MR Imaging Measurements of Altered Placental Oxygenation in Pregnancies Complicated by Fetal Growth Restriction

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Purpose:
To evaluate oxygen-enhanced and blood oxygen level–dependent (BOLD) magnetic resonance (MR) imaging parameters in normal pregnancies and those complicated by fetal growth restriction (FGR).

Materials and Methods:
This case-control study was approved by the local research ethics committee. Informed consent was obtained from all subjects. From October 2010 to October 2015, 28 women with uncomplicated pregnancies (individualized birthweight ratio [IBR] >20th percentile and delivery >37 weeks) and 23 with pregnancies complicated by FGR (IBR <5th percentile and abnormal Doppler ultrasonography [US] studies) underwent MR imaging. Differences in placental longitudinal R1 (1/T1) and transverse R2* (1/T2*) were quantified, with subjects breathing either air or oxygen. The difference in R1 (ΔR1) after hyperoxia was converted to change in partial pressure of oxygen (ΔP02).

Results:
The mean baseline R1 and R2* for normal pregnancies (R1: 0.59 sec⁻¹, 95% confidence interval [CI]: 0.58 sec⁻¹, 0.60 sec⁻¹; R2*: 17 sec⁻¹, 95% CI: 14 sec⁻¹, 20 sec⁻¹) were significantly different from those of pregnancies complicated by FGR (R1: 0.63 sec⁻¹, 95% CI: 0.62 sec⁻¹, 0.65 sec⁻¹; R2*: 26 sec⁻¹, 95% CI: 22 sec⁻¹, 32 sec⁻¹) (P < .0001). The ΔR1 showed a significant negative association with gestational age (P < .0001) in the combined cohort, with the FGR group having a ΔR1 that was generally 61.5% lower than that in the normal pregnancy group (P = .003). The area under the receiver operating characteristic curve for the differentiation between pregnancy complicated by FGR and normal pregnancy by using ΔP02, baseline R1, and baseline R2* was 0.91 (95% CI: 0.82, 0.99).

Conclusion:
R1, R2*, and ΔP02 were significantly different between normal pregnancies and those complicated by severe FGR. MR imaging parameters have the potential to help identify placental dysfunction associated with FGR and may have clinical utility in correctly identifying FGR among fetuses that are small for gestational age. A larger prospective study is needed to assess the incremental benefit beyond that offered by US.

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Fetal growth restriction (FGR) leads to increased neonatal morbidity and mortality and increased risk of adult disease (1–3). FGR is strongly associated with low fetal weight, but fetal weight alone is insufficiently sensitive or specific to identify all cases (4).

FGR is associated with placental peripheral hypovascularity and increased vascular resistance (5–8), which lead to uteroplacental hypoxia; accurate measurement of this placental dysfunction could potentially identify FGR independently of fetal size. Invasive measurements of placental partial oxygen pressure (P\textsubscript{O\textsubscript{2}}) have been reported (9–11) but are not possible in routine clinical practice. Blood oxygenation level–dependent (BOLD) and oxygen-enhanced magnetic resonance (MR) imaging offer alternative noninvasive ways to assess placental oxygenation (12,13).

In BOLD MR imaging, changes in paramagnetic deoxyhemoglobin concentration cause changes in transverse R\textsubscript{2*} (1/T2*) through the formation of field gradients inside the imaging voxel. Decreases in R\textsubscript{2*} with maternal hyperoxia, consistent with a reduction in placental deoxyhemoglobin concentration, have been previously demonstrated, suggesting increased placental blood oxygen saturation (12,13). Hyperoxia also increases levels of paramagnetic dissolved oxygen, and water protons in close proximity to each other experience short-range dipolar interactions, which in turn increase R\textsubscript{1} (1/T1) (oxygen-enhanced MR imaging). In contrast, the heme group, which is responsible for the paramagnetic changes in BOLD imaging, is within a large deoxyhemoglobin molecule; the lack of proximity of the heme to water protons diminishes the effect of saturation changes on R\textsubscript{1}. Increases in R\textsubscript{1} are therefore related to increases in P\textsubscript{O\textsubscript{2}}. We have demonstrated that oxygen-enhanced MR imaging is sensitive to changes in placental P\textsubscript{O\textsubscript{2}} in normal pregnancies (13). Furthermore, we observed a negative correlation between the change in R\textsubscript{1} (\Delta R\textsubscript{1}) after hyperoxia and gestational age (13). The change in P\textsubscript{O\textsubscript{2}} (\Delta P\textsubscript{O\textsubscript{2}}) is expected to vary linearly with \Delta R\textsubscript{1}, and although placental O\textsubscript{2} longitudinal relaxivity is unknown, an estimate of the change in placental P\textsubscript{O\textsubscript{2}} may be obtained by using a relaxivity value previously measured in water (14). The use of short-term hyperoxia poses no health risks to the mother or fetus. There is no significant change in maternal heart rate or mean arterial pressure (15,16) in the otherwise healthy mother owing to existing highly saturated hemoglobin. In the fetus, hyperoxia increases fetal movements (17) but does not change brain oxygenation, which is suggestive of a reversed brain-sparing mechanism (12).

