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Aughwane, R, Mufti, N, Flouri, D et al. (11 more authors) (2021) MRI Measurement of Placental Perfusion and Oxygen Saturation in Early Onset Fetal Growth Restriction. BJOG: An International Journal of Obstetrics & Gynaecology, 128 (2). pp. 337-345. ISSN 1470-0328

https://doi.org/10.1111/1471-0528.16387

MRI Measurement of Placental Perfusion and Oxygen Saturation in Early Onset Fetal Growth Restriction

Running Title: MRI of feto-placental oxygen level in FGR

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Abstract

Objective: We hypothesized that a multi-compartment MRI technique that is sensitive to fetal blood oxygenation would identify changes in placental blood volume and fetal blood oxygenation in pregnancies complicated by early-onset Fetal Growth Restriction (FGR).

Design: Case-Control study

Setting: London, UK

Population: Women with uncomplicated pregnancies (estimated fetal weight, EFW>10th centile for gestational age, GA and normal maternal and fetal Doppler ultrasound, n=12) or early-onset FGR (EFW<3rd centile with or without abnormal Doppler US<32 weeks GA, n=12) were studied.

Methods: All women underwent MRI examination. Using a multi-compartment MRI technique, we quantified fetal and maternal blood volume and feto-placental blood oxygenation.

Main Outcome Measures: Disease severity was stratified according to Doppler pulsatility index and the relationship to the MRI parameters investigated, including the influence of gestational age at scan.

Results: The FGR group (mean GA:27+5wks, range:24+2 to 33+6wks) had a significantly lower estimated fetal weight compared to the control group (mean GA:29+1wks) (-705g 95%CI=(-353, -1057g)). MR-derived feto-placental oxygen saturation was higher in controls compared to FGR (75 (±9.6)% vs 56 (±16.2)%, p=0.02, 95%CI=(7.8-30.3)%). Feto-placental oxygen saturation estimation correlated strongly with gestational age at scan in controls (r=-0.83)

Conclusion: Using a novel multimodal MRI protocol we demonstrated reduced feto-placental blood oxygen saturation in pregnancies complicated by early-onset FGR. The degree of abnormality correlated with disease severity defined by ultrasound Doppler findings. Gestational age dependent changes in oxygen saturation were also present in normal pregnancies.

Funding: Wellcome Trust (210182/Z/18/Z;WT101957;203148/Z/16/Z), EPSRC (NS/A000027/1;NS/A000049/1), Radiological Research Trust.

Keywords: Placenta,Fetal Growth Restriction,Relaxometry,Oxygenation,Pregnancy

Twitter Abstract: MRI reveals differences in feto-placental oxygen saturation between normal and FGR pregnancy that is associated with disease severity.

Introduction

Placental insufficiency, where the placenta cannot sufficiently supply the oxygen and nutritional demands of the growing fetus, is the most common cause of antenatal stillbirth in developed countries(1,2), and is associated with lifelong consequences(3,4). Placental development and function are difficult to measure. In clinical practice, indirect placental function is inferred via fetal growth and fetal Doppler ultrasound (US), looking for evidence of circulatory redistribution secondary to chronic hypoxia.

Placental insufficiency results in fetal (or intrauterine) growth restriction (FGR). According to a Delphi consensus(5), FGR is diagnosed when a fetus is small for gestational age, has a small abdominal circumference (AC) or an abnormal growth trajectory, with or without abnormal placental and fetal Doppler blood flow(6,7); early onset FGR is defined as being identified before 32 weeks of gestation. It is often challenging to differentiate between the small healthy fetus and those with FGR as tests based on maternal predictors(8–10) are so far insufficiently sensitive.

Poor placental development associated with inadequate spiral artery remodeling in early pregnancy is believed to be the underlying causative pathology of early-onset FGR(11). Chronic hypoxia is a critical feature (12,13), and understanding this pathophysiology is key to timely diagnosis and management of FGR(12,14–16). Measurement of fetal oxygen saturation or oxygen exchange may be useful in optimising diagnosis and management of affected pregnancies, to allow estimation of timing of placental failure, and to determine the effectiveness of potential treatments on chronic hypoxia.

