Perfusion fraction derived from diffusion-weighted MRI in the assessment of placental vascular malperfusion antenatally

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Dansk resume


Formål: Målet med dette studie var at vurdere om den placentale perfusionsfraktionen (f), deriveret fra diffusionvägget magnet resonans skanning (DWI), kan bruges til at identificere specifikke typer af placental vaskulær malperfusion antenatalt.

Metode: 93 kvinder der havde gennemgået placental DWI og post-partum histopatologisk placentaundersøgelse, blev identificeret i den lokale MRI forskningsdatabase. Baseret på resultatet fra den histopatologiske placentaundersøgelse, blev 44 defineret som normale kontroller, og 49 som cases med placental vaskulær malperfusion. Vaskulær malperfusion blev yderligere inddelt i de specifikke subtyper føtal vaskulær malperfusion (n=13), maternel vaskulær malperfusion (n=30) og cases med begge tilstande tilsted (n=6). Placental DWI blev udført i gestationsuge 23.9 – 41.3. For hver placenta indtegnedes regions of interest på tre placentale slices og det gennemsnitlige f for hele placentaen blev estimeret gennem intravoxel incoherence motion analyse.

Resultater: I normale kontroller var det gennemsnitlige f 26.02% SD ± 4.55 og vi fandt ingen lineær korrelation mellem f og gestationsalder, p=0.72. Vi fandt ingen signifikant forskel i f mellem cases med vaskulær malperfusion (gennemsnit 24.74% SD ± 5.83) og normale kontroller, p=0.25. I placentærer med føtal vaskulær malperfusion (gennemsnit 22.73% SD ± 4.43) fandt vi at f var signifikant lavere sammenlignet med normale kontroller, p=0.03. Denne forskel i f kunne ikke detekteres i placentærer med maternel vaskulær malperfusion (gennemsnit 25.24 SD ± 6.40, p=0.55).

Konklusion: Vores resultater viser at f deriveret fra DWI kan differentiere føtal vaskulær malperfusion fra normal placenta histologi in vivo og at f potentielt kan fungere som et komplement i den antenatale diagnostikken af specifikke placentapatologier. Der er dog behov for yderligere forskning indenfor dette område før at metoden kan blive apliceret i klinikken.
Abstract

Introduction: Today most placental pathologies that impact fetal development, such as vascular malperfusion, are diagnosed postpartum. We aimed to evaluate if placental perfusion fraction ($f$) derived from diffusion-weighted magnetic resonance imaging (DWI) can be used to identify specific types of placental vascular malperfusion antenatally.

Method: 93 women who underwent placental DWI and postpartum histopathological examination were identified in the local placental MRI research database. Based on the placental examination, 44 were defined as normal controls and 49 cases had placental vascular malperfusion. Vascular malperfusion was subdivided into the specific subtypes fetal vascular malperfusion (n=13), maternal vascular malperfusion (n=30) or both fetal and maternal (n=6). Placental DWI was performed at gestational week 23.9 – 41.3. For each placenta, regions of interest were drawn on three placental slices and their mean $f$ was estimated using intravoxel incoherence motion analysis.

Results: In normal placentas mean $f$ was 26.02% SD ± 4.55 and no linear correlation between $f$ and gestational age was found, $p = 0.72$. When comparing $f$ between normal placentas and cases of vascular malperfusion (mean 24.74% SD ± 5.83), no significant difference could be demonstrated, $p = 0.25$. Placentas with fetal vascular malperfusion showed a significantly lower $f$ (mean 22.73% SD ± 4.43) compared to normal controls, $p = 0.03$. In cases of maternal vascular malperfusion (mean 25.24 SD ± 6.40), we could not detect a significant difference in $f$, $p = 0.55$.

Conclusions: These results show that DWI-derived $f$ can distinguish fetal vascular malperfusion from normal placental histology in vivo. However, this method requires further exploration before it can be applied in clinical practice.