The aim of this study was to determine the potential utility of placental BOLD and oxygen-enhanced MR imaging in a comparison of normal pregnancies and those complicated by FGR.

### Advances in Knowledge
- There was a negative correlation in the change in R\textsubscript{1} (\Delta R\textsubscript{1}) with hyperoxia with gestational age in normal pregnancies and those complicated by fetal growth restriction (FGR) (r\textsuperscript{2} = 0.3).
- The \Delta R\textsubscript{1} in pregnancies complicated by FGR is significantly lower than that in normal pregnancies (P = .003), reflecting relative placental hypoxia.
- The \Delta R\textsubscript{1} and values of longitudinal relaxivity of oxygen can be applied to estimate the change in partial pressure of oxygen within the placenta after hyperoxia.

### Materials and Methods
This study was approved by a regional ethics committee (REC:09/H1013/77 and 14/NW/0195), and written informed consent was obtained from each of 65 subjects between October 2010 and October 2015 (gestational age, 20 weeks + 5 days to 37 weeks + 5 days, by means of a dating ultrasonographic [US] scan). Data were acquired prospectively, with retrospective interpretation. Women were recruited from routine antenatal clinics or from specialized high-risk clinics according to their risk of FGR. Low-risk pregnancies were defined as those without risk factors or antenatal suspicion for FGR and with normal uterine and umbilical artery Doppler US studies. High-risk pregnancies were defined as those with risk factors for FGR (previous infant with individualized birthweight ratio [IBR] <10th percentile with Gestation-related Optimal Weight [Perinatal Institute, Birmingham, England] (18) or abnormal maternal serum markers) or an antenatal suspicion for FGR and abnormal uterine or umbilical artery Doppler US studies. Each subject underwent a single 1.5-T MR examination.

### Implications for Patient Care
- Identification of infants with true FGR from those who are small for gestational age could reduce unnecessary anxiety, tailor antenatal surveillance, and reduce medical intervention.
- A diagnostic model that uses MR imaging markers may provide additional phenotyping information for the diagnosis and treatment of early onset FGR in high-risk pregnancies.
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A whole-body coil was used for transmission and reception. Baseline R1 and R2* maps were acquired while subjects breathed medical-grade air. This was followed by a dynamic R1-weighted sequence during which the inspired gases were switched to 100% oxygen (13). The ΔR1 for each image in the sequence was calculated from the signal intensity change between the dynamic sequence and the baseline R1 map, enabling confirmation that ΔR1 coincided with a change of inspired gases.

Using T2-weighted half-Fourier rapid acquisition with relaxation enhancement (repetition time = 1200 msec, echo time = 86 msec, partial Fourier factor = 0.6) for the assessment of placental position (Fig 1). Data were subsequently acquired in a single section, transverse through the body at the level of the uterus and perpendicular to the placenta at the level of the cord insertion (Fig 2). Structural, R1, and R2* acquisition sequences had a field of view of 450 × 450 mm, matrix size of 128 × 128, and in-plane resolution of 3.52 × 3.52 mm. A whole-body coil was used for transmission and reception.

