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**ORIGINAL ARTICLE**Submitted to *Magnetic Resonance in Medicine*

# Combined Diffusion-Relaxometry MRI to Identify Dysfunction in the Human Placenta

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**Purpose:** A combined diffusion-relaxometry MR acquisition and analysis pipeline for in-vivo human placenta, which allows for exploration of coupling between T2\* and apparent diffusion coefficient (ADC) measurements in a sub 10 minute scan time.

**Methods:** We present a novel acquisition combining a diffusion prepared spin-echo with subsequent gradient echoes. The placentas of 17 pregnant women were scanned in-vivo, including both healthy controls and participants with various pregnancy complications. We estimate the joint T2\*-ADC spectra using an inverse Laplace transform.

**Results:** T2\*-ADC spectra demonstrate clear quantitative separation between normal and dysfunctional placentas.

**Conclusions:** Combined T2\*-diffusivity MRI is promising for assessing fetal and maternal health during pregnancy. The T2\*-ADC spectrum potentially provides additional information on tissue microstructure, compared to measuring these two contrasts separately. The presented method is immediately applicable to the study of other organs.

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**KEYWORDS**

placenta, diffusion, relaxometry, microstructure, multimodal MRI, inverse Laplace transform

## 1 | INTRODUCTION

The placenta provides the vital link between mother and fetus during pregnancy. It is implicated in many major pregnancy complications, such as pre-eclampsia (PE) and fetal growth restriction (FGR) [1]. PE affects 3-5% of pregnancies [2] and is a major cause of maternal and perinatal mortality [3, 4]. Late onset FGR, defined as that diagnosed after 32 weeks [5], affects 5-10% of pregnancies [6]. It is strongly associated with stillbirth [7, 8], pre-eclampsia [9], and late preterm birth [10]. For all these disorders, it is likely that placental dysfunction occurs before the onset of symptoms. New techniques for imaging the placenta therefore have the potential to improve prediction, diagnosis, and monitoring of pregnancy complications.

Placental MRI is emerging as a technique with substantial promise to overcome some disadvantages of ultrasound. For example, ultrasound parameters of fetal wellbeing are imperfect for determining which fetuses have late-onset FGR and are at greatest risk of adverse perinatal outcome, as opposed to those that are constitutionally small but healthy [11, 6]. Assessing the placenta with MRI has the potential to make this distinction. Two MRI modalities that show great promise for assessing placental function are  $T2^*$  relaxometry - which has the potential to estimate oxygenation levels [12, 13], and diffusion MRI (dMRI) - which can estimate microstructure and microcirculatory properties [14, 15, 16, 17].

$T2^*$  relaxometry exploits the inherent sensitivity of the transverse relaxation time to the biochemical environment of tissue. In particular, the paramagnetic properties of haemoglobin mean that the  $T2^*$  relaxation rate can be used as a proxy estimation of oxygenation [18]. In placental studies,  $T2^*$  is generally lower in FGR cases [19, 20, 21, 22]. A typical experiment acquires gradient echo data at several echo times (TE), either in separate or multi-echo scans, and hence estimates the  $T2^*$  relaxation rate of the tissue. No diffusion weighting is typically applied to these scans. Applying diffusion gradients with different strengths (b-value) and directions provides sensitivity to various microstructural length scales and orientations. These measurements are usually taken at a fixed TE. In the placenta, dMRI has shown promise for discrimination between normal pregnancies and FGR [23, 24, 14, 25, 15, 26], and early onset PE [16]. However, despite the large number of placental  $T2^*$  and dMRI studies in the literature, no method has shown sufficient discrimination between healthy pregnancies and those with complications to be introduced into routine clinical practice. Methods which combine multiple distinct measurements may provide a way to overcome this. Table S1 summarises  $T2^*$  and dMRI studies in the placenta to date.

$T2^*$  and dMRI-derived measures are both influenced by the presence and composition of distinct tissue compartments (or *microenvironments*). Recently, combined diffusion-relaxometry MRI is emerging as a promising technique with the potential for increased sensitivity to these tissue microenvironments [27, 28, 29, 30]. Diffusion-relaxometry MRI can simultaneously measure multiple MR contrasts; for example by varying both TE and b-value it is possible to probe the multidimensional  $T2$ -diffusivity (or  $T2^*$ -diffusivity) space. This could provide a more eloquent way of probing microstructure at the subvoxel level. These novel acquisitions naturally pair with multidimensional analysis techniques which quantify multiple tissue parameters simultaneously, and therefore have great potential to yield fine-grained information on tissue microstructure. Such combined diffusion-relaxometry experiments have been conducted successfully in the context of nuclear magnetic resonance (NMR) spectroscopy, improving the ability to distinguish different compartments [31, 32]. Recent work has extended these techniques to imaging, with applications in the  $T1$ -diffusivity [27],  $T2$ -diffusivity [28, 29], and  $T1$ - $T2$ -diffusivity [30] domains. These studies have shown that combining diffusion

with other MR contrasts leads to more specific quantification of microscopic tissue compartments. One recent study demonstrated combined T2-diffusivity in the placenta [33], with the aim to separate signals from fetal and maternal circulations.

A major disadvantage of previous diffusion-relaxometry experiments are the very long scan times required when varying multiple contrast mechanisms, such as the TE and diffusion encoding. In this paper, we propose a combined acquisition and analysis technique which can estimate the T2\*-ADC spectrum within a clinically viable timeframe. We apply this novel method in the placenta, an organ where T2\* and ADC have both been shown to be informative. As well as demonstrating simultaneous estimation of T2\* and diffusivity parameters within a clinically viable time, we hypothesise that the joint T2\*-ADC spectrum will provide additional information compared to the individual measures.

## 2 | METHODS

### 2.1 | Acquisition: Integrated T2\*-Diffusion sampling

We adapt a novel MRI acquisition strategy, termed ZEBRA [34], in order to sample multiple TEs and diffusion encodings within a single repetition time (TR). The method combines a diffusion prepared spin echo sequence with subsequent gradient echoes. This allows simultaneous quantification of T2\* and ADC, as opposed to standard independent multi-echo gradient echo and diffusion sequences (e.g. Fig 1a). Our technique also offers significant speed ups compared to existing T2-diffusivity techniques - which only sample a single TE-diffusion encoding pair for each TR (i.e. Fig 1a). The proposed combined acquisition is shown in Fig. 1b. The multiple gradient echoes are acquired with minimal spacing after the initial spin echo and diffusion preparation. We note that by using gradient echo readouts rather than spin echoes, we measure T2\* rather than T2 (see Fig. 1c).

Figure 2 illustrates the resultant sampling of the TE-diffusion encoding domain for the three acquisition techniques presented in Figure 1. Separate multi-echo gradient echo and diffusion sequences do not adequately sample the full domain (Fig. 2a). With repeat acquisitions of diffusion encodings at different TEs full sampling of the domain is possible, but very slow (Fig. 2b). The proposed acquisition is able to sample the same domain in a much shorter, and clinically viable, scanning time (i.e. Fig. 2c).

