Association of placental perfusion, as assessed by magnetic resonance imaging and uterine artery Doppler ultrasound, and its relationship to pregnancy outcome

I. Derwig [a], D.J. Lythgoe [b], G.J. Barker [b], L. Poon [a], P. Gowland [c], R. Yeung [d], F. Zelaya [b,1], K. Nicolaides [a,e,*,1]

[a] Harris Birthright Research Centre, Kings College Hospital, London, UK
[b] Department of Neuroimaging, Institute of Psychiatry, King's College London, London, UK
[c] Sir Peter Mansfield Magnetic Resonance Centre, The University of Nottingham, UK
[d] Applied Science Laboratory, GE Healthcare, Chalfont St Giles, Bucks, UK
[e] Department of Fetal Medicine, University College Hospital, London, UK

ARTICLE INFO

ABSTRACT

Purpose: To investigate (a) if placental perfusion in the second trimester of pregnancy, measured by two non-invasive magnetic resonance imaging (MRI) techniques, is related to impedance to flow in the uterine arteries, as assessed by Doppler ultrasound; and (b) if these measures are associated with future gestational outcome.
Methods: In 37 singleton pregnancies at 24–29 weeks' gestation, uterine artery pulsatility index (PI) was measured by Doppler ultrasound and placental perfusion was measured by Arterial Spin Labelling (flow-sensitive alternating inversion recovery (FAIR)) and intravoxel incoherent motion (IVIM) echo-planar imaging at 1.5 T in basal, central and placental regions of interest. The values were compared between those delivering small for gestational age (SGA) and appropriate for gestational age (AGA) neonates.
Results: In 23 pregnancies that resulted in delivery of SGA neonates, compared to the 14 with AGA neonates, the median basal FAIR measure was significantly lower (923.0 vs. 2359.0 arbitrary units; $p = 0.003$) as were IVIM measures of perfusing fraction (f) in basal, central and whole-placental regions (37.8 vs. 40.7%; $p = 0.046$; 24.3 vs. 35.1%; $p = 0.014$ and 27.9% vs. 36.2%; $p = 0.001$, respectively). In the SGA group, the median uterine artery PI was increased (1.96 vs. 1.03; $p = 0.001$). There were significant associations between uterine artery PI and placental perfusion assessed by both FAIR and IVIM.
Conclusion: Pregnancies that result in SGA neonates exhibited reduced placental perfusion as assessed by MRI during the second trimester. This measurement was found to be strongly associated with impedance to flow in the uterine arteries. We suggest that FAIR or IVIM MRI examinations may be used to directly and non-invasively determine placental perfusion, and that the measured values are strong indicators of future gestational outcome.

1. Introduction

Small for gestational age (SGA) neonates have increased risk of perinatal death and handicap. The condition includes neonates who are both constitutionally small and who are growth restricted due to impaired placentation, genetic disease or environmental damage. Abnormal placentation [1–4] leads to increased impedance to flow measured by the uterine artery pulsatility index (PI) on Doppler ultrasound [5] at 22–24 weeks gestational age (GA) in pregnancies that subsequently develop preeclampsia and, to a lesser extent, in those delivering SGA neonates without preeclampsia [6,7].

Power Doppler ultrasound measurements of placental perfusion have limited depth, reliability and reproducibility, and quantification remains unclear [8,9]. In contrast, magnetic resonance imaging (MRI) can clearly image the placenta, independent of GA or location [10] Ultrafast MRI sequences, such as echo-planar imaging (EPI) and single shot fast spin echo imaging (SS-FSE), can overcome the

effects of fetal motion [11,12]. Fetal MRI is considered to be safe, and follow-up studies have found no adverse effects [13–15] and non-invasive MR perfusion measurements have been employed in several studies of the placenta [16–21]: the flow-sensitive alternating inversion recovery (FAIR) sequence [22] Arterial Spin Labelling (ASL; [23,24]) and intravoxel incoherent motion (IVIM; [25]) sequences.

In FAIR, arterial blood flowing into the imaged region is labelled non-invasively using radio-frequency pulses. In IVIM, a pulsed field gradient is used to impose diffusion dependent contrast, with the degree of contrast being summarised by the '*b*-factor' [25]. In tissue the MR signal decays bi-exponentially with *b*-factor; the first component of the signal decay is dominated by blood motion and the second by diffusion, so that the relative size (*f*) of the first component can be interpreted as the fractional perfusing blood volume. Two previous studies related FAIR measures of placental perfusion to birth weight; the first found no differences in pregnancies that delivered SGA neonates [16], but the second found a difference in the distribution of perfusion values across the placenta between the SGA and AGA groups [17]. Two other studies found changes in pregnancies that delivered SGA neonates and those with preeclampsia using IVIM [21].

The aim of this study was to compare placental perfusion measured using FAIR and IVIM in SGA fetuses, to relate results to uterine artery PI and to determine whether detected changes in perfusion precede the clinical onset of SGA.

2. Methods

The study was carried out at the Harris Birthright Research Centre (HBRC), London, between February 2006 and May 2008. It was approved by the local NHS Research Committee and all participants provided written, informed consent. Consecutive women with singleton pregnancies attending for scan at 22–24 weeks, and those referred with a known SGA fetus or a minor congenital abnormality were invited to participate. Many of the women who participated in this study also participated in our study on placental T_2 relaxation [26]. All the pregnancies were dated by ultrasound scan in the first trimester.