List of abbreviations:
MVM: Maternal vascular malperfusion
FVM: Fetal vascular malperfusion
IUGR: Intrauterine growth restriction
DWI: Diffusion-weighted magnetic resonance imaging
IVIM: Intravoxel incoherent motion
$f$: Perfusion fraction
D: Diffusion coefficient
D*: Pseudo-diffusion coefficient
GA: Gestational age
SGA: Small for gestational age
ROI: Region of interest
AGA: Appropriate for gestational age
1. Introduction

The placenta is vital for fetal growth and development, providing the fetus with the essential nutrients and oxygen throughout the pregnancy. Pathologies in the highly vascularized placenta can affect both the maternal and the fetal circulation, leading to suboptimal placental function and possible diverse effects on the fetus [1]. Currently, there are limited options in the assessment of placental function and pathologies in vivo. Sonographic examinations are standard procedures in the antenatal care. This examination provides estimates of fetal weight by fetal biometrics and measurements of fetal and umbilical circulation using Doppler flow, which is an indirect estimate of the placental function [2]. However, sonographic examinations are limited in the detection of specific pathologies, which are typically diagnosed at the postpartum histopathological examination. Therefore a sensitive non-invasive technique to identify placental pathology during pregnancy would be ideal, to optimize the antenatal care and the timing of delivery [3,4].

Placental vascular pathologies like maternal vascular malperfusion (MVM) and fetal vascular malperfusion (FVM) may compromise the fetal supply of oxygen and nutrients. These conditions are associated with serious pregnancy complications such as intrauterine growth restriction (IUGR), asphyxia and stillbirth [5]. Recently the Amsterdam International Consensus group established reviewed terminologies for placental vascular pathologies [6]. MVM is a constellation of pathologies affecting the maternal decidual vessels and chorionic villi [7]. Manifestations of MVM include gross pathological findings as well as microstructural abnormalities, likely caused by defective remodeling of the myometrial spiral arterioles [7–9]. Similarly, FVM is a term covering pathologies affecting the fetal circulation. FVM manifests as pathological findings seen throughout the fetal vascular tree, from the umbilical cord vessels to terminal villi and can be global as well as segmental [9,10]. These findings include thrombosis and avascular villi, and the etiology can be placental, maternal as well as fetal [6,9]. Pathologies like MVM and FVM lead to alterations in microcirculation and the placental perfusion, possibly detectable in vivo by using appropriate imaging techniques [7,11].

Diffusion-weighted magnetic resonance imaging (DWI) may provide information of tissue pathology non-invasively. DWI measures the movement and diffusion of water molecules within tissues, which depends on factors like cell membranes, density of the tissue, and extracellular space [3,12]. By applying intravoxel incoherent motion (IVIM) analysis on DWI-data it is possible to acquire information about both tissue diffusion and perfusion. Diffusion coefficient (D) refers to small-scale diffusion, whilst pseudo-diffusion coefficient (D*) refers to large-scale diffusion and microcirculation. Perfusion fraction (f) refers to the percent of moving blood volume in a given tissue, reflecting blood microcirculation in this area [13]. Previous studies have investigated DWI as a potential method to assess placental function in vivo, correlating placental perfusion with gestational age (GA) and complications like IUGR and preeclampsia [8,14–16]. A previous small pilot study by Anderson et al. investigated the correlation between f and specific types of placental pathology, showing a significantly lower f in pregnancies complicated by IUGR and FVM when compared to normal pregnancies. This finding suggests that f may be an additional tool in the assessment of placental function in vivo [8]. Vascular pathologies like MVM and FVM affects the placental microcirculation leading to altered perfusion, and are usually detected postpartum [7,11]. The objective of this study was to evaluate DWI-derived f as a potential non-invasive method to detect placental vascular malperfusion antenatally.
2. Methods

2.1 Subjects
This is a case control study, using data retrieved from the local placental MRI research database. We included 93 women with singleton pregnancies, who underwent placental DWI at varying GA (week 23.9 – 41.3) and postpartum placental histopathological examination at Aalborg University hospital from 2017 – 2020. Out of these, 44 were defined as normal placental controls, as the postnatal histopathological placental examination revealed no sign of vascular malperfusion, delayed villous maturation, or villitis. 49 placentas were classified as cases of placental vascular malperfusion. Vascular malperfusion was then further subdivided into MVM (n=30), FVM (n=13) and these conditions combined (n=6). Small for gestational age (SGA) was defined as birth weight – 22 % of the expected for gestational age by the reference of Maršál el al. [17]. Cases of mosaic pregnancies were not included in this study. Characteristics of the study populations are described in table 1. This study was approved by the Regional Committees on Biomedical Research Ethics of Central Denmark Region and North Denmark Region. Oral and written consent were obtained from all participants.