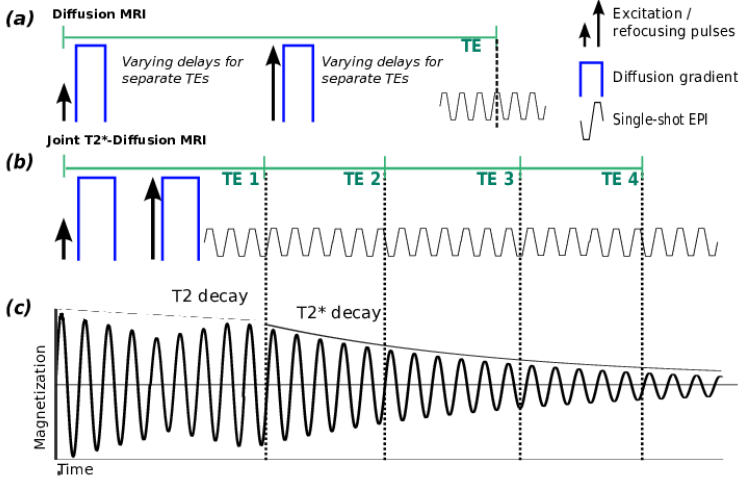
### 2.2 | Modelling

The simplest model for analysing the data assumes single tissue compartments, so that the signal attenuations caused by T2\* relaxation and diffusion are both described by a single exponential decay. The MR signal for this combined ADC-T2\* model is given by

$$S(T_E, b) = S_0 e^{-T_E/T_2^*} e^{-bADC} \quad (1)$$

where  $T_E$  is the echo time,  $b$  is the b-value,  $ADC$  is the apparent diffusion coefficient,  $T_2^*$  is the effective transverse relaxation time, and  $S_0$  is the signal at the spin-echo time with zero diffusion weighting.  $S_0$  is the product of proton density, T2 weighting caused by finite spin echo time, receiver coil properties, and system gain, so we do not treat it as an absolute quantity in the analysis.

A shortcoming of this model is that it assumes the attenuation due to diffusion is mono-exponential, when it is well established that the placental dMRI signal in-vivo is at least bi-exponential, as in the intravoxel incoherent motion (IVIM) model [35]. In this model, the slow and fast attenuating components are associated with diffusion in tissue and



**FIGURE 1** The considered acquisition schemes. (a) Conventional Diffusion MRI acquisition for one echo time (TE) showing the diffusion gradients (blue), the excitation and refocusing pulses as well as the single-shot EPI read-out train. Repeating this acquisition with varying delays between the diffusion gradients and the read-out leads to different TEs and thus combined T2-Diffusion MRI. (b) Proposed combined acquisition with an initial spin-echo acquired after the diffusion gradients followed by multiple Gradient echos. (c) Magnetization for the combined acquisition, with both T2 and T2\* decay. The signal evolution neglects effects of all applied gradients.

pseudo-diffusion in capillaries respectively. Incorporating T2\* decay into the IVIM model gives

$$S(T_E, b) = S_0 e^{-T_E/T_2^*} \left[ f e^{-bD^*} + (1-f) e^{-bADC} \right] \quad (2)$$

where  $f$  is the perfusion fraction and  $D^*$  is the pseudo diffusion coefficient. However, it seems likely that the diffusion and pseudo-diffusion compartments have different T2\* values. A model incorporating this was proposed by Jerome *et al.* [36]

$$S(T_E, b) = S_0 \left[ f e^{-bD^*} e^{-T_E/T_{2p}^*} + (1-f) e^{-bADC} e^{T_E/T_2^*} \right] \quad (3)$$

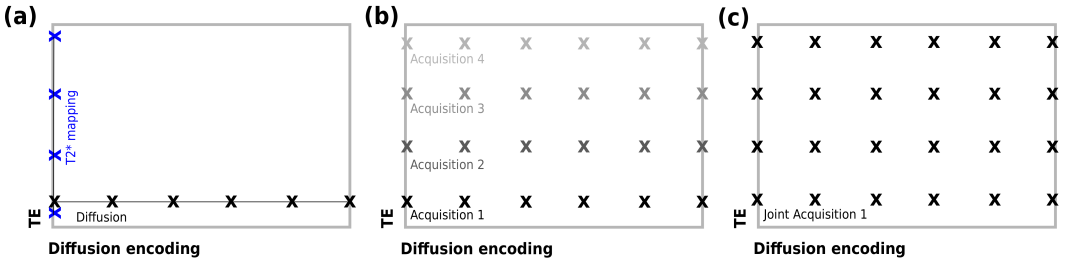
where  $T_{2p}^*$  and  $T_2^*$  are the T2\* values specific to the pseudo-diffusion and diffusion compartments respectively.

A significant limitation of the models presented in Equations (1) (2) and (3) is that the number of tissue compartments is assumed to be known. An alternative approach for analysing the signal is a continuum model, which considers that spins have a spectrum of relaxivity (or diffusivity) values all contributing to the MRI signal. Following Menon *et al.* [37] the 1D continuum models for  $T_2^*$  relaxometry and diffusion are

$$S(T_E) = \int p(T_2^*) e^{-T_E/T_2^*} dT_2^*$$

$$S(b) = S_0 \int p(ADC) e^{-bADC} dADC.$$

Here  $p(T_2^*)$  and  $p(D)$  are the  $T_2^*$  relaxation and diffusivity spectra to be estimated from the data. We can solve for these



**FIGURE 2** Schemes for the three considered diffusion-relaxometry experiments illustrated in the TE-Diffusion encoding acquisition parameter plane. (a) Schematic of conventional separate  $T_2^*$  mapping and Diffusion MRI showing the encoding of different echo times for  $b=0$  in blue and different diffusion encoding settings at fixed echo time. (b) Parameter space illustrating the sampling of the TE-diffusivity space with diffusion acquisitions at several TEs. Shading illustrates separate diffusion acquisitions at fixed TEs. (c) Proposed combined  $T_2^*$ -diffusion acquisition illustrating a denser sampling scheme achieved in a single acquisition.

spectra using an inverse Laplace transformation, although this is an ill-posed problem requiring regularisation to smooth the resulting spectra [38, 39, 40, 30, 28]. The extension to combined diffusion-relaxometry acquisitions is simple. For the acquisition presented here, where  $T_E$  and  $b$  are simultaneously varied, the signal is

$$S(T_E, b) = S_0 \int_0^\infty \rho(T_2^*, ADC) e^{-TE/T_2^*} e^{-bADC} dT_2^* dADC \quad (4)$$

The function we are interested in is the two-dimensional  $T_2^*$ -diffusivity spectrum,  $\rho(T_2^*, D)$ , which can be estimated by a regularised 2D inverse Laplace transform. This contains more information than the individual 1D spectra, and is hence more likely to resolve multiple distinct tissue compartments.