Using Magnetic Resonance Imaging (MRI), the entire placenta can be imaged at any gestational age. The placenta is often smaller in FGR compared to controls(17). Several studies have conducted Diffusion Weighted Imaging (DWI) of the growth-restricted placenta(18–22). In the placenta T2 and T2* relaxation time decrease with increasing gestation(23,24) and are significantly reduced in placentas from FGR pregnancies(25,26). In T1-weighted Oxygen-Enhanced (OE) MRI(25) the absolute signal is significantly lower in FGR pregnancies. The exact physiologic alterations that are assessed by placental MRI are not yet well established; there are likely to be distinct flow compartments from the fetal capillaries, trophoblast space and maternal blood pool which have separate MR diffusion and relaxation properties. By applying a multi-compartment model of placental tissue it may be possible to disentangle the signal from each compartment.

105 The aim of this study was to apply such multi-compartment MRI to a cohort of
106 pregnancies complicated by early onset FGR.

107 **Materials and Methods**

108 *Data*

109 The study was approved by the UK National Research Ethics Service and all participants
110 gave written informed consent (London - Hampstead Research Ethics Committee, REC
111 reference 15/LO/1488). Women beyond 24 weeks' gestational age (confirmed by dating
112 scan) with uncomplicated pregnancies and consecutive cases where early-onset FGR
113 was diagnosed were invited to participate. Early onset FGR was defined here according
114 to a Delphi consensus, as an estimated fetal weight (EFW) <10th centile (using the
115 Hadlock equation(27) to estimate fetal weight, and Hadlock centile charts with no
116 customisation(27)), with uterine or umbilical artery Doppler pulsatility index (PI)>95th
117 centile[34], or EFW<3rd centile with or without Doppler USS abnormality before 32 weeks
118 gestational age (28,29). Our control group was defined as women whose fetus had an
119 estimated fetal weight greater than 10th centile. Pregnancies complicated with fetal
120 structural anomalies, aneuploidy or maternal virus infections (cytomegalovirus,
121 toxoplasma, rubella, HIV) were excluded. Women attending anatomy USS in the main
122 obstetric US department were invited to form our control cohort. Pregnant women with
123 maternal medical complications other than pre-eclampsia were also excluded. All women
124 (FGR and control) underwent a detailed ultrasound assessment of fetal structure, size,
125 maternal (UtA) and fetal (UA, Middle Cerebral Artery (MCA), and Ductus Venosus in
126 FGR cases) close to the time of MR imaging (KM/RA) (22/24 subjects had an MRI within
127 3 days of the corresponding ultrasound, the last two within one week). Pre-eclampsia
128 was defined as persistently raised maternal blood pressure of 140/90mmHg with
129 significant proteinuria (spot urinary protein to creatinine ratio$\geq$0.3). Women continued
130 under routine clinical care and were delivered as clinically indicated. Pregnancies were
131 followed up at birth to record birthweight and gestational age at delivery. Placental
132 histological analysis was performed for all cases of FGR using the Amsterdam Placental
133 Workshop Group Consensus Statement for processing and reporting(30).

134 *Patient Involvement*

We involved our Wellcome Trust supported Public and Patient Advisory Group from the beginning of our study to inform our ethics applications, ascertain the broad acceptability of MRI imaging and guide patient and volunteer recruitment.

MRI

MR Imaging was performed in unsedated women placed in left lateral tilt to prevent aorto-caval compression. Imaging was performed in 3D on 1.5T Siemens Avanto, at 7 diffusion-weighting b-values (**b**) (0, 50, 100, 150, 200, 400, 600$s.mm^{-2}$) and ten echo times (**t**) (81, 90, 96, 120, 150, 180, 210, 240, 270, 300ms). All echo times were acquired at b-value 0, to allow T2 fitting, and all b-values at **t**=$96ms$. In addition, data was acquired at b-value 50 and 200 for **t**=(81, 90, 120, 150, 180, 210, 240)ms. Voxel resolution was 1.9x1.9x6mm with full placental coverage (26 slices). To minimise the effect of motion we first used an in-house non-rigid registration routine to align all volumes(31).