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Structural images were acquired in multiple 10-mm-thick sections by
Data for R1 mapping were acquired by using a respiratory-triggered inversion-recovery turbo spin-echo sequence with four inversion times of 50, 300, 1100, and 2000 msec and a turbo spin-echo sequence without an inversion pulse to measure the fully relaxed signal (20). For all sequences, the minimum repetition time was the inversion time plus 8000 msec (repetition time was variable owing to respiratory triggering) and the echo time was 5.4 msec. Each inversion time image was acquired twice to provide a higher signal-to-noise ratio. The acquisition time was approximately 3 minutes.

R2* mapping data were acquired by using a single-shot breath-hold multiple gradient-recalled-echo sequence with 10 echo times of equal spacing (echo time = 5–50 msec) and a flip angle of 40°. Each acquisition lasted 8 seconds.

Dynamic T1-weighted data were acquired by repeating the respiratory-triggered inversion-recovery turbo spin-echo sequence at an inversion time of 1400 msec for 40 time points at a temporal resolution of approximately 12 seconds, resulting in a sequence duration of approximately 8 minutes. The gas supply was switched from air to oxygen at the 10th time point. Equilibration of R1 measures occurred over approximately 10 minutes after changing to 100% oxygen, with the duration dependent on maternal respiratory rate, before calculation of R1 from the last 15 dynamics.

Image analysis was performed by using software (MATLAB R2012b; MathWorks, Natick, Mass). R2* maps and a baseline R1 map were fitted on a voxel-by-voxel basis from an ROI for each subject. ROIs were drawn from the co-localized structural image by selecting the largest contiguous region of placental tissue possible. This ROI was then superimposed onto every inversion time and echo time in every R1 and R2* map and adjusted to remove any nonplacental tissue introduced as a result of fetal and maternal motion (Figs 2, 3). Baseline R1 and R2* were calculated as the mean values across the ROI on the baseline map. The mean ΔR1 across the ROI was calculated for each time point in the dynamic series, and the overall mean ΔR1 was calculated as the mean of the last 15 time points during oxygen breathing. The ΔR1 was multiplied by a value for the longitudinal relaxivity of O₂ in water of 2.49 × 10⁻⁴ sec/mm Hg (21) to determine the value as a change in placental Po₂ (ΔPo₂) to aid in the clinical interpretation. The change in R2* (ΔR2*) was calculated by subtracting the mean R2* on the baseline map from that on the map acquired after the dynamic under-oxygen breathing.

Differences in pregnancy characteristics were assessed by using the Mann-Whitney U test. Differences in imaging parameters between groups were investigated with unpaired t tests for baseline R1, baseline R2*, and ΔR1 after confirmation of normal distribution (D’Agostino-Pearson normality test). The ΔR2* was investigated by using nonparametric tests owing to a positively skewed distribution. The effect of gestational age on parameters was investigated by using linear regression, with incorporation of FGR as an interaction term. Discriminatory models for the detection of FGR with use of ΔPo₂ (adjusted for gestation), in combination with the baseline R1 and R2*, were developed by using logistic regression. Model fit was compared by using likelihood ratio testing. All statistical analyses were conducted with software (Stata 13.0; StataCorp, College Station, Tex). A formal sample size calculation was not conducted, as no prior data were available. P < .05 was indicative of a statistically significant difference.

Results

A summary of the demographic characteristics of the study population is provided in the Table. There was no significant difference in gestational age at imaging between subjects with normal pregnancy and those with pregnancy complicated by FGR (P = .42).

Baseline Differences

The mean baseline R1 was 0.59 sec⁻¹ (95% confidence interval [CI]: 0.58 sec⁻¹, 0.60 sec⁻¹) in subjects with normal pregnancy and 0.63 sec⁻¹ (95% CI: 0.62 sec⁻¹, 0.65 sec⁻¹) in those with...
pregnancy complicated by FGR ($P < .0001$) (Fig 4). The mean baseline $R2^*$ was significantly lower in subjects with normal pregnancy ($17$ sec$^{-1}$ [95% CI: 14 sec$^{-1}$, 20 sec$^{-1}$]) than in those with pregnancy complicated by FGR ($26$ sec$^{-1}$ [95% CI: 22 sec$^{-1}$, 32 sec$^{-1}$]) ($P < .0001$) (Fig 4). There was no correlation between either baseline $R1$ ($P = .82$, $r^2 = 0.03$) or baseline $R2^*$ ($P = .09$, $r^2 = 0.24$) and gestational age.