### 2.3 | Experiments

The sequence described in the methods section was implemented on a clinical Philips Achieva-Tx 3T scanner using the 32ch adult cardiac coil placed around the participant's abdomen for signal reception. All methods were carried out in accordance with relevant guidelines and regulations; the study was approved by the Riverside Research Ethics Committee (REC 14/LO/1169) and informed written consent was obtained prior to imaging. 17 pregnant women, with gestational age ranging from 23+5 to 35+4 (weeks + days), were successfully scanned using the described technique. Three of these participants, one of whom also had FGR, were diagnosed with pre-eclampsia according to standard definitions [41]. Three participants had chronic hypertension in pregnancy and were analysed distinct from normotensive pregnancy women (the control group). One pregnant woman with chronic hypertension was scanned twice, four weeks apart, and developed superimposed pre-eclampsia by the second scan. The full participant details are given in Table 1.

The combined  $T_2^*$ -diffusivity scan was acquired with the proposed sequence, a dMRI prepared spin echo followed by multiple gradient echos. The number and timing of the gradient echos varied across scans (see Table 1), with most scans having five TEs. The diffusion encodings were chosen specifically for the placenta, as previously reported [42, 43], with 3 diffusion gradient directions at  $b = [5, 10, 25, 50, 100, 200, 400, 600, 1200, 1600]$   $\text{s mm}^{-2}$ , 8 directions at  $b = 18 \text{ s mm}^{-2}$ , 7 at  $b = 36 \text{ s mm}^{-2}$ , and 15 at  $b = 800 \text{ s mm}^{-2}$ . Further parameters were FOV =  $300 \times 320 \times 84 \text{ mm}$ , TR = 7 s, SENSE = 2.5, halfscan = 0.6, resolution =  $3 \text{ mm}^3$ . One participant was scanned at higher resolution:  $2 \text{ mm}^2$  isotropic. The total acquisition time was 8 minutes 30 seconds.

**TABLE 1** Participant details. PE - pre-eclampsia, CH - chronic hypertensive, FGR - fetal growth restriction.

Participant ID	GA at scan (weeks)	Cohort	TEs (ms)
1	23.72	Control	78, 114, 150, 186, 222
2	23.86	Control	78, 114, 150, 186, 222
3	25.43	Control	78, 114, 150, 186, 222
4	25.72	Control	78, 114, 150, 186, 222
5	26.14	Control	78, 114, 150, 186, 222
6	26.72	Control	78, 114, 150, 186
7	26.72	Control	78, 114, 150, 186, 222
8	27.14	Control	78, 114, 150, 186, 222
9	28.29	Control	78, 114, 150, 186, 222
10	28.86	Control	82, 175, 268, 361, 454
11	28.86	Control	78, 114, 150, 186, 222
12	29.67	Control	85, 145, 205, 265, 325
13	26.86	CH	80, 121, 162, 203, 245
14	34.43	CH	78, 114, 150, 186, 222
15	27.7	PE+FGR	78, 114, 150, 186, 222
16	30.58	PE	78, 114, 150
17 (scan 1)	30.71	CH	78, 114, 150, 186, 222
17 (scan 2)	34.14	CH+PE	78, 114, 150, 186, 222

## 2.4 | Model fitting

We first manually defined a region of interest (ROI) containing the whole placenta and adjacent uterine wall section on the first  $b=0$  image with the lowest TE. We fit the  $T2^*$ -ADC model described in Equation (1) voxelwise to the data (all TEs and all  $b$ -values). The fitting consisted of two-step (grid search followed by gradient descent) maximum log-likelihood estimation assuming Rician noise, similar to that previously described [17], with the exception that we use the unnormalised MRI signal. The gradient descent fitting constraints were as follows:  $T2^*$  was constrained between 0.001 s and 1 s, the ADC between  $10^{-5}$  and  $1 \text{ mm}^2 \text{ s}^{-1}$ , and  $S0$  between 0.001 and  $10^5$ . We fixed the SNR for fitting to 20 for all voxels in all scans.

We calculated the  $T2^*$ -ADC spectrum for each participant from the signal averaged over the ROIs, using the MERA toolbox [44], which incorporates minimum amplitude energy regularization as described by Whittall *et al.* [45]. We also calculated the  $T2^*$ -ADC spectra voxelwise in all participants. We next quantified the spatial variation in  $T2^*$ -ADC spectral components across the placenta and uterine wall with volume fraction maps, using a similar approach to Benjamini *et al.* [30] and Kim *et al.* [28]. Specifically, by inspecting the ROI-averaged spectra we chose a set of boundaries - based on the most common peak areas - which split the  $T2^*$ -ADC domain into regions. These boundaries were the same across all participants, and are given in Table 2. For each voxel's  $T2^*$ -ADC spectrum, we then calculated the weight of

**TABLE 2** Boundaries selected to segregate most common peak areas in T2\*-ADC spectra.

Region	ADC Bounds ( $\times 10^{-3} \text{ mm}^2 \text{ s}^{-1}$ )	T2* Bounds (s)
Peak 1	$0 < \text{ADC} < 25$	$0 < \text{T2}^* < 0.1$
Peak 2	$25 < \text{ADC} < 200$	$0 < \text{T2}^* < 0.1$
Peak 3	$200 < \text{ADC} < 1000$	$0 < \text{T2}^* < 0.1$

the voxelwise spectra contained in each of these regions. By normalising these weights to sum to 1 across all regions, we produced spectral volume fraction estimates for each voxel. Figure 3 shows an illustrative example of this calculation; the spectral volume fraction essentially quantifies the proportion of each voxel's spectrum which lies in each of the highlighted regions in the top-left panel.

### 3 | RESULTS

Figure 3 demonstrates the full analysis pipeline output for a single participant. We next present the parameter maps from combined ADC-T2\* model fits (Figures 4 and 5) and spectral volume fraction maps (Figures S3, S4 and S5) for all participants. We probe the changes across gestation and in disease cases by examining the T2\*-ADC spectra across all participants (Figures 6 and 7). Finally, in order to assess the independence of our diffusivity and relaxometry measurements, we plot the correlation between the derived ADC and T2\* values (Figure S6).