2.2 DWI protocol
All women underwent the same MRI protocol on a 1.5 T MRI scanner (GE450, GE Healthcare, Milwaukee, WI, USA) using an eight-channel receiver coil placed on the abdomen, covering the entire uterus. To avoid aorto-caval compression, all women were placed in a left lateral tilt position during the examination. To provide an overview of the anatomic orientation of the placenta, an initial T2-weighted localizing scan was performed. An echo-planar DWI sequence with 10 different b-values was obtained (0, 10, 20, 30, 50, 80, 100, 200 and 1000 s/mm²) perpendicular or longitudinal to the placenta. The number of slices varied between 7-10 slices, depending on the size of the placenta, with slice spacing of 1 mm and slice thickness of 5 mm (FOV: 40 x 40 mm, TE: ~ 54 ms, TR: 8000 ms). The examination time for the total MRI research protocol was approximately 30 min, of which the acquisition time for the DWI sequence was approximately 1 min and 15 s.

2.3 Data processing
Regions of interest (ROI) were drawn covering the entire placenta in three transversal or sagittal slices using RoiTool, an in-house developed tool written in MATLAB (The MathWorks Inc., Natick, MA, USA). Each ROI covered as much of the placenta as possible. The three placental slices were chosen with an even distance between each slice, to represent tissue throughout the whole placenta. The shape of each ROI was manually modified for all b-values, to adjust for maternal and fetal movements during DWI. For all placentas, IVIM analysis was used to estimate the f for each of the three placental slices. IVIM initially uses a robust linear fit of the log transformed signal values for b >= 200, followed by a nonlinear least squares fit of the IVIM equation using M0, f, D and D* as free parameters, including B0. Finally, a mean value for f was calculated as an average of the three placental slices.

2.4 Histopathological examination
A single experienced placental pathologist assessed all placentas at the postpartum histopathological examination. The pathologist had access to clinical information but was blinded to the MRI results. Placental pathology was classified according to the recently formulated international consensus by the Amsterdam Placental Workshop Group [6].
2.5 Statistics
To investigate the correlation between GA and $f$ in normal controls, linear regression analysis was used. Logistic regression was used to investigate the relation between $f$ and placental localization and the relation between $f$ and birth weight. Student’s t-test was used to compare mean $f$ between normal controls and cases of vascular malperfusion as well as the subgroups MVM and FVM. Variation in $f$ within each placenta was estimated for normal controls and correlated to GA using linear regression. A student’s t-test was performed to investigate whether there was a significant difference in the variation in $f$ between normal controls and cases of vascular malperfusion. For all analyses, p-values < 0.05 were considered significant. The data analysis was performed using the statistical software package Stata®15.1 (StataCorp LP, College Station, TX, USA).

Fig. 1 A: Illustration of three selected placental slices extracted from RoiTool with slice thickness of 5 mm, slice spacing of 1 mm and FOV: 40 x 40 mm. Regions of interest covering the entire placenta are marked in color. B: Illustration of 10 b-values (0, 10, 20, 30, 50, 80, 100, 200 and 1000 s/mm²) obtained from slice 3 presented in figure 1A.
3. Results

The characteristics of the study population are presented in table 1.

3.1 Perfusion fraction in normal controls
In normal controls (n=44) mean placental $f$ was 26.02% SD ± 4.55. When investigating the correlation between GA and $f$ in this group, no linear correlation was found, $p = 0.72$. The location of placetas in our normal controls was defined as either primarily anterior (n=18) or posterior (n=26). Anterior placentas had a mean $f$ of 25.22% SD ± 5.00 and posterior placentas had a mean $f$ of 26.57% SD ± 4.22, and no significant difference in mean $f$ was detected between the groups, $p = 0.17$.

3.2 Perfusion fraction in vascular malperfusion
Cases of vascular malperfusion (n=49) included placentas with MVM (n=30), FVM (n=13) and these two conditions combined (n=6). This group had a mean $f$ of 24.74% SD ± 5.83. When comparing this to mean $f$ in normal controls (26.02% SD ± 4.55), no significant difference was detected, $p = 0.25$. When comparing mean $f$ in the subgroup MVM (25.24 SD ± 6.40) to mean $f$ in normal controls, we detected no significant difference between these groups, $p = 0.55$. Placentas with FVM showed a significantly lower $f$ (mean 22.73% SD ± 4.43) than normal controls (mean 26.02% SD ± 4.55), $p = 0.03$.