DECIDE is a multicompartment placental-specific MRI model(32). The model combines the T2 relaxometry and diffusion-weighting data above to separate and quantify signals relating to fetal and maternal placental perfusion based upon differences in their respective diffusivity and relaxation (Appendix S1). Intracapillary fetal blood has high pseudo-diffusivity, d^*, and long T2 relaxation time, $T_2^{fb} = 1/R_2^{fb}$ and volume fraction f. Maternal blood with volume fraction v, is in the intervillous space, as opposed to intravascular, and therefore has lower apparent diffusivity d, and slow relaxation R_2^{mb}. Finally, the remaining signal from the tissue has low apparent diffusivity d, and rapid relaxation, R_2^{ts}, associated with dense tissue (see Figure 1). The model has previously been described and applied to a small cohort of normal pregnancies(32). The DECIDE model was applied for voxel-wise fit of fetal (f) and maternal (v) perfusion, and feto-placental blood T2 relaxation, was converted into blood saturation(33) (MATLAB R2016b).

This model provides a mechanism to estimate feto-placental blood oxygen saturation(34). Given the estimated feto-placental T2, we can convert this to oxygen saturation values using data previously reported(32). Feto-placental oxygen saturation values are estimated by curve fitting to these previously published results (Appendix S1).

Statistics

Data is shown as mean ± standard deviation. Regions of interest (ROI) were manually defined as pure-placental regions within the boundary of the placenta tissue and average parameters found. Masks were drawn manually over the area of interest (RA) in the registered multiple slices of the 2D stack (itk-SNAP Version 3.2.0, 2014). Statistical analysis was performed with independent Student t-test. Where medians and interquartile ranges (IQR) are reported a Mann Whitney U-test is used to determine significance. The FGR cohort was sub-grouped *a priori* based on the ultrasound findings at the time of the MRI scan: 1) FGR with uterine and umbilical artery Doppler PI >95th centile (abnormal uterine and umbilical Doppler FGR); 2) FGR with uterine artery Doppler >95th centile and umbilical artery Doppler <95th centile (abnormal uterine Doppler FGR); 3) FGR with umbilical and uterine Doppler <95th centile (normal uterine and umbilical Doppler FGR).

MRI parameter comparison between groups was done using Kruskal Wallis testing to account for the low number of samples, with post hoc analysis correcting for the multiple comparisons using Tukey Kramer correction. We also investigate if any trends exist within the groups by gestational age at scan or birth. Correlations were calculated using Pearson Correlation. Significance was set at a threshold of $p<0.05$.

Histograms of regional placental function In addition to means and standard deviation, we present histogram-driven results as a function of each whole region of interest. This approach avoids the influence of artefacts from amniotic fluid or myometrium and from residual motion. Specifically, we report the inverse of the placental cumulative histogram of feto-placental oxygen saturation which describes a measure of the fraction of placental tissue above any given oxygen saturation threshold; this is conceptually similar to a continuous ROC curve. We investigate the effect of varying this threshold and find the maximal group separation using a leave-one-out analysis, finding how the maximal separation varies leaving out each subject in turn. This is a post hoc parameter related to the MRI apparent total placental function.