**Dynamic Change**

Overall, 44 of the 51 subjects had a positive response to hyperoxia, as demonstrated by an increase in $R1$ in the mean $R1$ between subjects with normal pregnancy and those with pregnancy complicated by FGR (0.0204 sec$^{-1}$ [95% CI: 0.015 sec$^{-1}$, 0.026 sec$^{-1}$] and 0.0092 sec$^{-1}$ [95% CI: 0.0042 sec$^{-1}$, 0.014 sec$^{-1}$], respectively; $P = .0028$). There was no significant difference in the median $ΔR2^*$ between the two groups ($−1.3$ sec$^{-1}$ [95% CI: −3.0 sec$^{-1}$, 1.0 sec$^{-1}$] and $−3.0$ sec$^{-1}$ [95% CI: −4.6 sec$^{-1}$, 1.4 sec$^{-1}$], respectively; $P = .06$) (Fig 4).

A negative correlation was seen between $ΔR1$ and gestational age, with a mean decrease in $ΔR1$ of 0.002 sec$^{-1}$ per week ($P < .0001$, $r^2 = 0.39$) for the whole cohort. Pregnancy outcome (FGR or normal weight) was included in an analysis of covariance model as an interaction term to determine whether the effect of gestational age differed between the two groups ($P = .071$). The regression equation for the group with normal pregnancies was as follows:

$$DΔR1 = 0.094 \times (95\% \text{ CI: 0.063, 0.124}) + 0.0027 \times \text{gestational age} (95\% \text{ CI: −0.0038, 0.0016}).$$

The $ΔR1$ in the FGR group was, on average, 0.009 sec$^{-1}$ lower than that in the group with normal pregnancy at any given time ($P = .003$) (Fig 5), with a regression equation as follows:

$$DΔR1 = 0.039 \times (95\% \text{ CI: −0.002, 0.081}) + 0.00106 \times \text{gestational age} (95\% \text{ CI: −0.0025, 0.00039}).$$

There was no correlation between $ΔR2^*$ and gestational age ($P = .72$, $r^2 = 0.05$).

**Development of Predictive Model of FGR**

The odds ratio for the identification of FGR was 2.9 (95% CI: 1.34, 6.25) for every 30 mm Hg reduction in $ΔPo2$ ($P = .007$). The area under the receiver operator characteristic curve for the identification of FGR with use of $ΔPo2$ alone (corrected for gestational age) was 0.76 (95% CI: 0.61, 0.88) (Fig 6).

The performance of binary logistic regression models combining $ΔPo2$ with other biologic markers with significant group differences, such as baseline $R1$ and $R2^*$, is illustrated in Figure 6. There was a significant difference between model 1 and models 2 ($χ^2 = 0.041$) and 3 ($χ^2 = 0.040$). There was no statistically significant difference between the models incorporating $R1$ or $R2^*$ and the model that included both baseline measures of $R1$ and $R2^*$ (model 4) ($χ^2 = 0.21$). Measures of $R1$ and $R2^*$ were not directly related and contributed independently to model 4 (interaction term $P = .39$). The sensitivity and specificity of model 4 in the identification of FGR were 65% and 96%, respectively, with use of a probability cutoff of 0.65.

**Discussion**

In this study, we compared changes at oxygen-enhanced and BOLD MR imaging in closely phenotyped normal and FGR pregnancies, demonstrating the potential clinical utility of functional placental MR imaging for differentiating fetuses of normal weight from those that are pathologically small for gestational age.

The $ΔR1$ with hyperoxia showed a negative correlation with gestational age in normal pregnancy, as previously described (13), but were also observed in FGR. A decrease in placental hemoglobin saturation has been previously demonstrated (9,11); therefore, during hyperoxia more of the additional oxygen may become bound to hemoglobin, reducing the dissolved oxygen fraction and, hence, $ΔR1$. In FGR, $ΔR1$ was significantly reduced. The difference in $ΔR1$ between normal pregnancies and those complicated by FGR implies that baseline placental hemoglobin saturation in the FGR group is lower than that in the normal pregnancy group, reflecting relative hypoxia. More of the supplied oxygen is required to initially saturate placental deoxyhemoglobin, leading to less surplus dissolved oxygen and, therefore, a diminished $ΔR1$.