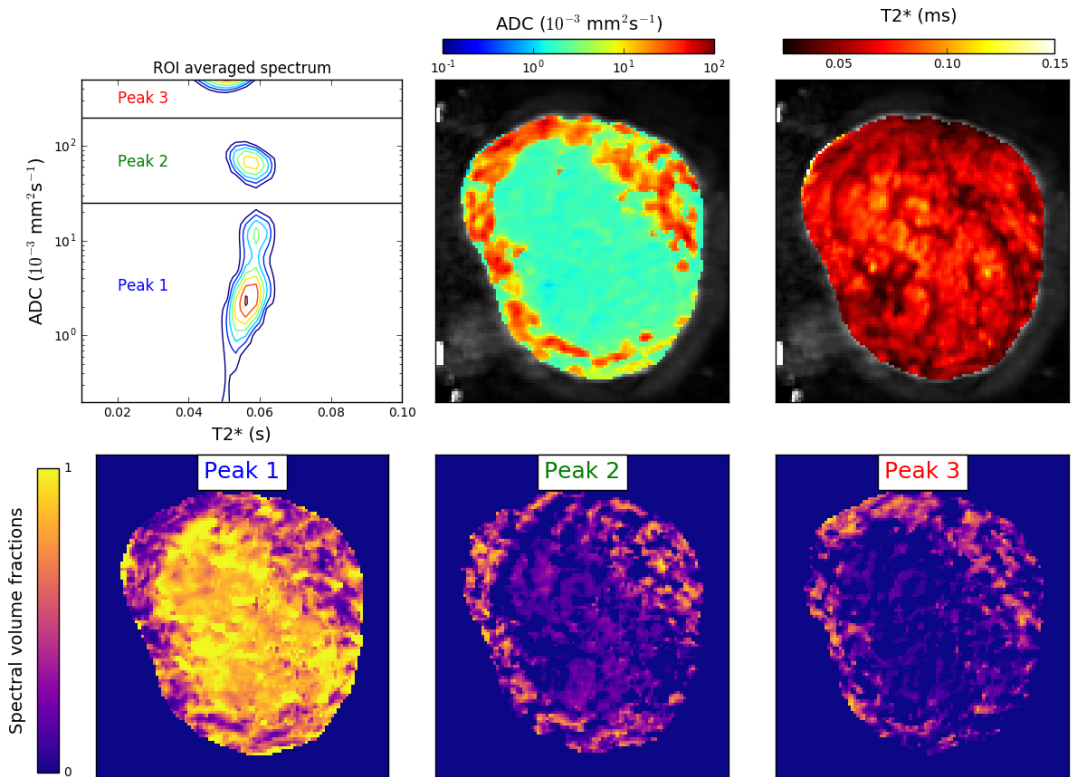
The first panel in Figure 3 shows the placenta and uterine wall ROI averaged T2\*-ADC spectrum for a single participant (scanned at higher resolution). We observe three peaks, clearly separated by ADC value but with similar T2\* values. ADC and T2\* maps show distinctive spatial patterns. The ADC is much higher in the uterine wall than the placenta. T2\* maps show distinct 'lobes' surrounded by a patchwork of low T2\* values, with many lobes displaying a small region of higher T2\* in the centre. The bottom row of Figure 3 displays voxelwise spectral volume fractions, obtained by integrating (i.e. summing spectral weights) within three regions of the T2\*-ADC space, as described in Methods. The domain with the lowest ADC (e.g. peak 1) is associated with areas within the placenta, and the two domains (peaks 2 and 3) with higher ADC are more prominent in the uterine wall.

Figure 4 shows T2\* maps across all participants from the combined T2\*-ADC fit. The patterns are consistent with those previously reported in the literature [46, 43]. In most participants regions of high T2\* encircled by low T2\* borders are clearly visible, and most likely correspond to placental lobules. In agreement with previous observations the regions with low T2\* are more prominent in pre-eclampsia [43], and FGR [22, 47] placentas.

ADC maps (Figure 5) also show anatomically-linked qualitative features which are consistent across participants. In all scans from the healthy pregnant group the ADC shows a significant increase at the border between the placenta and the uterine wall. This is most likely explained by the high levels of blood flow in these areas. This bordering area of high ADC is absent from many disease placentas. Additionally placentas from women with chronic hypertension and pre-eclampsia often show a distinctive pattern - small patches of high ADC surrounded by very low ADC.

Figure 6 displays the spatially averaged T2\*-ADC spectra for ROIs containing the placenta and uterine wall. We clearly observe separate peaks in all control participants, strongly suggesting the presence of multiple tissue compartments with distinct properties. In the vast majority (11/12) of these spectra from healthy controls we see at least three clearly separated peaks. These peaks, and their corresponding tissue compartments, appear more clearly separated by ADC (note the log-scale on the y-axis) than by T2\* value. We also observed three distinct peaks in placentas from chronic hypertensive women. Interestingly, we did not see three distinct peaks in any spectra from participants with pregnancy



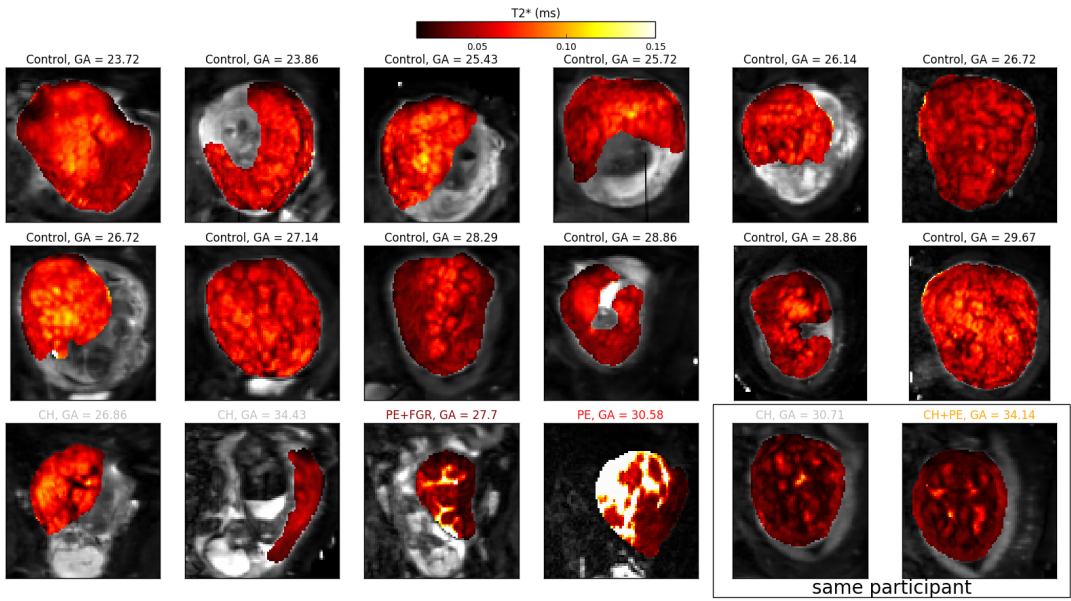


**FIGURE 3** T2\*-ADC spectra show anatomical specificity. Spatial maps for a single scan with higher resolution. Top row: T2\*-ADC spectrum derived from inverse Laplace transforms of the spatially averaged signal within an ROI comprising the entire placenta and uterine wall, and ADC and T2\* maps from combined T2\*-ADC fit. Bottom row, spectral volume fraction maps derived by summing the weight of the spectra in the 3 domains displayed in the ROI averaged spectrum, as describe in Methods.

complications (three PE, one PE+FGR). There is a distinct pattern in the T2\*-ADC spectra for the three PE participants - a left and downward shift in the lowest peak. This suggests a decrease in both ADC and T2\* distributions compared to control placentas. There is a similar leftward shift in the PE+FGR placental spectrum; however, the downward shift is not as pronounced, with the middle peak appearing to merge with the lowest peak. The peak with highest ADC often appears to span the boundary of the domain in which the inverse Laplace transform is calculated. This is likely because we are unable to sample enough low b-values to accurately estimate this very fast diffusing component - i.e. there is signal in the  $b = 0$  volume, which has all attenuated by the  $b = 5 \text{ s mm}^{-2}$  volume.

