changes in contrast at different time points allowing calculation of \( T_2 \) relaxation time. Echo times (a) 40 ms, (b) 80 ms, (c) 120 ms, (d) 180 ms, (e) 240 ms, (f) 300 ms, (g) 360 ms, (h) 440 ms.
There were two groups of SGA neonates: one in which the fetuses at the time of the MRI studies had low estimated fetal weight (LEFW) below the 10th percentile for gestational age (n = 11), and another in which the fetuses had normal estimated fetal weight on or above the 10th percentile for gestational age at the time of the MRI (n = 14).

3.1. Placental T2 relaxation time

In the 40 cases included in the study, regression analysis demonstrated that placental T2 relaxation was significantly affected by whether the neonate was SGA or AGA (p < 0.0001) but not by maternal age (p = 0.719), maternal body mass index (p = 0.971), racial origin (p = 0.230) or gestational age at examination (p = 0.268).

In 25 pregnancies that resulted in the delivery of SGA neonates, compared to the AGA neonate group, the median placental T2 relaxation time was significantly lower (88.0 ms vs. 149.0 ms, p < 0.0001). This difference persisted when the SGA group was subdivided into those with and without preeclampsia, and in those who at the time of the MRI examination had low estimated fetal weight below the 10th percentile or had normal estimated fetal weight on or above the 10th percentile (Table 2).

3.2. Uterine artery pulsatility index

In the 40 cases included in the study, regression analysis demonstrated that log10 uterine artery PI was significantly affected by whether the neonate was SGA or AGA (p < 0.0001) but not by maternal age (p = 0.298), maternal body mass index (p = 0.429), racial origin (p = 0.054) or gestational age at examination (p = 0.147).

In the group with SGA neonates, compared to the AGA neonate group, the median uterine artery PI was higher (1.96 vs. 1.00, p < 0.0001) and this difference persisted when the SGA neonate group was subdivided into those with and without preeclampsia, and in those who at the time of the MRI examination had low estimated fetal weight below the 10th percentile or had normal estimated fetal weight on or above the 10th percentile (Table 2).

3.3. Relationship between placental T2 relaxation time, uterine artery PI and birth weight percentile

There were significant associations between placental T2 relaxation time and log10 uterine artery PI (r = −0.749, p < 0.0001; Fig. 4), and between placental T2 relaxation and birth weight percentile (r = 0.693, p < 0.0001; Fig. 4).

4. Discussion

The findings of our study demonstrate that: firstly, measurement of T2 relaxation times in the second trimester of pregnancy can be successfully accomplished using conventional clinical MRI scanning protocols typical of those available in many facilities; secondly, in pregnancies that subsequently result in delivery of SGA neonates the T2 relaxation times are significantly lower than in those of uncomplicated pregnancies; and thirdly, the T2 relaxation times are significantly related to the degree of uterine perfusion reflected in the PI of the uterine arteries.

Placental morphology is altered in pregnancies complicated by preeclampsia and/or the birth of SGA neonates [16–20]. These morphological changes are thought to be the consequence of two processes, which result in reduction of placental weight, intervillous space volume and terminal villous volume and surface area. Firstly, there is impaired placental perfusion because of inadequate

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### Table 1

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Appropriate for gestation (n = 15)</th>
<th>Small for gestation (n = 25)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maternal age in years, median (IQR)</td>
<td>31.0 (27.0–33.0)</td>
<td>30.0 (24.0–34.0)</td>
</tr>
<tr>
<td>Maternal body mass index in kg/m², median (IQR)</td>
<td>25.1 (20.8–28.3)</td>
<td>23.8 (21.5–27.2)</td>
</tr>
<tr>
<td>Gestational age in wks at MRI, median (IQR)</td>
<td>26.5 (26.2–26.5)</td>
<td>26.5 (26.1–27.4)</td>
</tr>
<tr>
<td>Gestational age in wks at birth, median (IQR)</td>
<td>40.3 (37.6–40.9)</td>
<td>33.4 (29.5–38.0)*</td>
</tr>
</tbody>
</table>

**Ethnicity**
- Caucasian, n (%) 10 (66.7) 11 (44.0)
- African, n (%) 5 (33.3) 12 (48.0)
- South Asian, n (%) 0 1 (4.0)
- East Asian, n (%) 0 1 (4.0)
- Cigarette smoker, n (%) 1 (6.7) 1 (4.0)
- Birth weight percentile, median (IQR) 41.0 (21.0–64.0) 1.0 (0.0–4.5)*

Comparison between variables by χ²-test or Fisher’s exact test for categorical variables; *p < 0.05.
trophoblastic invasion of the maternal spiral arteries and their physiological conversion from small muscular vessels into large unresponsive channels supplying the intervillous space. Secondly, there is perturbed growth and development of the placental villi. Duncan et al. [21] carried out a longitudinal study on 14 healthy singleton pregnancies between 20 and 42 weeks gestation and reported that there was a significant reduction in $T_2$ relaxation times of the normal placenta with advancing gestation. This was confirmed in a recent study by Wright et al. [22] where 30 women with healthy singleton pregnancies underwent MRI examinations between 20 and 41 weeks. Placental $T_2$ showed a significant negative correlation with gestational age which was influenced by changes in placental structure as confirmed by stereological analysis. This finding supports histological evidence whereby the placenta has been found to mature and alter in structure as pregnancy progresses. In our study we did not find this negative correlation between $T_2$ relaxation time and gestational age. This is probably because we examined women within a narrow gestational range of between 24 and 29 weeks.