Results

Twelve women were recruited to each group (Table S1) based on effect sizes seen in previous studies (23,25) . All FGR cases had an estimated fetal weight <3rd centile(35) (Median FGR 681g (IQR:297g) vs median control 1358g (IQR:428g), p=0.001). There

was no difference between groups by mean gestational age at scan (control=29+1weeks+days, FGR=27+4weeks+days p=0.15). At the time of MR imaging of the 12 FGR cases, 4 had uterine artery Doppler PI >95th centile with umbilical artery Doppler PI >95th centile, 4 had uterine artery Doppler PI >95th centile with umbilical artery Doppler PI <95th centile, and 4 had normal uterine and umbilical Doppler indices (PIs <95th centile). All women in the control group had normal range umbilical artery Doppler indices, one had uterine artery Doppler PI > 95th centile. Middle Cerebral Artery (MCA) Doppler values were not significantly different between groups. Ductus Venosus was positive in all FGR cases.

Two women in the FGR group had a diagnosis of pre-eclampsia. Both women had abnormal uterine artery Doppler indices at MR imaging; one also had an abnormal umbilical artery Doppler at the time of the MRI (26+1) and subsequently she suffered a stillbirth at 27+1 weeks of gestation. All women in the control group delivered at term.

Placental histological analysis showed evidence of maternal vascular malperfusion(36) in four out of the twelve FGR cases (both cases with pre-eclampsia, one case with umbilical and uterine artery Doppler PI > 95th centile, and one with normal Doppler indices); no pregnancies had evidence of chronic histiocytic intervillositis or chorioamnionitis.

MRI Differences between groups

For the MR derived parameters (Table S2), we found no difference in mean apparent diffusivity, *d*, (0.0017 (±0.0001) vs 0.0016 (±0.0002) mm^2s^{-1} control vs FGR, p=0.09), maternal perfusion fraction (0.39 (±0.12) vs 0.32 (±0.11), p=0.18) or fetal perfusion fraction (0.20 (±0.03) vs 0.19 (±0.02) (p=0.1)) between groups. There was a significant difference in mean placenta T2 relaxation time (204 (±50)ms vs 143 (±67)ms, p=0.03) and MR-derived feto-placental blood oxygen saturation estimation (75 (±9.6)% vs 56 (±16.2)%, p=0.02) between groups.

We studied MR-derived maternal and fetal perfusion fraction and feto-placental blood oxygen saturation with gestational age (Figure 2 top row). There was no significant correlation between fetal perfusion fraction and gestational age in the control cohort (r=-0.16), however there were significant negative correlations between maternal perfusion fraction (r=-0.75) and feto-placental blood oxygen saturation (r=-0.80).

Data was sub-grouped based on the ultrasound findings at the time of MRI scan. Pregnancies with abnormal Doppler findings tended to have the greatest difference from the control cohort. Further plots were drawn for each parameter, separating FGR by ultrasound doppler indicators of disease severity: FGR with uterine and umbilical artery Doppler >95th centile (abnormal uterine and umbilical Doppler FGR, n=4), FGR with uterine artery Doppler >95th centile and umbilical artery Doppler <95th centile (abnormal uterine Doppler FGR, n=4), FGR with umbilical and uterine Doppler <95th centile (normal uterine and umbilical Doppler FGR, n=4), and control (n=12) (Figure 2 bottom row).

There was no significant difference between group means for maternal perfusion fraction (0.27(±0.03) vs 0.33(±0.08) vs 0.37(±0.17) vs 0.39 (±0.12) *abnormal uterine & umbilical Doppler FGR vs abnormal uterine doppler FGR vs normal doppler FGR vs control*, p=0.26), however for the fetal perfusion fraction there was a significant difference between groups (0.16(±0.02) vs 0.20(±0.02) vs 0.20(±0.01) vs 0.20 (±0.03), p=0.048 *groups as above)* with post hoc analysis showing the difference lay between the abnormal uterine & umbilical Doppler FGR group (0.16(±0.02)) and the control group (0.20(±0.03)). There was also a significant difference in MR-derived feto-placental blood oxygen saturation (42+7(±8.5) vs 59.2(±20.0) vs 66.5(±9.9) vs 75 (±9.6)%, p=0.0079, *groups as above*), with a significant difference between the abnormal uterine & umbilical Doppler FGR group and normal Doppler FGR group (p=0.006) and the control group (p=0.0005) (Figure 2 bottom row).