All participants had an ultrasound scan on the same day as the MRI exam, to measure fetal weight (estimated from measurements of head circumference, abdominal circumference and femur length [27]) and amniotic fluid volume; and pulsatility indices (PIs) assessing impedance to flow in the maternal uterine arteries (averaged over left and right sides), umbilical arteries, fetal cerebral vessels and ductus venosus. Uterine artery blood flow is routinely assessed by transvaginal sonography to determine the women's risk of developing preeclampsia and/or a SGA fetus [6]. The fetal weight percentile was determined from the mother's height and weight, ethnicity and parity, the GA and sex of the fetus and the estimated fetal weight using the GROW centile calculator v5.15_UK [28].

Data on pregnancy outcome were obtained from maternity records or the women's general medical practitioners. The outcome measures were preeclampsia, as defined by the International Society for the Study of Hypertension in Pregnancy [29], and SGA if the birth weight was <10th percentile for GA at delivery, using the GROW centile calculator.

Three groups of subjects were defined. Group 1: estimated fetal weight >10th percentile of the reference range and uterine artery PI <95th percentile of the reference range (*n* = 9). These fetuses were complicated by isolated minor congenital abnormalities. Group 2: estimated fetal weight >10th percentile but uterine artery PI >95th percentile (*n* = 21). These women had structurally normal fetuses but were at risk of preeclampsia or an SGA fetus. Group 3: estimated fetal weight <10th percentile and uterine artery PI >95th percentile (*n* = 10). These fetuses were known SGA at the time of the MRI, with seven having abnormal fetal Doppler measurements and four also having reduced amniotic fluid volume.

MRI was performed on a 1.5 T GE Signa HDx scanner (General Electric, Waukesha, USA), with a body coil for RF transmission and a torso array coil for signal reception. The mother was placed supine in the scanner feet first to minimise claustrophobia, but angled 20° onto her left hand side with pads to reduce aorto-caval compression.

Localiser images were obtained to determine the overall position of the uterus and placenta. Oblique sagittal (sequence 1 – see Table 1) and axial (sequence 2) T_2-weighted single shot fast spin echo (SS-FSE) images were acquired across the whole uterus, to visualise the placenta in detail. The axial images were used to determine where to examine placental blood flow. Three contiguous true axial slices were acquired in an additional axial SS-FSE scan whose field of view (FOV) was matched to those to be used for the FAIR and IVIM scans (sequence 3). If these images

Table 1
Summary of scanning parameters for the different sequences used.

Sequences	Scanning parameters
1	TE 140 ms, TR 4000 ms; Sagittal; slice thickness 6 mm, slice gap 1 mm, 28 slices, FOV 28 × 28 cm, matrix 256 × 224, scan time 3 min
2	TE 140 ms, TR 4000 ms; Axial; slice thickness 4 mm, slice gap 1 mm, 46 slices, FOV 40 × 40 cm, matrix 320 × 224, scan time 5 min
3	TE 140 ms, TR 4000 ms; Axial; slice thickness 4 mm, slice gap 0 mm, three slices, FOV 24 × 24 cm, matrix 192 × 192, scan time 15 s
4	TE 35 ms, TR 2500 ms; Axial; slice thickness 4 mm, slice gap 0 mm, three slices, FOV 24 × 24 cm, matrix 64 × 64, reconstructed resolution 1.875 mm, scan time 5 min
5	TE 69 ms, TR 2000 ms; Axial; slice thickness 4 mm, slice gap 0 mm, three slices FOV 24 × 24 cm, matrix 64 × 64, scan time 8 min

TE = echo time, TR = repetition time, FOV = field of view.

demonstrated good placental and basal plate coverage (Fig. 1), these slices were used for the FAIR and IVIM scans; if not, sequence 3 was repeated with different slice positions until good visualisation was achieved.

Single shot spin echo EPI FAIR images (sequence 4) were acquired labelled (after inverting the magnetisation within the image volume) and non-labelled (after inverting a region 1.35 times wider than the image volume). A post-labelling delay (T_i) of 1.2 s between the inversions and readouts allowed the labelled blood to move into the image volume. Twenty-five pairs of labelled and non-labelled images were collected to increase signal-to-noise ratio (SNR), and the average difference image ('non-label' – 'label') was calculated. This perfusion weighted image (arbitrary units) showed signal attenuation proportional to the amount of inverted blood that perfused into the image volume during the post-labelling delay. Whilst the raw values of the tagged and un-tagged images may have differed slightly between subjects due to small differences in the transmitter and receiver settings, the values of the *difference* images are comparable between subjects. We therefore employed these as a measure of tissue perfusion. It was not possible to convert these to physiological units of ml of blood per 100 g of tissue per minute, as there is no suitable model to perform this conversion in the placenta. IVIM data were acquired using spin echo EPI (sequence 5) with pulsed magnetic field gradients applied in the through-slice direction with 11 logarithmically spaced *b*-values (0, 0.7, 3, 9, 18, 32, 54, 88, 147, 252, 500 s/mm^2).

The FAIR time series of one slice was displayed as a movie, and images in which the placenta was displaced by more than two pixels in-plane were excluded from
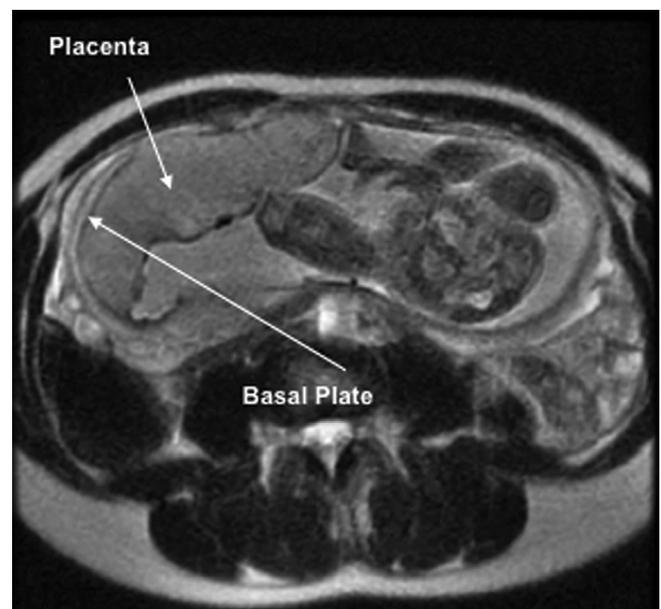
Fig. 1. T_2-weighted magnetic resonance image demonstrating the placental anatomy and basal plate.