$T_2$ is a measure of how long it takes for the transverse magnetisation to lose coherence after the tissue signal has been excited by a radiofrequency (RF) pulse, and is a complex process depending on many factors including water binding, macromolecular concentration and blood oxygenation. Consequently, $T_2$ relaxation reflects a variety of biochemical and physical mechanisms including placental structure and morphology (albeit in a complex and nonspecific manner), and a reduction in this measurement indicates that in pregnancies complicated with SGA at the time of the MRI studies (group 3) placental morphology is altered. This is consistent with the findings of Gowland et al. [3] who also found reduced $T_2$ relaxation in pregnancies with SGA at late gestation. An important additional finding of our study is that $T_2$ is significantly reduced in the second trimester in pregnancies that subsequently deliver infants that are SGA at birth. This is also true for fetuses who have normal estimated fetal weight on or above the 10th percentile at the time of MRI but who subsequently deliver SGA. This suggests that in the second trimester MRI $T_2$ measurements of the placenta may be a more sensitive predictor of SGA at birth than uterine artery Doppler PI.

In addition to $T_2$ relaxation, the MRI signal is also dependent on $T_1$ relaxation processes, which determine how long it takes for the longitudinal magnetisation to recover after the tissue has been excited, and depends on similar processes to $T_2$. Gowland et al. [3] and Wright et al. [22] reported similar findings for both placental $T_1$.

### Table 2

<table>
<thead>
<tr>
<th>Group</th>
<th>$T_2$ relaxation time</th>
<th>$p$ Value</th>
<th>Uterine artery PI</th>
<th>$p$ Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Appropriate for gestation (n = 15)</td>
<td>149.0 (137.0–160.0)</td>
<td></td>
<td>1.00 (0.87–1.78)</td>
<td></td>
</tr>
<tr>
<td>Small for gestational age (SGA)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All cases (n = 22)</td>
<td>88.0 (69.0–100.0)</td>
<td>&lt;0.0001</td>
<td>1.96 (1.76–2.37)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Preeclampsia (n = 7)</td>
<td>90.0 (46.0–92.0)</td>
<td>&lt;0.0001</td>
<td>2.24 (1.78–2.57)</td>
<td>0.002</td>
</tr>
<tr>
<td>No preeclampsia (n = 18)</td>
<td>86.5 (69.8–113.5)</td>
<td>&lt;0.0001</td>
<td>1.93 (1.76–2.22)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>LFW at time of MRI (n = 11)</td>
<td>69.0 (46.0–82.0)</td>
<td>&lt;0.0001</td>
<td>2.02 (1.85–2.81)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Normal weight at time of MRI (n = 14)</td>
<td>93.0 (89.5–113.5)</td>
<td>&lt;0.0001</td>
<td>1.86 (1.75–2.22)</td>
<td>0.001</td>
</tr>
</tbody>
</table>

Comparison between variables by Mann–Whitney U-test; $p < 0.01$.  

![Fig. 4. Relationship between placental $T_2$ relaxation time and uterine artery pulsatility index and between placental $T_2$ relaxation and birth weight percentile in small for gestational age neonates (closed circles) and appropriate for gestation neonates (open circles).](image-url)
and T₂ relaxation times. In our study we chose to measure only T₂ relaxation times because these measurements are less susceptible to movement artefact resulting in a loss of results, and they are easier and faster to acquire, making them likely to be better tolerated by subjects [21].

There are a number of limitations to our study. Movement artefact (in the form of gross maternal movement, fetal movement and maternal respiration) is a potential issue and can lead to poor quality images. This is particularly problematic when peripheral regions of the placenta (or any other structure) are to be examined, but in the current study there was never an issue regarding where to draw the ROI, as it was very easy to see where the centre of the placenta was on each slice. Such a central ROI is less affected by movement artefact than other ROIs might be, because it was possible to check while the ROI was being drawn that it would always remain within the centre of the placenta. As described previously, the ROI was checked on each echo time image to ensure that it fell within the centre of the placenta. Despite this, it is still possible that errors from partial volume effects may have played a role, but there is very little that can be done to reduce this further.

Relaxation times are extremely sensitive to many physical, chemical and physiological parameters. They do not differentiate between them in a unique manner and are therefore limited in the interpretation that one can make in terms of a mechanistic or specific physical dependence. However, due to their sensitivity, they are very good for determining differences, for example, between pathological tissue and healthy tissue.

The study would have benefited from reproducibility measurements, however the women were already in the scanner for 30–40 min and adding an extra scan to the protocol may have led to the women being in the scanner for an intolerable amount of time.

As discussed previously, all the measurements were made by a single observer, who was not blinded to the three different study groups. The measurements were, however, made prospectively and therefore the final pregnancy outcome was not known at the time of the measurements. The study could have been improved by having a second observer to make similar measurements so that the interobserver variability could have been calculated; and by having a larger sample size so that it would have been possible to subdivide the abnormal Doppler group into those with normal and abnormal outcomes, and then to make comparisons between the groups and subgroups.

In conclusion, this study shows that T₂ relaxation of the placenta during the second trimester is shorter in those pregnancies which present with SGA but also in those which go on to deliver SGA neonates, and the measurement is strongly related to placental perfusion.

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