Spectral volume fraction maps showed similar patterns across all control participants (Figures S3, S4 and S5); peaks with higher ADC being more prominent in the uterine wall. This likely reflects the high flowing blood volumes in these areas, akin to the maps in Figure 5.

Figure S6 shows that we did not observe a consistent correlation between T2\* and ADC values across participants. This suggests that we acquire complementary information from these two MR contrasts. Interestingly, we did not observe the small placental areas with high T2\* and high ADC that we saw in previous work [43].



**FIGURE 4** T2\* maps from combined ADC-T2\* fit. Participants with pregnancy complications in colour. Note the failure of the model fit in some areas due to very low signal for one PE participant (GA = 30.58).

## 4 | DISCUSSION AND CONCLUSION

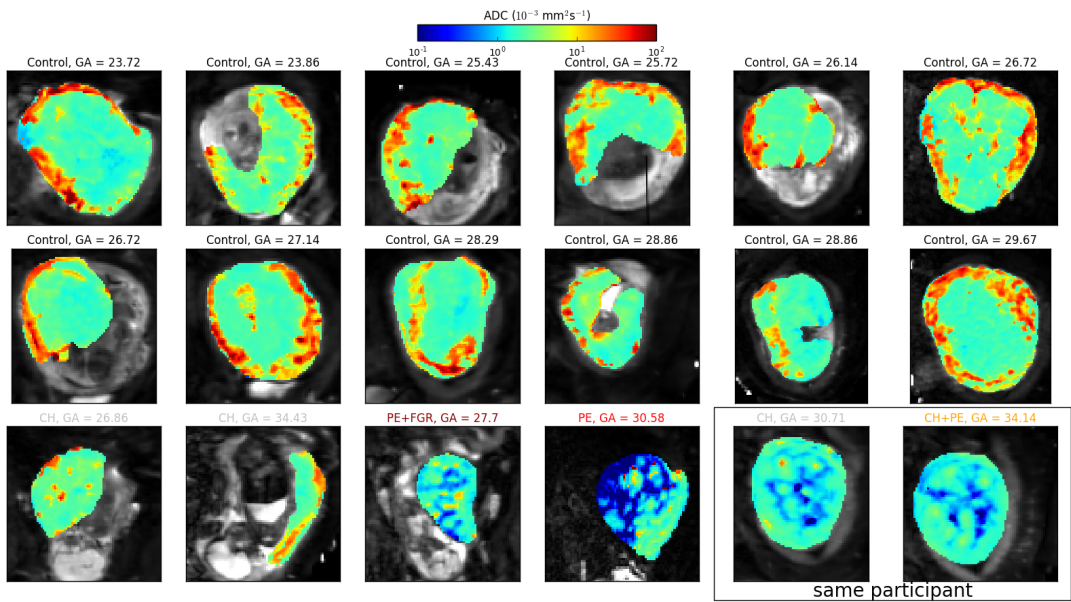
### 4.1 | Summary

This study demonstrates accelerated diffusion-relaxometry MRI on the in-vivo human placenta. Compared to existing approaches, it allows denser, faster, and more flexible sampling of the 2D (TE - diffusion encoding) acquisition space. This in turn allows visualization of the T2\*-ADC spectrum, and thus provides enhanced capacity to separate multiple tissue microenvironments. The technique was demonstrated on 17 pregnant participants, including 3 scans on placentas clinically assessed as from women with pregnancy complications. In the following sections, we first putatively associate the observed T2\*-diffusivity spectral peaks with distinct placental tissue microenvironments. We then hypothesise as to how the spectral changes observed in cases with complications reflect changes in these tissue microenvironments. Finally we discuss the clinical potential of the presented technique, which we emphasise is independent of the biological interpretation.

### 4.2 | Biological interpretation of T2\*-diffusivity spectra

In all controls, we observed a peak with high ADC, typically above  $10^{-1} \text{ mm}^2 \text{ s}^{-1}$ . Additionally, in nearly every control participant (11/12) we observe two further clearly distinct peaks, with ADC around  $2 \times 10^{-3} \text{ mm}^2 \text{ s}^{-1}$  for the lower, and between  $10^{-2}$  and  $10^{-1} \text{ mm}^2 \text{ s}^{-1}$  for the middle peak (Figure 6).

The appearance of three peaks clearly separated by diffusivity in all but one control placenta is consistent with each peak corresponding to a distinct placental tissue microdomain. Solomon et al. previously reported three placental compartments in mice [48], with these attributed to a slow-diffusing maternal blood compartment, a fetal blood



**FIGURE 5** ADC maps from combined ADC-T2\* fit. Note the log-scale colormap.

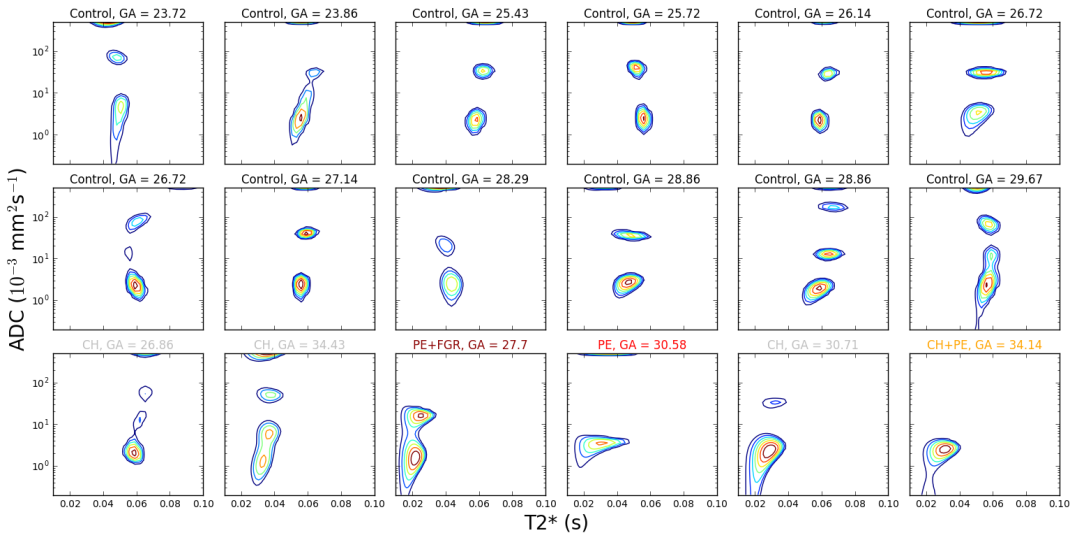
compartment with diffusivity around two orders of magnitude faster, and an intermediate compartment associated with active filtration of fluid across the fetal-maternal barrier. We therefore speculatively assign tissue compartments to each of these three peaks in healthy control placentas as follows. The compartment with the lowest ADC, which has typical values ( $2 \times 10^{-3} \text{ mm}^2 \text{ s}^{-1}$ ) comparable to the diffusivity of water in tissue, is associated with maternal blood and water within tissue. The highest ADC compartment is associated with perfusing fetal blood, and the intermediate compartment with fluid transitioning between the maternal and fetal circulations. This is consistent with the spectral volume fraction maps for the peaks with higher ADC (Figures S4 and S5), which show higher intensity in the vascular areas bordering the placenta.