subsequent analysis. Three regions of interest (ROIs) were drawn on the mean FAIR image for each slice: basal plate, placental and central regions (Fig. 2). The basal plate is the maternal aspect of the intervillous space (IVS) and is seen as a hypointense line on the T_2-weighted axial spin echo scan (Fig. 1) and the mean FAIR image. The placental region was drawn around the whole-placental region, including the basal plate and central regions. The central region was drawn centrally within the placenta to avoid contamination by other tissues due to movement. If areas of infarction or haematoma were observed, these were included as part of the ROI. All placentae were measured in the same way. The mean and standard deviation of the perfusion weighted signal were obtained for each ROI and then averaged over the three slices.

For IVIM a movie of the 11 b-value images of each slice was used to assess motion during this scan. The same above three ROIs were drawn and these ROIs were moved between b-values if necessary, which was more likely for the basal than central region. For each ROI on each slice, the mean image intensity, standard deviation (SD) and area were obtained and used to construct curves of intensity versus b-value. The curves were fitted to the following equation [18]:

$$S(b) = s(0)\left[(1-f)e^{-bD} + fe^{-bD^*}\right]$$

using the Levenberg–Marquardt non-linear least squares method (GNU Scientific Library [30]) here, $S(b)$ is the signal in the ROI for a specific value of the diffusion gradient factor b, and $S(0)$ is the fitted value of the signal for $b = 0$ s/mm². Fig. 3 demonstrates the bi-exponential IVIM curve. The early steep part of the curve corresponds to a 'fast diffusion' compartment, with a rate known as the pseudo-diffusion coefficient (D^*). The second part of the curve is less steep and corresponds to a compartment diffusing with the standard diffusion coefficient (D). The fractional blood volume (f) is the fraction of water molecules diffusing at the rate D^*. Fitted values of f and D are reproducible, whereas those for D^* are less reliable [19]. All of the curves were examined to ensure a good fit to the model ($\chi^2 \leq 0.0050$). The fitting procedure was repeated excluding up to two outlying data points, and the new f value was accepted if excluding the data point(s) reduced χ^2 by at least a factor of two. At least one data point was excluded in about 50% of the cases, with more being excluded for the basal plate region. The results from the three slices were then averaged to produce final f values for the three ROIs.

All ROIs were drawn by a single observer (ID), using the DispImage software [31]. To assess intra-observer variability, ROI drawing was repeated once after at least 24 h. This was possible for all three ROIs in the FAIR analysis. With the IVIM analysis, reproducibility was only assessed on central regions where the ROI was not moved between different b-values.
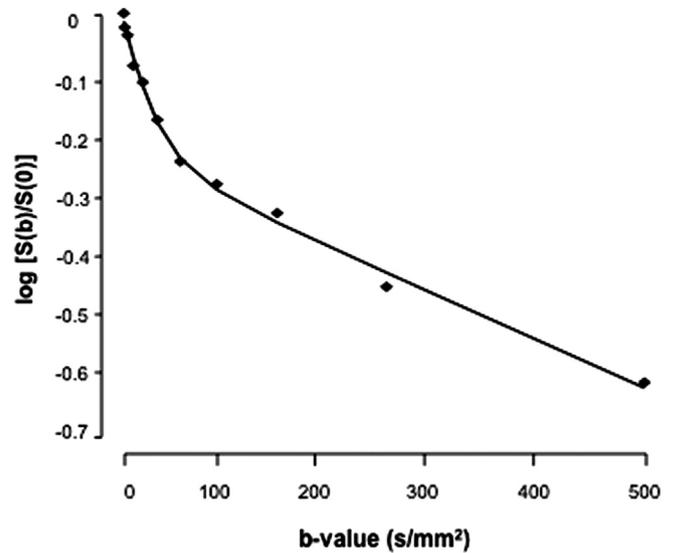
Fig. 3. Typical plot of the signal attenuation versus b-values demonstrating a typical IVIM curve with its bi-exponential nature.

