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Association of placental T_2 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 T_2 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 T_2 relaxation time was measured by echo planar MRI at 1.5 T. The significance of the associations between T_2 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 T_2 relaxation time was significantly decreased (88 ms vs. 149 ms, $p < 0.0001$) and uterine artery PI was increased (1.96 vs. 1.00, $p < 0.0001$). There were significant associations between placental T_2 relaxation time and $\log_{10}$ uterine artery PI ($r = -0.749$, $p < 0.0001$), and between T_2 relaxation and birth weight percentile ($r = 0.693$, $p < 0.0001$).
Conclusion: The T_2 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.

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 (T_2); 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.

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The aim of the current study was to extend the previous work by investigating whether placental T_2 relaxation is related to uterine artery PI during the second trimester of pregnancy and whether alterations in T_2 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 [10]. 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 [11]. Colour flow mapping is used to identify the left and then the right uterine artery and pulsed-wave imaging is used to measure the pulsatility index (PI) on each side from which the mean value is calculated.

In this study, the fetal weight percentile was determined by the height and weight of the mother; her ethnicity; her parity; the GA of the fetus at the USS examination; the estimated fetal weight; and the sex of the baby. The GROW centile calculator v5.15_UK [12] was used for this.

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 T_2 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 records or 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

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 uterine artery PI was below the 95th percentile of the reference range (Normal group; $n = 10$). These fetuses were complicated by isolated minor congenital abnormalities such as borderline/mild ventriculomegaly and hydronephrosis. They required serial scans to monitor their minor abnormalities but all the fetuses recruited had normal growth and normal placental perfusion. In the second group, the estimated fetal weight was above the 10th percentile but the uterine artery PI was above the 95th percentile (Abnormal Doppler group; $n = 22$). These women had structurally normal fetuses but were at risk of developing preeclampsia and/or an SGA fetus. In the third group, the estimated fetal weight was below the 10th percentile and the uterine artery PI was above the 95th percentile of the reference range (low fetal weight group; $n = 11$) These fetuses were known SGA at the time of the MRI, with most ($n = 7$) having abnormal fetal Dopplers; and several ($n = 4$) also having reduced amniotic fluid volume.

2.2. Measurement of placental T_2 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 defenders were provided for the mother. The fetus was protected by the maternal abdomen and the amniotic fluid filling his/her ears. The participant was put into the scanner feet first to reduce the feeling of claustrophobia and optimise the location of the image volume at the scanner iso-centre. Pads 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.

Localiser images were obtained to determine the overall position of the uterus and placenta. This took 20 s. T_2-weighted structural images were then acquired in (oblique) sagittal and axial orientations, in order to visualise in detail the placenta and fetus. The sagittal images were collected with a Single Shot Fast Spin Echo (SS-FSE) scan covering the whole uterus. From this, an axial SS-FSE scan was planned, again covering the whole uterus. The parameters for the SS-FSE scans were an echo time of 140 ms, a repetition time of 4000 ms, and a slice thickness of 6 mm with a gap of 1 mm for the sagittal sequence, and a slice thickness of 4 mm with a gap of 1 mm for the axial sequence. The field of view was 28 × 28 cm for the sagittal sequence, and 35 × 35 cm for the axial sequence. The matrix size was 256 × 224 for the sagittal sequence and 320 × 224 for the axial sequence. In general, 28 slices were collected for the sagittal sequence and 46 slices for the axial sequence, although slice numbers were changed if necessary to ensure complete coverage of the anatomy. The total scan time was 3 min for the sagittal scan and 5 min for the axial scan.

The SS-FSE axial images were used to determine the best position to further examine the placental structure. Three contiguous true axial slices (labelled slices 1, 2 and 3, with 1 being the most superior) were chosen with a field of view of 24 × 24 cm and slice thickness of 8 mm, with a 0 mm gap between the slices. They were used to perform a further axial T_2-weighted SS-FSE. The parameters of this scan were an echo time of 140 ms, a repetition time of 4000 ms and a matrix size of 192 × 192. The total scan time was 15 s. The aim of this short scan was to visualise clearly what the placenta looked like in the selected area (Fig. 1), with orientation and slice thickness matching those to be used for the quantitative assessment of T_2 described below. If the images showed good placental coverage (i.e. a representative cross sectional appearance of the placenta), the same three contiguous true axial slices were used for the T_2 measurements; if not the prescription was modified and the scan repeated until good visualisation of the placenta was achieved. Once suitable slices had been determined, the T_2 measurements comprised of eight flow compensated spin echo EPI scans. The parameters of these scans were echo times of 40, 80, 120, 180, 240, 300, 360 and 440 ms, a repetition time of 4000 ms and a matrix size of 64 × 64. These scans were acquired sequentially and took 7 min to perform.