3.3 Variation in perfusion fraction
To estimate the variation in $f$ over gestational age in normal controls, the spread of $f$ within each placenta was calculated and represented as SD. We found a mean variation in $f$ of 2.94 SD, ranging from 0.28 – 8.95 SD in normal controls. No linear correlation with GA was found in this group, $p = 0.24$. Following, we compared mean variation between normal controls (2.94 SD ± 2.07) and cases of vascular malperfusion (3.27 SD ± 2.10) and found no significant difference, $p = 0.45$.

3.4 Perfusion fraction and birth weight
When investigating the correlation between $f$ and birth weight, no significant difference was detected between the group with normal birth weight (n=77) and SGA (n=16) with mean $f$ 25.05 SD ± 4.68 and 26.77 SD ± 7.57 respectively, $p = 0.27$.
Table 1 Characteristics of normal controls and cases of vascular malperfusion, further divided into subgroups fetal vascular malperfusion and maternal vascular malperfusion. Values are presented as median (interquartile range) or n (%). Wilcoxon rank-sum were used for continuous variables and Pearson's chi-squared test for binary variables when comparing groups. The standardized reference curves for birth weight used in Denmark are defined after Maršíal et al.

<table>
<thead>
<tr>
<th>Variables</th>
<th>Normal histology</th>
<th>Vascular malperfusion</th>
<th>p-value</th>
<th>Subgroups vascular malperfusion</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N=44</td>
<td>N=49</td>
<td></td>
<td>N=30</td>
</tr>
<tr>
<td>Maternal age in years, median (IQR)</td>
<td>29 (28-33)</td>
<td>28 (24-31)</td>
<td>0.050</td>
<td>27 (24-31)</td>
</tr>
<tr>
<td>Nullipar, n (%)</td>
<td>19 (43%)</td>
<td>29 (59%)</td>
<td>0.12</td>
<td>20 (67%)</td>
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<td>Caucasian, n (%)</td>
<td>40 (95%)</td>
<td>45 (92%)</td>
<td>0.87</td>
<td>28 (93%)</td>
</tr>
<tr>
<td>BMI, median (IQR)</td>
<td>27.2 (23.7-30.8)</td>
<td>27.7 (24.0-31.5)</td>
<td>0.78</td>
<td>27.6 (23.8-32.0)</td>
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<tr>
<td>Current smoker, n (%)</td>
<td>4 (9%)</td>
<td>9 (18%)</td>
<td>0.20</td>
<td>6 (20%)</td>
</tr>
<tr>
<td>Diabetes, n (%)</td>
<td>3 (7%)</td>
<td>3 (6%)</td>
<td>0.89</td>
<td>3 (10%)</td>
</tr>
<tr>
<td>Systolic blood pressure, median (IQR)</td>
<td>120 (114-128)</td>
<td>127 (118-132)</td>
<td>0.076</td>
<td>128 (118-132)</td>
</tr>
</tbody>
</table>

At the time of MRI
- Gestational age at MRI, median (IQR)
  - GDW < -2SD at MRI, n (%) for four MRI
- Location of placenta
  - Anterior, n (%) for five MRI
- Posterior, n (%) for four MRI

At the time of birth
- Gestational age at birth in weeks, median (IQR)
- Birth weight in grams, median (IQR)
- Birth weight z-score, median (IQR)
- Birth weight < -2SD, n (%) for three MRI

Fig. 3 Perfusion fraction (f).
A: The correlation between f and gestational age in normal controls. B: The correlation between f and placental location, defined as either primarily anterior (black rhombus) or posterior (open rhombus), in normal controls over gestational age. C: f in normal controls (black circle) and cases of vascular malperfusion (grey triangle) over GA. D: f in normal controls (black circle), cases of fetal vascular malperfusion (grey triangle), and maternal vascular malperfusion (open triangle) over gestational age.
Variation in perfusion fraction
Normal histology

Variation in perfusion fraction
Normal histology and vascular malperfusion

**Fig. 4** Variation in $f$. **A:** The correlation between variation in $f$ and gestational age in normal controls. **B:** Variation in $f$ in normal controls (black circle) and cases of vascular malperfusion (grey triangle) over gestational age.