The intra-observer variability of the three ROI areas, FAIR perfusion and IVIM perfusion values was assessed using Bland–Altman Plots [32]. Variables were compared using a χ^2-test or Fisher's exact test for categorical variables and the Mann–Whitney U-test for continuous variables. The distributions of FAIR, IVIM and uterine artery PI values were examined for Gaussian normality using probability plots and histograms. The basal, central and placental IVIM values were normally distributed whereas the basal, central, placental FAIR values and uterine artery PI were logarithmically transformed to achieve normality. Multiple regression analysis was used to determine which of the factors amongst the maternal characteristics, gestation and outcome were significant predictors of basal, central and placental $\log_{10}$ FAIR, IVIM and $\log_{10}$ uterine artery PI values. Regression analysis was used to
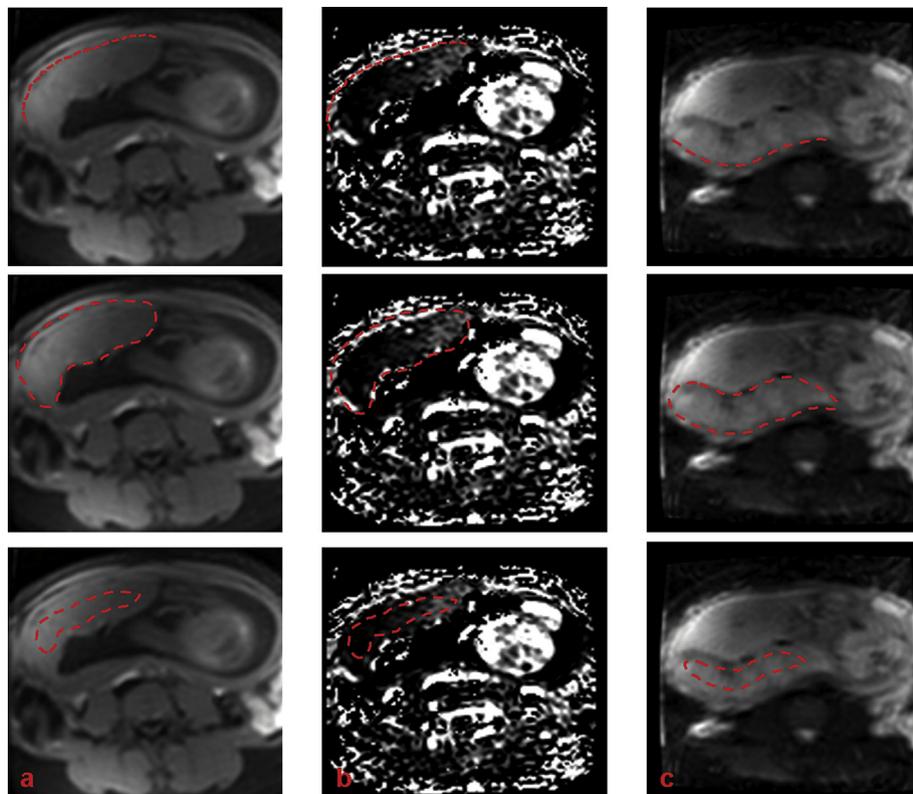
Fig. 2. Basal region (top), placental region (middle) and central region (bottom) shown on (a) a typical mean FAIR slice, (b) a typical FAIR perfusion map and (c) a typical raw image (b-value 0.7 s/mm²) of the IVIM sequence.

Table 2
Maternal and pregnancy characteristics in the study groups.

Characteristic	Appropriate for gestation (n = 14)	Small for gestation (n = 23)
Maternal age in years, median (IQR)	30.5 (25.8–32.3)	30.0 (24.0–34.0)
Maternal body mass index in kg/m^2, median (IQR)	25.3 (22.0–28.5)	23.7 (21.2–26.7)
Gestational age in wks at MRI, median (IQR)	26.5 (26.0–26.5)	26.5 (26.0–27.4)
Ethnicity		
Caucasian, n (%)	9 (64.3)	11 (47.8)
African, n (%)	5 (35.7)	10 (43.5)
South Asian, n (%)	0	1 (4.3)
East Asian, n (%)	0	1 (4.3)
Cigarette smoker, n (%)	1 (7.1)	1 (4.3)
Birth weight percentile, median (IQR)	42.0 (20.3–65.5)	1.0 (0.0–4.0)*

Comparison between variables by χ^2-test or Fisher's exact test for categorical variables and Mann–Whitney U-test for continuous variables; *$p < 0.05$.

examine the significance of the association between $\log_{10}$ FAIR, IVIM and $\log_{10}$ uterine artery PI values and birth weight percentile. The statistical software package SPSS 16.0 (SPSS Inc., Chicago, IL) was used for data analyses.

Henceforth FAIR and IVIM measures in the basal, central and whole-placental regions will be referred to as "basal perfusion(FAIR)", "basal f(IVIM)", "placental perfusion(FAIR)" and so on.

3. Results

Characteristics in the study population are described in Table 2. Subjects in Group 1 had no pregnancy complications and delivered phenotypically normal neonates at term with birth weight ≥10th percentile (AGA). In Group 2 there were five uncomplicated pregnancies delivering AGA neonates and 10 delivering SGA neonates, three that developed preeclampsia but delivered AGA neonates and three that developed preeclampsia and delivered SGA neonates. In Group 3, three women developed preeclampsia and all 10 delivered SGA neonates. The data from the three mothers who delivered AGA neonates and had preeclampsia (isolated preeclampsia) were excluded from further analysis, leaving 14 AGA and 23 SGA neonates.

The signal-to-noise ratio (SNR) of the component images was satisfactory and sufficiently good to make imaging based measurements with some degree of confidence, in spite of all the potential sources of artefacts in this study. In all cases, the time series images of the FAIR acquisition showed a SNR of approximately 25 – 3 depending on the region. For the IVIM, it varied between approximately 10 and 3.

Intra-observer variability between the repeated FAIR and IVIM measurements was less than 8% in 95% of cases.