All the images were automatically transferred to a network of workstations where they were converted into the appropriate format for the locally written analysis software. This conversion procedure removed any personal identifiable information from the image headers.

The raw relaxation data comprised of eight separate images for each of the three contiguous slices. Fig. 2 shows images at each echo time for slice 1 for a typical subject. A central region of interest (ROI) was drawn onto the placenta on the 120 ms echo time image (Fig. 3). This echo time image was chosen as it demonstrated the placental borders best. The ROI covered a representative area of the central part of the placenta; it was placed away from edges and any large vessels, and was positioned such that any movement artefact would not cause it to move out of the central part of the placenta. The effect of motion was checked by displaying the central ROI sequentially overlaid on the eight echo time images. The same ROI was used for all eight images (40 ms–440 ms), unless there had been too much movement, in which case a ROI was drawn directly onto the appropriate image.

Each subject's placenta was measured in the same way to try and standardise the ROI being produced. The mean ROI was 1765 voxels (range 743–3035); 621 cm^2 (range 261 cm^2–1067 cm^2). 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 placentae. Regression analysis showed that there was no significant association with gestational age (central region $p = 0.690$), 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 sittings at least 24 h apart, resulting in two ROIs per image per slice. All measurements were performed by the same observer (ID).

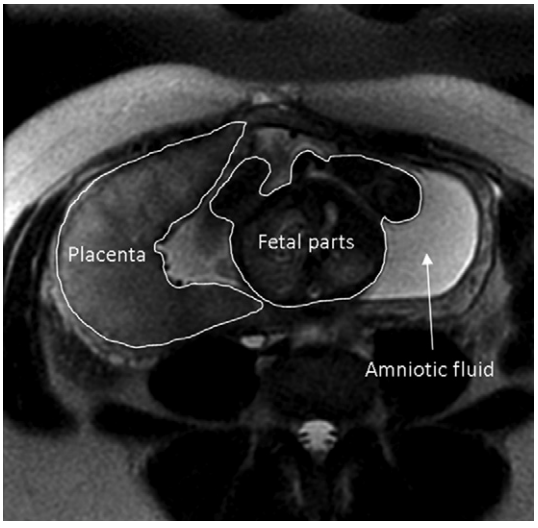

Fig. 1. T_2-weighted magnetic resonance demonstrating the placental anatomy.