**Fig. 5** $f$ in the total study population divided into normal birth weight (black circle) and small for gestational age (grey rhombus) defined as birth weight $< -22\%$.

### 4. Discussion

#### 4.1 Principle findings
We found that $f$ is significantly reduced in cases of FVM as compared to normal controls, but not in cases of MVM or cases of vascular malperfusion in general. Secondarily, we could not detect any association between $f$ and low birth weight.

#### 4.2 Strengths and limitations
To our knowledge, this is the largest study that investigates $f$ as a method to detect vascular malperfusion [8,15,16,18]. To ensure uniform pathological classifications, the same expert placental pathologist performed all histopathological exams, blinded to placental MRI results but not the clinical outcomes. The classification of placental pathologies is complex, and despite efforts to standardize the diagnostic procedure there is still a degree of subjectivity in these diagnoses. Two trained research assistants, blinded to all clinical data, assessed each placental image to ensure that the placental ROIs were as accurate as possible. In this study $f$ was estimated as an average of three placental slices to give a general $f$ of the whole placenta, rather than calculating $f$ from a single slice that reflects placental perfusion on that specific level. It would however be ideal if all placental tissue could be included in the analysis to acquire the most truthful estimate of $f$. 
4.3 Perfusion fraction in normal controls
In this study we found a mean $f$ of 26.02% in normal controls, defined as placentas with no histological signs of vascular malperfusion or other significant pathologies. This is comparable to the results of a previous study with a mean $f$ of 26% in normal healthy pregnancies [19]. Other studies have reported slightly higher $f$ values of 29%, 36.2%, and 40.65% in placentas in pregnancies with normal birth outcome [16,18,20]. However, there are some differences in study design as these studies define normal controls based on birth outcome whereas our study define normal controls based on the histopathological placental examination. Also, the study that reported the median $f$ value of 29% only included placentas that were located anteriorly in the uterus, due to MRI technical reasons [18]. To investigate whether location of the placenta had an effect on $f$, we compared mean $f$ in anterior and posterior placentas and found no difference, implying that the method used in this study is applicable regardless of placental location.

In the analysis of $f$ in normal controls, we could not find a linear correlation between $f$ and GA in the interval 23.9 – 41.3 weeks. Previous literature on this topic is conflicting [8,15,18-21]. A previous study evaluated changes in $f$ in a narrow interval of GA (week 24 – 29) in pregnancies with newborns appropriate for gestational age (AGA), and found no correlation between $f$ and GA [20]. On the contrary, a study including 26 normal pregnancies found an increase in $f$ over GA in the central placental region, as well as in the peripheral placental region after week 30 [15]. However, other studies of similar sample size, including the entire placenta in the ROIs, demonstrated a negative linear correlation between $f$ and GA in normal pregnancies [8,18]. The present study included a larger cohort of normal controls, where $f$ values were more evenly distributed over GA, instead of representing $f$ at early and late GA respectively. The results of this study suggest that $f$ remains relatively constant throughout pregnancy, which might be explained by the fact that DWI derived $f$ reflects the percent of moving blood volume in a given region. Although the vascular bed grows and the placental flow increases with GA, it can be hypothesized that the fraction of blood flow will remain relatively constant throughout pregnancy to allow optimized diffusion across the villi [20,22].