### 4.3 | Spectral changes in disease

We observed three main trends in the T2\*-diffusivity spectrum which discriminated between control and placentas from women with pregnancy complications:

1. The disappearance of one (or both) of the middle and higher peaks
2. A leftwards shift in the lowest peak
3. A downwards shift in the lowest peak

In placentas from women with pre-eclampsia we generally saw all three trends (Figure 6). The leftward shift mirrors the previously reported decrease in T2\* in pre-eclampsia placentas [43]. We saw the same leftward shift in the FGR+PE case, and note that lower T2\* values have also been observed in FGR placentas [49, 22]. Regarding the downward shift in the lowest peak, our initial speculation is that lower diffusivity could reflect increased water restriction due



**FIGURE 6**  $T_2^*$ -ADC spectra derived from inverse Laplace transforms of the spatially averaged signal within placenta and uterine wall ROIs.

to inflammation - since placental inflammation is associated with PE [50]. This may relate to the disappearance of the middle peak, which we hypothesize could reflect decreased maternal-fetal fluid exchange. Inflammation is a potential mechanism facilitating the reduction in exchange.

Figure 7 presents these observed changes in the  $T_2^*$ -ADC spectrum in a single plot, showing clear separation between the control and pregnancy complication (i.e. PE, PE+FGR) participants. We plot the position of the spectral peak with the lowest ADC in the  $T_2^*$ -ADC domain, with the marker area corresponding to the peak's volume fraction. In this way, we capture both the peak shift, and the higher volume fraction due to the disappearance of the middle or higher peaks. Although these results are highly encouraging, we clearly need to scan many more participants, both control and women with pregnancy complications, to determine the discriminative power of these measures.

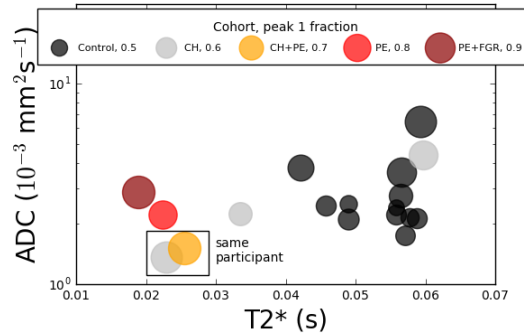
## Limitations and Future Work

We used an “out-of-the-box” inverse Laplace transform toolbox to calculate the  $T_2^*$ -ADC spectrum. There are a number of known weaknesses for this method, including the need for regularization. In this study we chose minimum amplitude energy regularization. Future work could assess the utility of alternative optimization approaches, such as spatially constrained [28], or constrained by the 1D spectra [30].

Our  $T_2^*$  estimates are generally lower than those previously reported [43]. This may be due to the larger voxel size, leading to partial volume effects around areas with high  $T_2^*$ , such as spiral artery inlets. It could also be due to signal attenuation due to diffusion during the gradient echoes, something which we did not account for in our analysis.

The presented  $T_2^*$ -ADC spectral analysis assesses the data in two dimensions, but there are more dimensions to the data - such as diffusion gradient direction - which we did not include in our analysis. Therefore this dataset has the potential to be further analysed, for example with microstructural models that account for anisotropy in the signal.

In this study, we used b-values and gradient directions optimised for dMRI at a single TE [42, 43], and the TEs



**FIGURE 7** Position of the peak with the lowest ADC within the ADC- $T_2^*$  spectrum. Each marker corresponds to a single scan. Markers are colored by disease cohort, and marker area is proportional to the spectral volume fraction of the peak.

were constrained by the EPI read-out train length. Separate optimisation of  $T_2^*$  relaxometry and dMRI acquisition parameters is 1D (choice of TEs, choice of b-values). However, when moving to combined  $T_2^*$ -diffusion this becomes a 2D problem - for example, in the isotropic case we need to choose optimal TE-diffusion encoding pairs. In future, we plan to optimise these TE-diffusion encoding values in order to give the best sampling of the 2D parameter space, and enhance estimation of the 2D spectra.

We manually segmented whole placenta and uterine wall ROIs - a time-consuming step - to calculate the  $T_2^*$ -diffusivity spectra. However a single within-placenta ROI, such as the one defined during our scans in order to aid shimming, may be sufficient to discriminate control and disease cases. This would speed up data processing, and also remove the difficulties when segmenting poorly functioning placentas, which often have little functional tissue.

#### 4.4 | Outlook and clinical application

The combined acquisition and analysis technique presented here offers fast, simultaneous, and multidimensional assessment of placental  $T_2^*$  and diffusivity in less than 10 minutes. These two MR contrasts have been shown elsewhere to be sensitive to placental pathologies, we hypothesise that their simultaneous assessment could enable better separation of healthy and poorly functioning placentas. This is supported by the fact that we did not see consistent correlation between  $T_2^*$  and ADC values (Figure S6), suggesting that these modalities offer complementary information. This reinforces the value of the novel technique presented here as a quantitative tool for assessment of pregnancy complications, with the potential to ultimately inform clinical decisions. Furthermore, we believe that fast calculation of the  $T_2^*$ -ADC spectrum has many potential applications in other areas of biomedical research.

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## CONFLICT OF INTEREST

The authors have no conflicts of interest to declare.