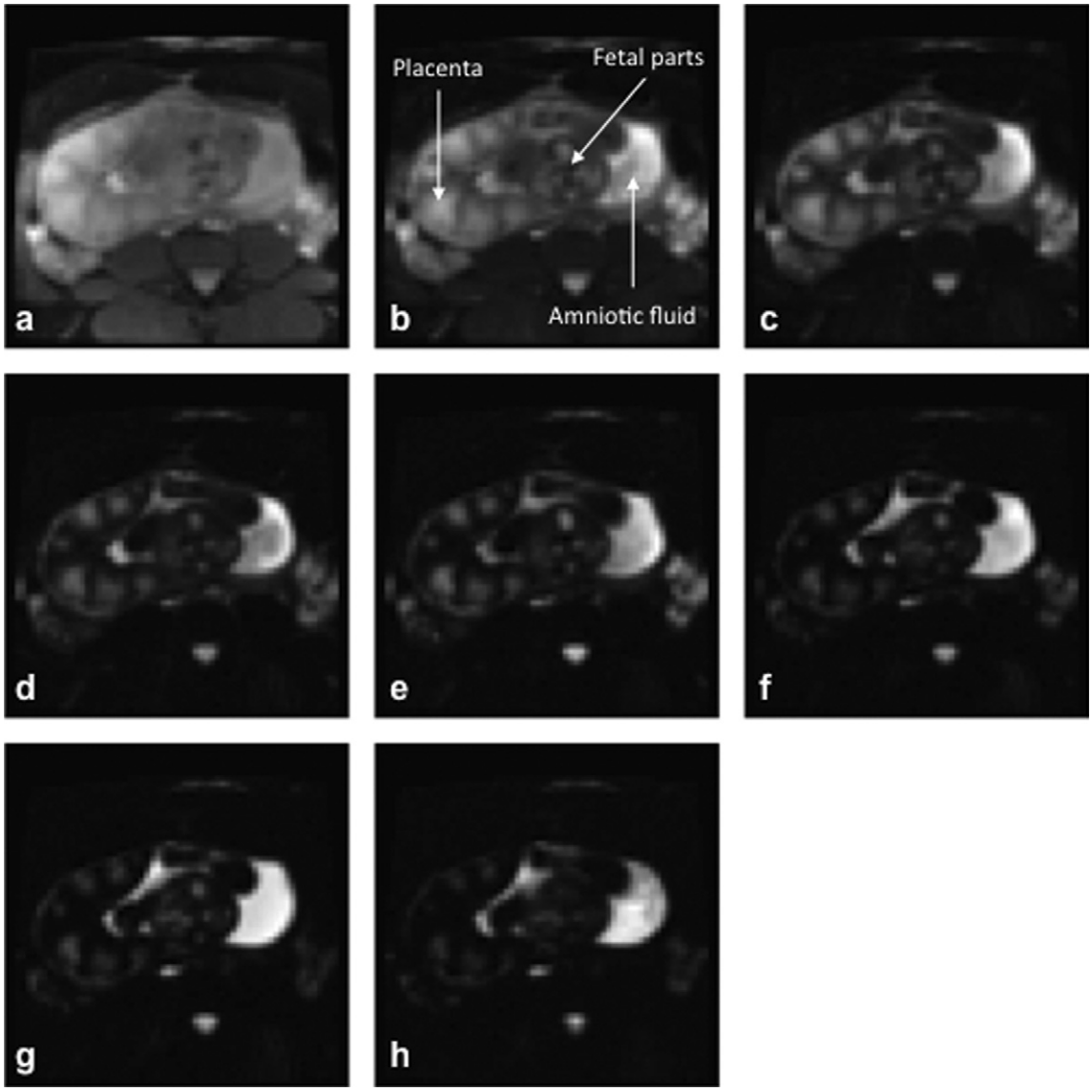

Fig. 2. T_2-weighted images of slice 1 showing changes in contrast at different time points allowing calculation of T_2 relaxation time. Echo times (a) 40 ms, (b) 80 ms, (c) 120 ms, (d) 180 ms, (e) 240 ms, (f) 300 ms, (g) 360 ms, (h) 440 ms.

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

$$S^2(\mathrm{TE}) = S_0^2 e^{-\mathrm{TE}/T_2^\dagger} + N$$

where $S(\mathrm{TE})$ is the mean signal in the ROI at echo time TE, $T_2^\dagger = T_2/2$, S_0 is the signal for $\mathrm{TE} = 0$, and N is a parameter related to the noise level. The parameters S_0^2, $T_2^\dagger$, 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 χ^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 logarithmically 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

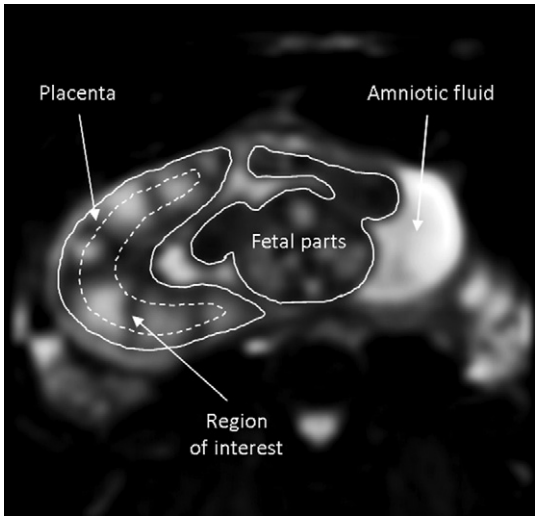

Fig. 3. T_2-weighted image demonstrating the central placental region of interest drawn onto the 120 ms echo time image.

neonates at term with birth weight on or above the 10th percentile, i.e. appropriate for gestational age (AGA). In the 22 cases of group 2, with normal estimated fetal weight but high uterine artery PI, there were five uncomplicated pregnancies with delivery of AGA neonates, 10 uncomplicated pregnancies with delivery of SGA neonates, three that developed preeclampsia but delivered AGA neonates and four that developed preeclampsia and delivered SGA neonates. In the 11 cases of group 3, of low estimated fetal weight fetuses and high uterine artery PI, three women developed preeclampsia and all 11 delivered SGA neonates. The group of AGA neonates whose mother's had isolated preeclampsia ($n = 3$) was excluded from further analysis because this group has a different pathophysiology and placental structure to pregnancies complicated by SGA (with or without preeclampsia).

Once the analysis was done it became clear that the sample size was too small to make meaningful comparisons between the three groups and therefore it was decided to re-classify the three groups into two final outcome groups (1) normal size (AGA) neonates or (2) SGA neonates. In total, there were 15 cases with delivery of AGA neonates and 25 cases of SGA neonates.

Table 1
Maternal and pregnancy characteristics in the study population.

Characteristic	Appropriate for gestation ($n = 15$)	Small for gestation ($n = 25$)
Maternal age in years, median (IQR)	31.0 (27.0–33.0)	30.0 (24.0–34.0)
Maternal body mass index in kg/m^2, median (IQR)	25.1 (20.8–28.3)	23.8 (21.5–27.2)
Gestational age in wks at MRI, median (IQR)	26.5 (26.2–26.5)	26.5 (26.1–27.4)
Gestational age in wks at birth, median (IQR)	40.3 (37.6–40.9)	33.4 (29.5–38.0)*
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 χ^2-test or Fisher's exact test for categorical variables and by Mann–Whitney *U*-test for continuous variables; *$p < 0.05$.