Regional placenta function

Figure 3A shows the average histogram of MR-derived feto-placental blood oxygen saturation for each of the control and FGR populations. Figure 3A indicates that the control and FGR distributions have different overall patterns across the placenta. Figure 3B shows the average curve for the control and FGR populations. The difference between these curves (control (n=12) vs all FGR (n=12)) is also shown, with maximal group separation at an oxygen saturation threshold of 61% (Figure 3B). Investigating how this maximal separation varies using a leave-one-out analysis finds the maximal separation to be stable at 60.2% (±2.32%). We use this value to define the Placental Function Index (PFI), which describes the fraction of placental tissue in which the mean feto-placental blood oxygen saturation is greater than 60%. At this level we find a

significant difference in PFI between the control and FGR cohort (0.94 (±0.06) vs 0.67 (±0.22) control vs FGR, p=0.0004) (Table S2, Figure 3C).

We plotted PFI against gestational age at MRI scan for the control cohort, showing a negative correlation (r=-0.53) (Figure 4A). We also find significant differences between groups (0.49*(±0.15) vs 0.67(±0.24) vs 0.84(±0.11) vs 0.9 (±0.06) abnormal uterine & umbilical Doppler FGR vs abnormal uterine doppler FGR vs normal doppler FGR vs control* p=0.006) comparable to the oxygen saturation level in Figure 3C. Group differences were found between the normal Doppler FGR group and the abnormal uterine and umbilical Doppler group (p=0.005) (Figure 4B). We found a significant positive correlation between the PFI and gestational age at birth in the FGR cohort (r=0.75, p=0.005, Figure 4B).

Discussion

Main findings

In this study we have used a novel multi-modal MRI model to examine the placenta of women with normal fetal size and those affected by early onset FGR. Our MRI model uses multiple imaging parameters to weight the signal toward blood saturation and perfusion(32). We show that our estimates of feto-placental blood oxygen saturation significantly differ between the control and FGR cohorts, and that the measure correlated to the disease severity as indicated by the presence of abnormal Doppler indices.

Strengths & Limitations

Our results support our understanding of FGR whereby FGR fetuses with normal Doppler indices may have normal oxygen saturation, whereas FGR fetuses with abnormal Doppler are hypoxic. The findings are in keeping with previous studies which directly analysed the oxygen saturation from fetuses with FGR, defined as AC<5th centile for gestational age(13). The authors found that fetal blood oxygen was significantly lower in FGR versus normally grown fetuses. We defined a Placental Function Index (PFI), between control and FGR placenta to encode the increased spatial heterogeneity seen in FGR placentas. This measure differed according to the severity of the Doppler abnormalities, suggesting that PFI could be a potential marker of disease severity. It may also have a role in the prediction of optimal gestational age at delivery, although this link between gestational age at birth and disease severity is likely to be highly complex. It was also relatively stable in our cohort under a leave-one-out analysis. In the control

cohort PFI decreased with increasing gestational age, suggesting it may also be sensitive to the maturation of placental tissue, where areas within the placenta may no longer be functioning as efficiently. We define this marker here as a post hoc parameter, meaning that it is unlikely to eventually be the most robust measurement obtained from this type of data. However, summary measures such as this may in future inform on placental function.