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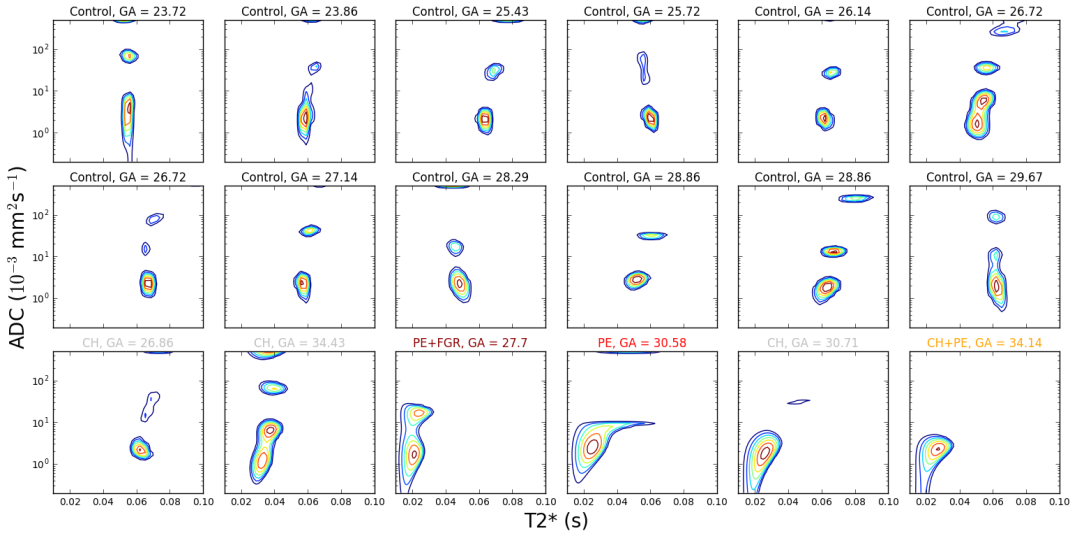
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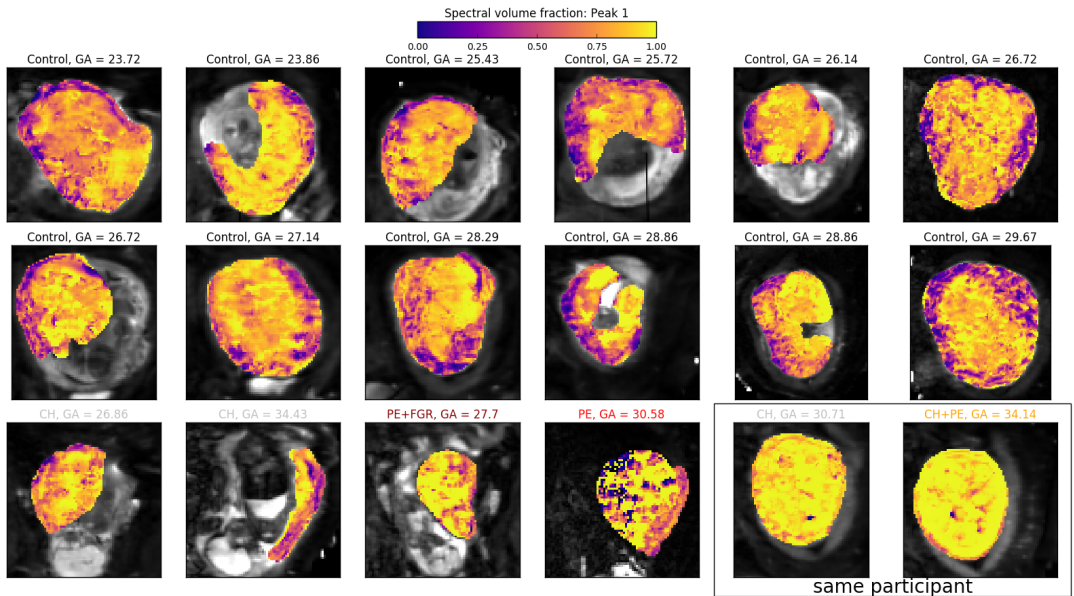
## 5 | SUPPORTING FIGURES AND TABLES

**TABLE S1** Overview of placental T2\* and dMRI studies to date.

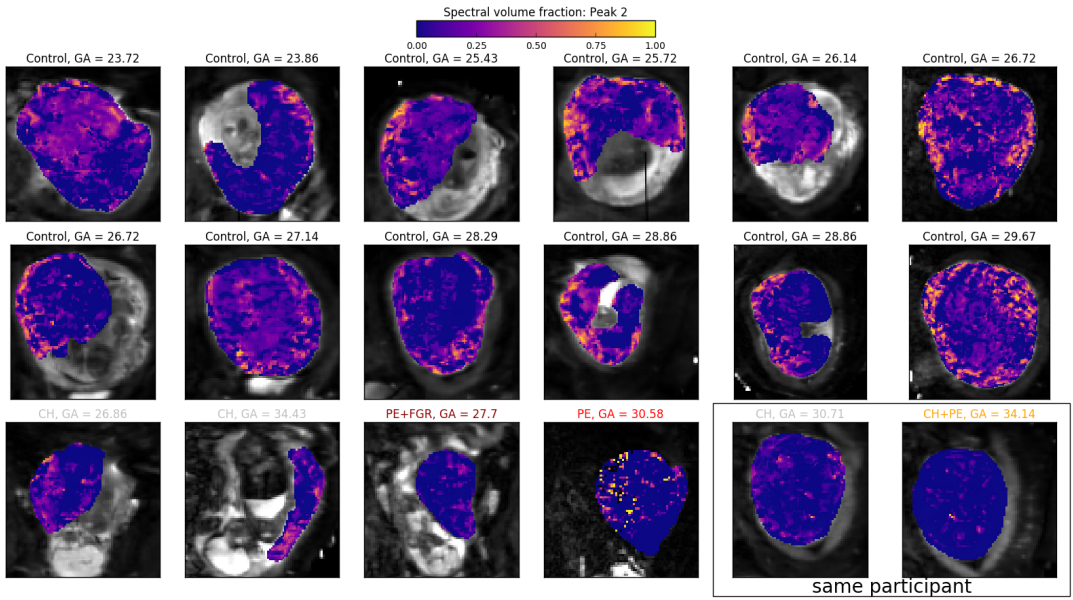
Reference	Parameters	Resolution	ROI selection
<b>T2*</b>			
Sinding2016[49]	1.5T, gradient-recalled echo) 16 TEs(3-67.5) BH 12s, 16 controls with repetitions	1.37x2.73x8mm (2 slices, gap 2mm)	Entire placenta, outer border not crossed
Sinding2017[19]	1.5T, gradient-recalled echo) 16 TEs(3-67.5) BH 12s	1.37x2.73x8mm 3 slices transverse evenly	Entire placenta, outer border not crossed
Sinding2018[22]	1.5T, gradient-recalled echo) 16 TEs(3-67.5) BH 12s, 16 HC with repetitions	1.37x2.73x8mm 3 planes evenly	entire placenta adjusted for movements
Derwig2013a[21]	1.5T, flow-compensated SE (ind. scans) TEs= 40,80,120,180,240,300,360,440	3.76x3.75x8 3 slices, no gap	representative area of central part away from vessels
Ingram2017 [20]	gradient-recalled echo 5-50ms, 8 sec BH, under O <sub>2</sub>	3.52x3.52 1 slices transverse	largest contiguous placental region non-placental tissue removed
Hutter2018[51]	2D ss EPI Multi-echo GE	2x2x2	conservative
<b>dMRI</b>			
Moore2000a[52]	0.5T, 11 b-values (0-468 s mm <sup>-2</sup> )	3.5x2.5x7 mm	Entire placenta
Moore2000b[14]	0.5T, 11 b-values (0-468 s mm <sup>-2</sup> )	3.5x2.5x7 mm	Entire placenta
Derwig2013b[15]	1.5T, 11 b-values (0-500 s mm <sup>-2</sup> )	3.75x3.75x4 mm	Two: central, whole
Sohlberg2015[25]	1.5T, 5 b-values (0-800 s mm <sup>-2</sup> )	??x??x6 mm	excluding artefactual signal loss areas
You2017[53]	1.5T, 9 b-values (0-900 s mm <sup>-2</sup> )	4.38x4.38x4 mm	Entire placenta
Capuani2017[54]	1.5T, 7 b-values (0-1000 s mm <sup>-2</sup> )	2x2x4 mm	Three: central, peripheral, umbilical
Siauve2017[55]	1.5T, 11 b-values (0-1000 s mm <sup>-2</sup> )	??x??x5 mm	Three: entire placenta, fetal, maternal
Slator2017[17]	3T, 12 b-values (0-2000 s mm <sup>-2</sup> )	2x2x2 mm	Entire placenta
Jakab2017[56]	1.5T and 3T, 17 b-values (0-900 s mm <sup>-2</sup> )	2x2x4 mm	Central
Hutter2018[51]	3T, 14 b-values (0-1600 s mm <sup>-2</sup> )	2x2x2 mm	Entire placenta