There were two groups of SGA neonates: one in which the fetuses at the time of the MRI studies had low estimated fetal weight (LFW) 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 T_2 relaxation time

In the 40 cases included in the study, regression analysis demonstrated that placental T_2 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 T_2 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 $\log_{10}$ 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 T_2 relaxation time, uterine artery PI and birth weight percentile

There were significant associations between placental T_2 relaxation time and $\log_{10}$ uterine artery PI ($r = -0.749$, $p < 0.0001$; Fig. 4), and between placental T_2 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 T_2 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 T_2 relaxation times are significantly lower than in those of uncomplicated pregnancies; and thirdly, the T_2 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

Table 2
Median and interquartile range of placental T_2 relaxation time (ms) measured by magnetic resonance imaging (MRI) and uterine artery pulsatility index (PI) in pregnancies delivering small for gestational age (SGA) neonates compared to the appropriate for gestational age neonate group. The small for gestational age neonate group is subdivided into those with and without preeclampsia and into those who had and did not have low estimated fetal weight (LFW) at the time of the MRI examination.

Group	T_2 relaxation time	p Value	Uterine artery PI	p Value
Appropriate for gestation ($n = 15$)	149.0 (137.0–160.0)		1.00 (0.87–1.78)	
Small for gestational age (SGA)				
All cases ($n = 25$)	88.0 (69.0–100.0)	<0.0001	1.96 (1.76–2.37)	<0.0001
Preeclampsia ($n = 7$)	90.0 (46.0–92.0)	<0.0001	2.24 (1.78–2.57)	0.002
No preeclampsia ($n = 18$)	86.5 (69.8–113.5)	<0.0001	1.93 (1.76–2.22)	<0.0001
LFW at time of MRI ($n = 11$)	69.0 (46.0–82.0)	<0.0001	2.02 (1.85–2.81)	<0.0001
Normal weight at time of MRI ($n = 14$)	93.0 (89.5–113.5)	<0.0001	1.86 (1.75–2.22)	0.001

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

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 non-specific 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

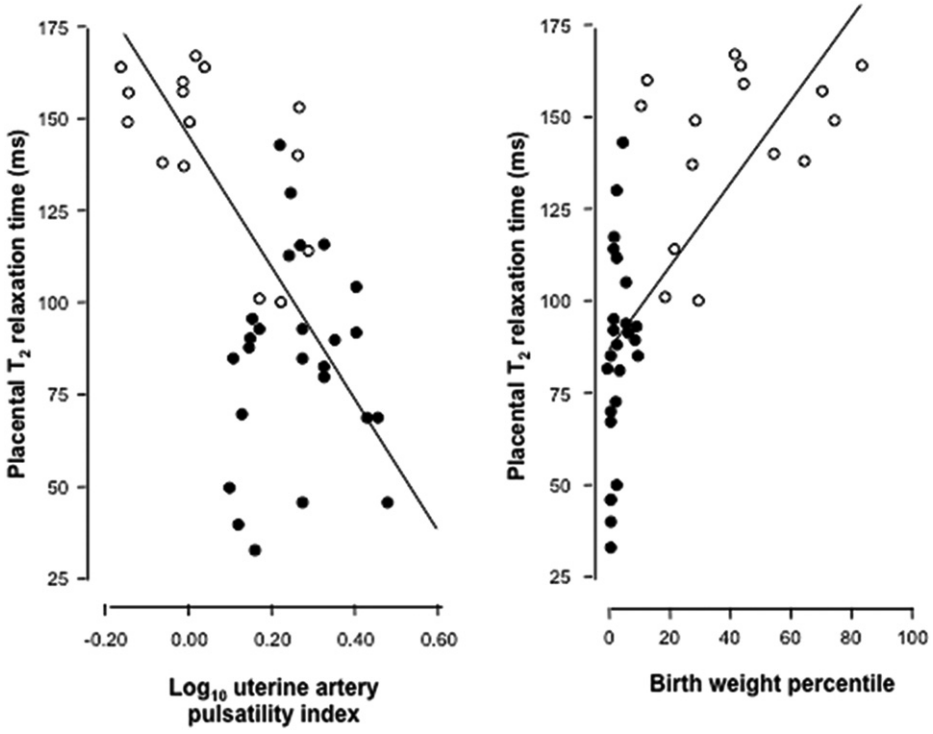

Fig. 4. Relationship between placental T_2 relaxation time and uterine artery pulsatility index and between placental T_2 relaxation and birth weight percentile in small for gestational age neonates (closed circles) and appropriate for gestation neonates (open circles).

and T_2 relaxation times. In our study we chose to measure only T_2 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 T_2 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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