Regression analysis demonstrated that $\log_{10}$ basal perfusion(FAIR) ($p = 0.002$), $\log_{10}$ placental perfusion(FAIR) ($p = 0.021$)
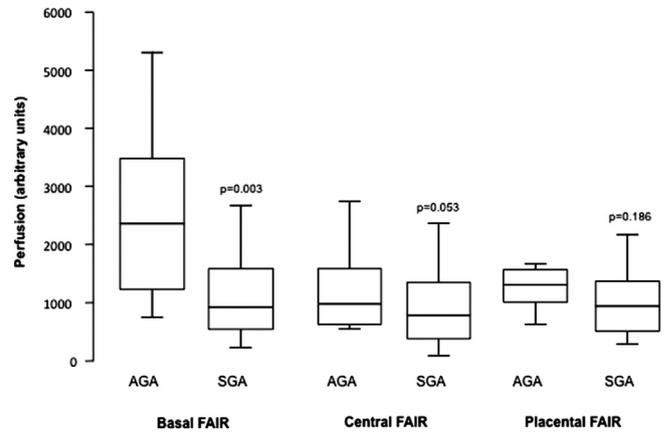
Fig. 4. Box and whisker plots of basal, central and placental FAIR measurements obtained by magnetic resonance imaging in appropriate for gestational age (AGA) and small for gestational age (SGA) neonates. The horizontal line in the box represents the median, the box represents the interquartile range and the whiskers indicate the minimum and maximum values.

and basal f(IVIM) ($p = 0.019$), central f(IVIM) ($p = 0.015$) and placental f(IVIM) ($p = 0.001$) were significantly affected by whether the neonate was SGA or AGA, unlike $\log_{10}$ central perfusion(FAIR) ($p = 0.087$). FAIR and IVIM values were not significantly associated with maternal age, maternal body mass index, racial origin or GA. $\log_{10}$ uterine artery PI was significantly affected by whether the neonate was SGA or AGA ($p < 0.001$) but not by maternal age, body mass index, racial origin or GA.

The median basal perfusion(FAIR) (923 vs. 2359 arbitrary units; $p = 0.003$), basal f(IVIM) (38 vs. 41%; $p = 0.046$), central f(IVIM) (24 vs. 35%; $p = 0.014$) and placental f(IVIM) (28 vs. 36%; $p = 0.001$) values were significantly lower in pregnancies that delivered SGA neonates compared to the AGA group. These differences were significant not only in those fetuses that had low estimated fetal weight at the time of the MRI examination but, for basal perfusion(FAIR) and placental f(IVIM), also in those fetuses that had normal estimated fetal weight at the time of the scan but subsequently delivered SGA neonates (Table 3, Figs. 4 and 5).

Median uterine artery PI was higher in the group who delivered SGA neonates compared with the group who delivered AGA neonates (1.96 vs. 1.03; $p < 0.001$). These differences were significant not only in fetuses that had low estimated fetal weight at the time of MRI, but also in those that had normal estimated fetal weight at the time of MRI but who subsequently delivered SGA neonates (Table 3).

There was a significant association between $\log_{10}$ uterine artery PI and $\log_{10}$ basal perfusion(FAIR) ($r = -0.563$, $p < 0.001$), $\log_{10}$ placental perfusion(FAIR) ($r = -0.396$, $p = 0.015$), placental f(IVIM) ($r = -0.477$, $p = 0.003$) and birth weight percentile ($r = -0.797$, $p < 0.001$). There was a significant association between birth weight

Table 3
Median and interquartile range of basal, central and placental values for FAIR and f IVIM measured by magnetic resonance imaging (MRI) and uterine artery pulsatility index (PI) in pregnancies delivering small for gestational age (SGA) neonates with and without preeclampsia, and in those who had and did not have low estimated fetal weight (LFW) at the time of the MRI, compared to the appropriate for gestational age neonate group.

	Appropriate for gestation (n = 14)	Small for gestational age (SGA)		
		All cases (n = 23)	LFW at MRI (n = 10)	Normal weight at MRI (n = 13)
Basal FAIR (arbitrary units)	2359.0 (1196.0–3542.8)	923.0 (465.0–1721.0)*	899.0 (428.3–1497.0)*	1116.0 (540.0–2160.5)*
Central FAIR (arbitrary units)	978.0 (624.3–1753.0)	780.0 (375.0–1461.0)	778.5 (476.0–1493.5)	787.0 (371.5–1329.5)
Placental FAIR (arbitrary units)	1305.5 (998.3–1840.3)	940.0 (478.0–1407.0)	916.0 (542.3–1397.3)	940.0 (467.0–1485.0)
Basal f IVIM %	40.7 (37.5–48.4)	37.8 (29.8–42.5)*	31.1 (26.6–40.5)*	39.9 (36.1–43.4)
Central f IVIM %	35.1 (25.8–38.1)	24.3 (21.1–33.2)*	24.1 (18.1–33.7)*	25.1 (21.5–33.6)
Placental f IVIM %	36.2 (30.2–39.8)	27.9 (22.2–31.0)*	26.1 (18.7–28.8)*	28.9 (24.2–32.4)*
Uterine artery PI unit	1.03 (0.92–1.81)	1.96 (1.76–2.24)*	2.13 (1.88–2.83)*	1.83 (1.75–2.15)*

Comparison between variables by Mann–Whitney U-test; *$p < 0.05$.
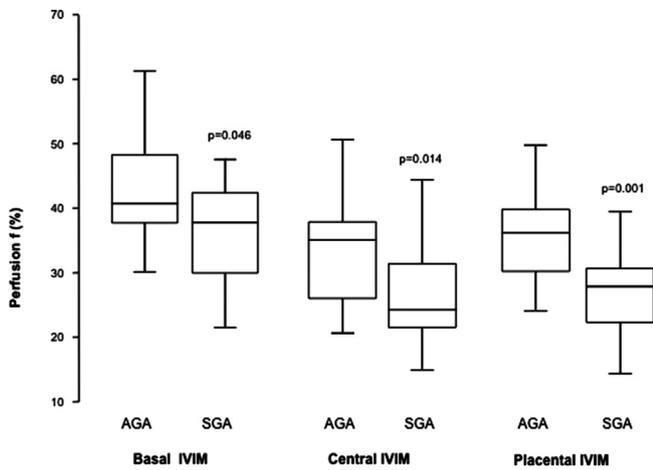
Fig. 5. Box and whisker plots of basal, central and placental *f* IVIM measurements obtained by magnetic resonance imaging in appropriate for gestational age (AGA) and small for gestational age (SGA) neonates. The horizontal line in the box represents the median, the box represents the interquartile range and the whiskers indicate the minimum and maximum values.