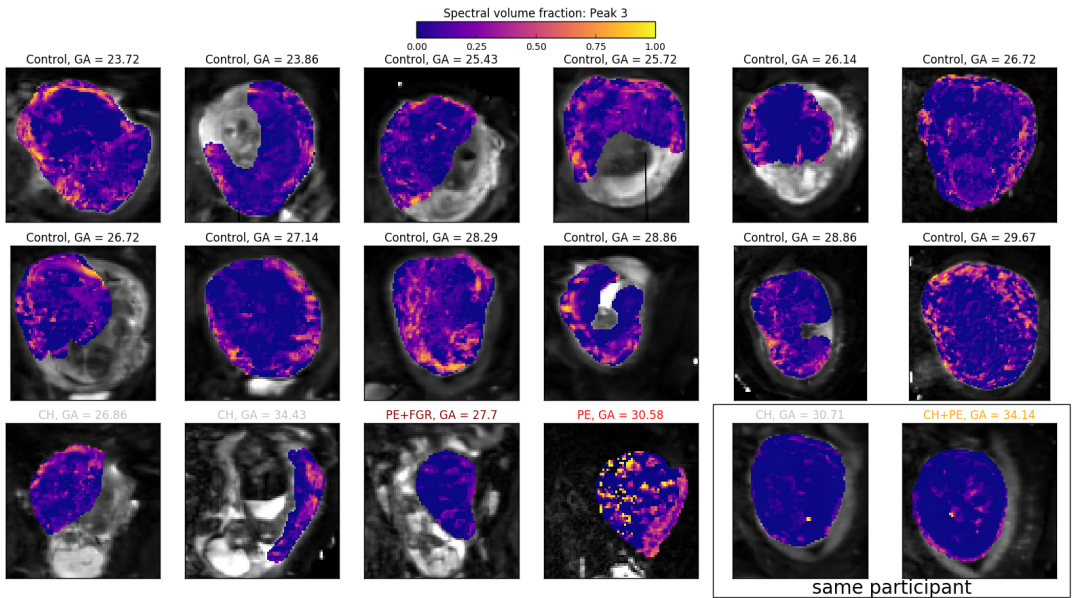
**FIGURE S2** T2\*-ADC spectra derived from inverse Laplace transforms of the spatially averaged signal within placenta ROIs.



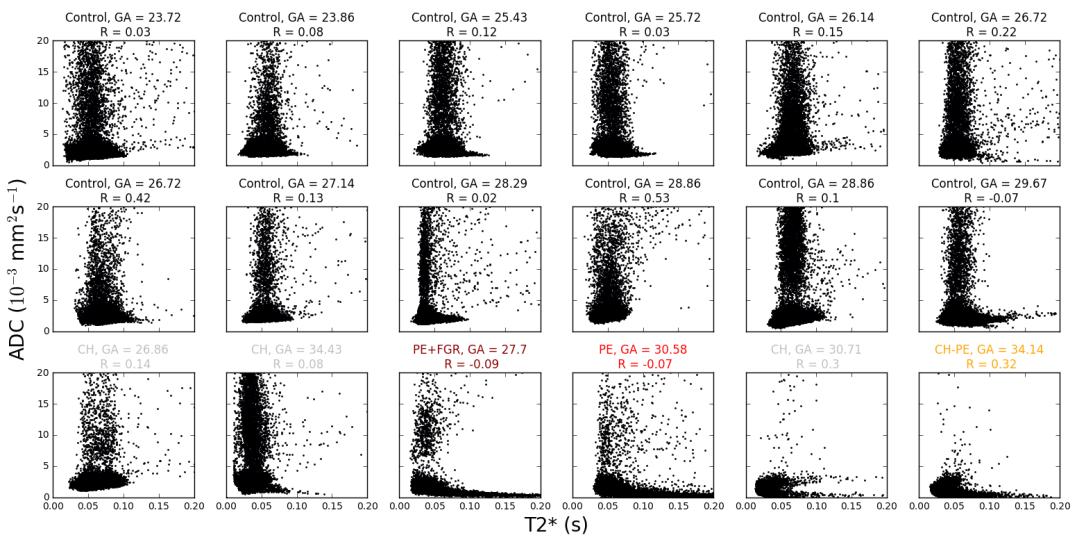
**FIGURE S3** Spectral volume fraction maps, obtained by summing the T2\*-ADC spectrum weight within the domain where  $ADC < 25 \times 10^{-3} \text{ mm}^2 \text{ s}^{-1}$ .



**FIGURE S4** As Figure S3, but for the domain where  $25 \times 10^{-3} \text{ mm}^2 \text{ s}^{-1} < \text{ADC} < 200 \times 10^{-3} \text{ mm}^2 \text{ s}^{-1}$ .



**FIGURE S5** As Figure S3, but for the domain where  $200 \times 10^{-3} \text{ mm}^2 \text{ s}^{-1} < \text{ADC} < 1000 \times 10^{-3} \text{ mm}^2 \text{ s}^{-1}$ .



**FIGURE S6** Correlation between T2\* and ADC from combined ADC-T2\* fit.