4.4 Perfusion fraction in cases of vascular malperfusion
Cases of vascular malperfusion, including both fetal- and maternal vascular malperfusion, did not differ in mean $f$ compared to normal controls, which might have an explanation in the pathophysiology of these conditions. MVM and FVM are not single lesions but newly established terminologies covering several pathological manifestations, in an attempt to uniform the international classification [6]. FVM covers a group of placental lesions related to impaired feto-placental perfusion, including thrombosis of the fetal chorionic plate and umbilical cord, avascular villi, and villous stromovascular karyorrhexis [6,9]. Manifestations of MVM include gross pathological lesions as well as histological findings, affecting the maternal decidual vessels and chorionic villi, which may alter the microcirculation and perfusion of the placenta [7,23]. A leading theory is that the lesions characterizing MVM are caused by defective remodeling of the myometrial segments of the spiral arterioles [23]. Unremodeled spiral arterioles can cause compromised uteroplacental blood flow and placental underperfusion, but also lead to increased velocity and turbulent blood flow due to rigid arterial walls [7].
We found a significantly lower $f$ in cases with FVM, as compared to normal controls. The reduced mean $f$ seen in this group might reflect the fetal underperfusion characterizing FVM, which is in line with the results from a previous pilot study [8]. However, corresponding to other similar studies, we found no significant difference in $f$ when comparing cases of MVM with the normal controls [8,16]. As the parameter $f$ measures the volume blood flow within each voxel compared to the total voxel volume, it reflects both the volume and velocity of the circulating blood. The difference in $f$ might therefore to some extent be related to the properties of the IVIM-analysis, and the physiology of the placenta. Both the placenta blood volume and velocity are dependent on the amount of functional capillaries and their diameter [13]. The maternal circulation is characterized by turbulent blood flow, due to the unrestricted movement of maternal blood in the intervillous space. The turbulence in blood flow and shifting velocity in combination with the pathological under- and overperfusion of MVM, might affect the accuracy of the estimated $f$. This could indicate that $f$ is not yet a suitable method in the detection of vascular impairment in the maternal placenta [13]. As opposed to this, the fetal circulation is characterized by high velocity blood flow, and since FVM results in reduced fetal blood flow and perfusion, $f$ could be a useful method in the detection of these vascular changes [11].

FVM has been estimated to be present in 25 % of preterm placentas and is strongly associated with IUGR and stillbirth [24,25]. Serious neonatal complications like intracranial hemorrhage, cerebral palsy, and necrotizing enterocolitis have also been linked to FVM [5,11]. Furthermore, FVM is associated with a higher rate of obstetric complications and an increased need for cesarean deliveries, as well as higher illness severity the first 24 hours [5,9]. Our finding is relevant since it suggests that FVM can already be detected antenatally instead of post-partum, to improve the antenatal monitoring and the timing of delivery.

4.5 Variation in perfusion fraction
To the best of our knowledge, the variation in $f$ within the placenta has not previously been investigated. We observed a large range in variation in $f$ within the individual placentas and found no correlation between this variation and GA. The variation in $f$ within the placenta might be explained by the heterogeneity of this organ, and in previous attempts to map the placental perfusion it has been shown that $f$ varies between regions [13,26]. The same study observed that $f$ seemed to be more homogenous in placentas in pregnancies complicated by IUGR, as compared to uncomplicated pregnancies [13]. However, in our study we could not demonstrate any differences in variation in $f$ between the cases of vascular malperfusion compared to normal controls. This could indicate that the variation in $f$ is naturally present in normal heterogenic placentas, and not necessarily associated with placental pathology.

4.6 Perfusion fraction and birth weight
The association between $f$ and birth weight have previously been investigated, while our study mainly explored the association between $f$ and placental histology. Birth outcome and placental histology are different measurements of placental function, and as a sub-analysis we aimed to investigate whether $f$ has a predictive value in the detection of fetal growth restriction. A previous study found no linear correlation between $f$ and birth weight [16]. Relatedly, we found no difference in mean $f$ when comparing SGA and normal birth weight. Our results stand in contrast to the results of a previous study that found $f$ to be significantly lower in pregnancies that delivered SGA neonates compared to AGA [20]. However, this study differs from ours in the regard that the fetal weight percentile was estimated using a software tool, whereas we used standardized references curves to define normal and low birth weight [17,20].
The interpretation of these results is problematic, since the definitions of growth restriction differ between studies [16,20]. Furthermore, fetal growth does not only depend on placental function, but also on other factors such as family history of IUGR and numerous maternal factors [27]. Therefore, $f$ could to be useful in the assessment of placental function, but might not be sufficient as an individual tool in the detection of growth restriction.

4.7 Conclusion
Our results show that DWI-derived $f$ could distinguish FVM from normal placental histology in vivo. These results suggest that $f$ could be a future complimentary tool in the detection of specific placental pathology. However, there is a considerable degree of variation in the estimate of $f$ using DWI and IVIM analysis, which may challenge the conclusions of this study. Further research is required in this field to improve the method and thereby the clinical potential of the antenatal identification of specific placental pathology.
5. References