percentile and $\log_{10}$ basal perfusion(FAIR) ($r = 0.528$, $p < 0.001$), $\log_{10}$ central perfusion(FAIR) ($r = 0.398$, $p = 0.015$), $\log_{10}$ placental perfusion(FAIR) ($r = 0.484$, $p = 0.002$), basal *f*(IVIM) ($r = 0.342$, $p = 0.038$) and placental *f*(IVIM) ($r = 0.398$, $p = 0.015$). There was a significant association between $\log_{10}$ basal perfusion(FAIR) and central and placental *f*(IVIM) ($r = 0.426$, $p = 0.008$ and $r = 0.457$, $p = 0.004$) and between $\log_{10}$ placental perfusion(FAIR) with placental *f*(IVIM) ($r = 0.350$, $p = 0.034$) (Fig. 6).

4. Discussion

Our study demonstrates that placental perfusion can be estimated successfully using MRI; that placental perfusion is significantly lower at 24–29 weeks in pregnancies that subsequently deliver SGA neonates compared to those with AGA neonates; that placental perfusion is related to uterine blood flow measured by uterine artery PI; and that FAIR is more practically useful than IVIM for investigating placental perfusion.

Whilst FAIR and IVIM do not measure tissue perfusion in the classical sense (because arterial ^{1}H spins are not exclusively intravascular; and their longitudinal magnetisation decays with T_1), the choice of post-labelling delay in the FAIR sequence (1.2 s) ensured that signal originated primarily from the tissue rather than the vascular compartment; and with sufficiently enough tagged magnetisation before the effects of T_1 nullified the label.

In the AGA group, perfusion assessed by both FAIR and IVIM was highest in the basal region followed by the placental and then the central regions. The results cannot be compared directly with previous studies that used different ROIs, although a previous study also reported that *f*(IVIM) was highest in the basal plate region [20]. The placental perfusion in our study was measured within the narrow gestational range of 24–29 weeks and was not significantly associated with maternal characteristics or with GA. This is in agreement with a previous longitudinal study, which used the FAIR sequence to examine singleton pregnancies at 20–40 weeks and reported that placental perfusion did not change with gestational age [18]. However two previous IVIM studies gave conflicting results: the first reported a decrease in *f*(IVIM) from 22–39 weeks' GA [19], but a subsequent study found no significant trend in basal plate *f*(IVIM) from 16–35 weeks' GA [21]. As the placenta grows, although the total flow to the uterus will increase, the flow per unit volume of the placenta, as measured by MRI, may stay relatively constant, since this will be optimised for maximum rate of transport across the villi.

Perfusion(FAIR) was lower in the SGA than the AGA group and this difference was most marked in the basal plate, for pregnancies that did, and did not, have low estimated fetal weight at the time of the MRI. A previous study found placental perfusion(FAIR) at 20–42 weeks in six women who delivered SGA neonates was not significantly different from 22 who delivered AGA neonates [16], but that study used a small sample size and low field (0.5 T) MRI scanner which would have produced images with a lower SNR.

f(IVIM) was also lower in the SGA group than the AGA group for all three ROIs, and particularly the placental region, in pregnancies that did, and did not, have low estimated fetal weight at the time of the MRI scan. A previous small study reported an apparent redistribution in *f*(IVIM) from the outer (maternal) part to the inner (fetal) part of the placenta in SGA [20].

IVIM was better than FAIR in demonstrating reduced placental perfusion in pregnancies that delivered SGA neonates, showing
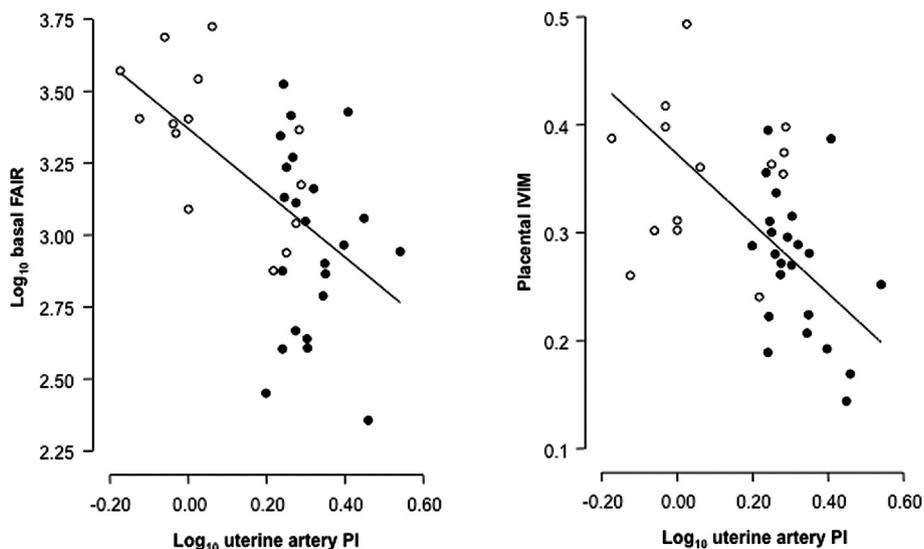
Fig. 6. Scatter plot demonstrating relationship of $\log_{10}$ basal FAIR and placental *f* IVIM measurements obtained by magnetic resonance with $\log_{10}$ uterine artery pulsatility index in appropriate for gestational age (open circles) and small for gestational age neonates (closed circles).

reduced perfusion in all three ROIs. FAIR only showed reduced perfusion in the basal region, although this reduction was more significant for FAIR than IVIM. FAIR and IVIM could not separate the AGA and SGA fetuses as well as uterine artery PI, but MR can assess heterogeneity of placental perfusion which may provide complimentary information to uterine artery PI for the assessment of the compromised placenta.