Baseline $R2^*$ was significantly different between FGR and normal placentas, which is also consistent with a lower blood oxygen saturation in FGR and the theory of a relatively hypoxic placenta. A lower $T2^*$ has previously been demonstrated in other studies of
FGR pregnancies with abnormal uterine and umbilical Doppler US studies (22,23). However, T2* may also be substantially affected by increased necrosis, fibrosis, and infarction within these FGR placentas (22). T2* is sensitive to variations in magnetic field strength caused by many factors in addition to blood oxygen saturation, including blood vessel size and density and tissue structure and composition, and may therefore not be specific to oxygenation. It is possible that the difference in R2* between groups may be dominated by these placental structural differences associated with FGR, rather than saturation. However, because we did not examine the placentas after delivery, we were unable to verify structural differences between the groups. The response to hyperoxia (ΔR2*) was not significantly different in FGR compared with normal pregnancies. This does not necessarily imply a similar baseline blood oxygen saturation. Because of the nonlinearity of the oxygen-hemoglobin dissociation curve, changes in R1 are expected to be dominated by near-saturated blood, that is, maternal arterial blood, whereas changes in R2* will be dominated by less-saturated blood, which includes both maternal venous blood as well as fetal blood, owing to the lower saturation of fetal blood for the same Po2. As a consequence, the contribution of fetal blood to the overall changes in R2* may be greater than its relative volume. Because the R2* was measured at two discrete time points (breathing air, breathing oxygen), rather than dynamically, it may also be the case that the measurement is not sufficiently sensitive to detect a difference in ΔR2*.

In this study, significant differences in baseline R1 and R2* in FGR, in combination with dynamic measurements (under hyperoxia), could be useful as a marker of placental function. Although ΔPo2 after hyperoxia can be derived from ΔR1, baseline measures of Po2 within the placenta are not possible with oxygen-enhanced MR imaging techniques. In addition, the relaxivity...
Inclusion of gestational age as a covariate in the diagnostic models developed in this study reduced the effect of gestational age within the model. However, it is unclear if any threshold can be used to differentiate between groups given the wide variation seen.

The use of respiratory triggering and end-expiratory breath holds for the assessment of R1 and R2*, respectively, meant that there was little effect of maternal motion despite a long imaging time. Only one subject had to be excluded owing to maternal motion. Adjustments in the ROI were necessary owing to small maternal and fetal movements that resulted in an ROI that was smaller than the whole placenta.

This study has several limitations. Early onset, severe FGR is a rare condition and, to fully assess the performance of any biomarker, a larger number of pregnancies must be assessed. Given that the logistic regression models in this study have been developed from a case-control study, there will inevitably be an element of overfitting owing to the small number of observations and the very substantial clinical differences between the groups. Furthermore, in this study the FGR group included only severe early onset cases with abnormal Doppler US examinations that were identifiable by using US; thus, the incremental benefit of MR measurements in differentiating those fetuses where growth restriction is suspected (eg, with reduced growth velocity) from normal fetuses has not yet been proven. The preliminary findings in this study will need to be used in a larger prospective study to demonstrate incremental benefit beyond that available with US.

In summary, in this study we demonstrated the ability of BOLD and oxygen-enhanced MR imaging to differentiate between placentas in normal pregnancies and those complicated by FGR. The significant differences observed in baseline R2* are related to placental structure. If changes in R2 are comparable to those observed with R2*, this would support the R1 and R2* changes reflect structural changes. There was a strong negative correlation between gestational age and ΔR1 in our data set. This effect was more pronounced in the normal cohort, with a larger response at earlier gestations; however, the interaction between gestational age and FGR status did not achieve statistical significance (P = .071).
Disclosures of Conflicts of Interest: E.I. disclosed no relevant relationships. D.M. disclosed no relevant relationships. J.N. disclosed no relevant relationships. E.J. disclosed no relevant relationships.

References