There are other limitations in this work. Our cohort is fairly small, although our results are significant and the effects we observe are substantive. Our results only apply to early-onset FGR associated with placental insufficiency and possibly, the FGR effects that we observe also have a gestational-age related component. The MRI parameters will require future validation work with invasive measurement of true oxygen saturation or recourse to sophisticated animal models of growth restriction. It will also be possible to assess reproducibility by longitudinal study of individual pregnancies. The DECIDE model is an early model of placental physiology in MRI, and so represents a first approximation of the complexity of placental function. With more advanced image acquisition and analysis it may be possible to develop a more refined model of how the MRI signal and so generate a more precise measurement of placental function. Although we do not observe a significant difference in the gestational ages of the control and FGR groups, nonetheless there are gestational age-dependent changes within the groups which may need to be corrected for in future analysis, or alleviated by precise and consecutive case-control gestational age matching. Here, the correction of gestational age dependent effects in our data would likely enhance the effects that we observe given the linear decrease in measured feto-placental oxygen level with increasing gestational age. Several other contrasts from MRI can inform on placental blood flow and function, each with their own advantages and disadvantages(39). In our work we have combined diffusion imaging and T2 relaxometry based on results from previous work in pregnancies with small fetuses. Alternative contrasts, for instance T2* relaxometry could also be incorporated into the type of multicompartment model that we have described. Arterial spin labelled MRI could be used to further establish the contribution of maternal perfusion although this imaging is not without its own challenges.

Our results will eventually help support the use of MRI for investigating placental insufficiency in less severe phenotypes which may support a role for MRI in the

management of FGR. The cost and complexity of MRI precludes its use as a screening modality; but non-invasive measurement of placental function and fetoplacental oxygen level may support prediction of the trajectory of the disease and inform on the optimal timing of delivery, balancing the complications of premature birth against those associated with chronic hypoxia *in utero*.

Interpretation

We found no significant difference in apparent diffusivity (*d*) between control and FGR placenta. This is different from previously published literature, where placental diffusivity values were found to be significantly lower in FGR pregnancies compared to normal controls, however this significance was found in a much larger cohort(18,19) and thus our results are consistent with the literature.

Previous work has found a difference in total perfusion fraction using a simpler perfusion model (Intra-Voxel Incoherent Motion)(21). Our model differs from this model by considering T2 relaxation time differences which can bias the measured value of this perfusion fraction(32,37). Without this modification, the measured value total perfusion fraction is dependent upon the chosen echo-time(37) and upon the unknown feto-placental blood saturation(33). Specifically, in our model, the value for fetal perfusion is combined with a lower value of T2 to compensate for lower fetal oxygen saturation and is therefore theoretically less biased by these effects, though our results remain consistent with previously published results(32,37).

We found no difference in MR-derived maternal or fetal perfusion in the FGR compared to the control cohort. With regard to maternal perfusion the pathophysiology of FGR is thought to be poor maternal placental perfusion secondary to inadequate spiral artery remodeling early in pregnancy(11). Our measured values however were associated with a large intra-subject variability that may reduce our ability to detect a difference. When categorized according to the severity of the Doppler abnormalities, fetal perfusion in the FGR cases was most reduced when both maternal and fetal Dopplers were abnormal, compared to those FGR cases with less severe or no Doppler abnormalities.

We found a moderate to strong negative correlation between MR-derived feto-placental blood oxygen saturation and increasing gestational age in the control group. This is in keeping with the findings of previous work(13,38) from directly sampled blood from the umbilical vessels.

Histograms of the MR-derived feto-placental blood oxygen level show a bimodal distribution particularly in those FGR pregnancies compromised by abnormal Doppler indices, with a large proportion of voxels having a fetal blood oxygen saturation less than 40% suggesting that those pregnancies with the lowest fraction of placental tissue with mean feto-placental blood oxygen saturation less than 60% were more compromised. This reflects the heterogeneity seen in structural placental MRI and suggests that these areas of low feto-placental blood oxygen saturation may represent parts of the placenta that are not functioning efficiently with regard to oxygen exchange.

Conclusion

In summary using multi-parametric MRI we have shown a strong link between measurement of feto-placental blood oxygenation and presence of fetal growth restriction. MRI measured feto-placental oxygen saturation correlates with FGR disease severity as indicated by the presence of abnormal umbilical and uterine artery Doppler indices. MRI markers are also correlated to gestational age at delivery in FGR. Multi-compartment MRI may offer the ability to improve our understanding of placental pathophysiology and better define clinical care of growth-restricted babies.

Disclosure of Interests We have no conflicts of interest to report.