The main limitations of these techniques are the effects of fetal and maternal movement and maternal respiration. Structural images were acquired before perfusion images, since fetuses tended to move less as they grew accustomed to the noise of the scanner. Maternal respiratory movement affected anterior more than posterior placentae. Artefacts related to bulk motion were more evident in the IVIM data, possibly because all non-linear molecular displacements are encoded by the magnetic field gradients, and because the FAIR sequence averages 25 pairs of images. The basal plate ROI was most susceptible to movement between scans (the central ROI least). Occasionally, the exact location of the basal plate was difficult to determine, either due to placental location, or movement during the acquisition. In these situations, it was drawn using the T_2-weighted spin echo scan and individual FAIR and IVIM images.

All the measurements were made by the same observer, who was not blinded to the study groups, but the measurements were made prospectively so that pregnancy outcome was not known. Future work should measure inter-observer repeatability and reproducibility.

The FAIR ASL scheme was chosen since labelling is performed on blood in the placenta, without having to locate the feeding artery. Since movement of blood in the IVS is not restricted to a vascular bed, FAIR will be sensitive to blood flowing into the slice from both directions, which may include blood flowing out of other slices back towards the draining veins, overestimating placental perfusion. However this is unlikely to affect the relative differences in perfusion weighted signals found here. We computed the perfusion weighted signal rather than fully quantifying perfusion, since quantification requires an estimate of the placental T_1, which would not be feasible (due to time constraints) on a subject by subject basis. The IVIM f parameter depends on blood movement, and is not actually directly dependent on tissue perfusion. Thus although FAIR and IVIM measure blood movement in placenta in different ways, the two methods may give more similar information than in other tissue beds where blood is confined to a vascular bed. The model used for calculating the perfusion weighted FAIR signal was simpler and more robust to low SNR, than the multi-component fitting needed for IVIM, although it is possible that an 'IVIM weighted' image could be acquired at a single b-value. Despite the differences between the methods, the results from the two sequences are positively correlated in some of the ROIs.

IVIM was more sensitive to changes in placental perfusion than FAIR, but FAIR was better at detecting reduced perfusion at the basal plate. Since FAIR is quicker to acquire and analyse, gives better slice coverage, and is less susceptible to movement artefact, it is likely to be more practically useful clinically.

Relaxometry techniques are a powerful alternative to obtain information on placental function, but these methods do not encode the relative displacements of spins (during the time between diffusion encoding gradients in the case of IVIM; or during the post-labelling delay in the case of ASL); and therefore do not provide a **direct** estimate of diffusion coefficient or perfusion rate. We have previously studied the placental T_2 relaxation times in this cohort of subjects. Although we have not reported it in detail here, a strong correlation was observed between the transverse relaxation time and the IVIM and FAIR results. Other studies using blood oxygen level dependent imaging (BOLD) or diffusion weighted imaging (DWI) have also yielded valuable information about fetal and placental function, however, IVIM and FAIR offer the ability to obtain direct, quantitative estimates of fluid motion in this organ.

In conclusion, this study shows that non-invasive measurement of placental perfusion by MRI, during the second trimester of pregnancy, is lower in pregnancies that subsequently deliver SGA neonates and that the measurement is related to uterine artery PI. Therefore, the techniques are worthy of further investigation to determine their potential applicability in the clinical setting. Improvements in ASL methodology and scanning hardware may also potentially enhance the sensitivity and specificity of the technique. Our results suggest that the FAIR sequence may offer a more pragmatically suitable method for routine clinical application than IVIM. These results suggest that these methods may provide a non-invasive and sensitive assessment of the tissue perfusion properties. In light of these encouraging results, further studies are required to evaluate and refine these techniques so that their predictive value may, in the future, offer a useful complement to conventional uterine artery PI assessment in the clinical setting.