Contribution of Authorship

Rosalind Aughwane Contributed to the conception and design of the study, analysis of the data and contributed substantially to the final version of the approved manuscript.

Nada Mufti Contributed to the collection of data, analysis of the data and contributed substantially to the final version of the approved manuscript.

Dimitra Flouri Contributed to the collection of data, analysis of the data and contributed substantially to the final version of the approved manuscript.

Kasia Maksym Contributed to the collection of data, analysis of the data and contributed substantially to the final version of the approved manuscript.

Rebecca Spencer Contributed to the collection of data, analysis of the data and contributed to the final version of the approved manuscript.

Magdalena Sokolska Contributed to the collection of data and contributed to the final version of the approved manuscript.

Giles Kendall Contributed to the collection of data and contributed to the final version of the approved manuscript.

David Atkinson Contributed to the collection of data, analysis of the data and contributed to the final version of the approved manuscript.

Alan Bainbridge Contributed to the collection of data and contributed to the final version of the approved manuscript.

Jan Deprest Contributed to the conception and design of the study and contributed to the final version of the approved manuscript.

Tom Vercauteren Contributed to the conception and design of the study and contributed to the final version of the approved manuscript.

Sebastien Ourselin Contributed to the conception and design of the study and contributed to the final version of the approved manuscript.

Anna L. David Contributed to the conception and design of the study, analysis of the data and contributed substantially to the final version of the approved manuscript.

Andrew Melbourne Contributed to the conception and design of the study, analysis of the data and contributed substantially to the final version of the approved manuscript.

Details of Ethical approval The study was approved by the UK National Research Ethics Service and all participants gave written informed consent (London - Hampstead Research Ethics Committee, REC reference 15/LO/1488, original approval 19th October 2015, latest amendment 28th February 2019).

Funding This research was supported by the Wellcome Trust (210182/Z/18/Z and Wellcome Trust/EPSRC NS/A000027/1) and the Radiological Research Trust. The funders had no direction in the study design, data collection, data analysis, manuscript preparation or publication decision

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Table S1: Summary cohort data for control and FGR pregnancies included in the study. IUD: intrauterine death which occurred after MR imaging. Star indicates statistical significance between groups with p<0.05.

Table S2: Summary of cohort group differences measured using DECIDE MRI.

Figure 1 Illustration of the division of the placenta into three different compartments (right hand side) and their respective MRI properties. Key placental features are shown on the left hand side.

*Figure 2 Top Row: Correlation of MRI-derived measures of ROI mean fetal perfusion and oxygenation with gestational age at scan and group (ab - Abnormal, Ut – Uterine, Um – Umbilical). Trendlines for control group only. Bottom Row: Correlation of MRI-derived measures of mean ROI fetal perfusion and oxygenation with gestational age at scan and group (ab - Abnormal, Ut – Uterine, Um – Umbilical). Group means shown as plus signs. * p<0.05, ** p<0.005.*

*Figure 3 Histograms of placental fetal blood oxygen level. A) Average histogram for controls (blue, n=12) and FGR groups (abnormal uterine & umbilical fetal Doppler FGR (red), abnormal uterine Doppler FGR (yellow), normal Doppler FGR (green), n=4 per group). B) Average inverse-cumulative histograms for control and FGR groups and difference between all FGR and control (magenta) (ab - Abnormal, Ut – Uterine, Um – Umbilical) C) Correlation of MRI Placental Functional Index with control and FGR groups with between-group significance marked. Group means shown as plus signs (ab - Abnormal, Ut – Uterine, Um – Umbilical). Placental Functional Index was calculated as described in the text. * p<0.05, ** p<0.005*

Figure 4 A) Placenta Functional Index with gestational age at scan in the control cohort showing a non-significant negative correlation (r=-0.53 p=0.07). B) Placenta Functional Index with gestational age at birth in the FGR group cohort, showing a statistically significant correlation (r=0.75, p=0.005) (ab - Abnormal, Ut – Uterine, Um – Umbilical).