References

[1] Sheppard BL, Bonnar J. An ultrastructural study of utero-placental spiral arteries in hypertensive and normotensive pregnancy and fetal growth retardation. Br J Obstet Gynaecol 1981;88(7):695–705.
[2] Khong TY, De Wolf F, Robertson WB, Brosens I. Inadequate maternal vascular response to placentation in pregnancies complicated by pre-eclampsia and by small-for-gestational age infants. Br J Obstet Gynaecol 1986;93(10):1049–59.
[3] Pijnenborg R, Vercruysse L, Hanssens M. The uterine spiral arteries in human pregnancy: facts and controversies. Placenta 2006;27(9–10):939–58.
[4] Brosens I, Pijnenborg R, Vercruysse L, Romero R. The "Great Obstetrical Syndromes" are associated with disorders of deep placentation. Am J Obstet Gynecol 2011;204(3):193–201.
[5] Gosling RG, King DH. Continuous wave ultrasound as an alternative and complement to X-rays in vascular examination. In: Reneman RS, editor. Cardiovascular applications of ultrasound. Amsterdam: North Holland; 1974. p. 266–82. 1976.
[6] Papageorghiou AT, Yu CK, Bindra R, Pandis G, Nicolaides KH. Multicenter screening for pre-eclampsia and fetal growth restriction by transvaginal uterine artery Doppler at 23 weeks of gestation. Ultrasound Obstet Gynecol 2001;18(5):441–9.
[7] Papageorghiou AT, Yu CK, Nicolaides KH. The role of uterine artery Doppler in predicting adverse pregnancy outcome. Best Pract Res Clin Obstet Gynaecol 2004;18(3):383–96.
[8] Gudmundsson S, Dubiel M, Sladkevicius P. Placental morphologic and functional imaging in high-risk pregnancies. Semin Perinatol 2009;33(4):270–80.
[9] Lai PK, Wang YA, Welsh AW. Reproducibility of regional placental vascularity/perfusion measurement using 3D power Doppler. Ultrasound Obstet Gynecol 2010;36(2):202–9.
[10] Duncan KR, Sahota DS, Gowland PA, Moore R, Chang A, Baker PN, et al. Multilevel modeling of fetal and placental growth using echo-planar magnetic resonance imaging. J Soc Gynecol Investig 2001;8(5):285–90.
[11] Chen Q, Levine D. Fast fetal magnetic resonance imaging techniques. Top Magn Reson Imaging 2001;12(1):67–79.
[12] Mansfield P, Stehling MK, Ordidge RJ, Coxon R, Chapman B, Blamire A, et al. Echo planar imaging of the human fetus in utero at 0.5 T. Br J Radiol 1990;63(755): 833–41.

[13] Baker PN, Johnson IR, Harvey PR, Gowland PA, Mansfield P. A three-year follow-up of children imaged in utero with echo-planar magnetic resonance. Am J Obstet Gynecol 1994;170(1 Pt 1):32–3.

[14] Clements H, Duncan KR, Fielding K, Gowland PA, Johnson IR, Baker PN. Infants exposed to MRI in utero have a normal paediatric assessment at 9 months of age. Br J Radiol 2000;73(866):190–4.

[15] Myers C, Duncan KR, Gowland PA, Johnson IR, Baker PN. Failure to detect intrauterine growth restriction following in utero exposure to MRI. Br J Radiol 1998;71(845):549–51.

[16] Duncan KR, Gowland P, Francis S, Moore R, Baker PN, Johnson IR. The investigation of placental relaxation and estimation of placental perfusion using echo-planar magnetic resonance imaging. Placenta 1998;19(7): 539–43.

[17] Francis ST, Duncan KR, Moore RJ, Baker PN, Johnson IR, Gowland PA. Non-invasive mapping of placental perfusion. Lancet 1998;351(9113):1397–9.

[18] Gowland PA, Francis ST, Duncan KR, Freeman AJ, Issa B, Moore RJ, et al. In vivo perfusion measurements in the human placenta using echo planar imaging at 0.5 T. Magn Reson Med 1998;40(3):467–73.

[19] Moore RJ, Issa B, Tokarczuk P, Duncan KR, Boulby P, Baker PN, et al. In vivo intravoxel incoherent motion measurements in the human placenta using echo-planar imaging at 0.5 T. Magn Reson Med 2000;43(2):295–302.

[20] Moore RJ, Strachan BK, Tyler DJ, Duncan KR, Baker PN, Worthington BS, et al. In utero perfusing fraction maps in normal and growth restricted pregnancy measured using IVIM echo-planar MRI. Placenta 2000;21(7): 726–32.

[21] Moore RJ, Ong SS, Tyler DJ, Duckett R, Baker PN, Dunn WR, et al. Spiral artery blood volume in normal pregnancies and those compromised by pre-eclampsia. NMR Biomed 2008;21(4):376–80.

[22] Kwong KK, Chesler DA, Weisskoff RM, Donahue KM, Davis TL, Ostergaard L, et al. MR perfusion studies with T1-weighted echo planar imaging. Magn Reson Med 1995;34(6):878–87.

[23] Williams DS, Detre JA, Leigh JS, Koretsky AP. Magnetic resonance imaging of perfusion using spin inversion of arterial water. Proc Natl Acad Sci U S A 1992;89(1):212–6.

[24] Detre JA, Leigh JS, Williams DS, Koretsky AP. Perfusion imaging. Magn Reson Med 1992;23(1):37–45.

[25] Le Bihan D, Moonen CT, van Zijl PC, Pekar J, DesPres D. Measuring random microscopic motion of water in tissues with MR imaging: a cat brain study. J Comput Assist Tomogr 1991;15(1):19–25.

[26] Derwig I, Barker GJ, Poon L, Zelaya F, Gowland P, Lythgoe DJ, et al. Association of placental T2 relaxation times and uterine artery Doppler ultrasound measures of placental blood flow. Placenta 2013;34(6):474–9.

[27] Hadlock FP, Harrist RB, Sharman RS, Deter RL, Park SK. Estimation of fetal weight with the use of head, body, and femur measurements – a prospective study. Am J Obstet Gynecol 1985;151(3):333–7.

[28] Gardosi J, Francis A. Software program for the calculation of customised birth weight percentiles. Version 5.15_UK; 2008.

[29] Brown MA, Lindheimer MD, de Swiet M, Van Assche A, Moutquin JM. The classification and diagnosis of the hypertensive disorders of pregnancy: statement from the International Society for the Study of Hypertension in Pregnancy (ISSHP). Hypertens Pregnancy 2001;20(1):IX–XIV.

[30] http://www.gnu.org/software/gsl/.

[31] Plummer DL. Dispimage: a display and analysis tool for medical images. Riv Neuroradiol 1992;5:489–95.

[32] Altman DG, Bland JM. Measurement in medicine: the analysis of method comparison studies. Statistician 1983;32:307–17.