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Diffusion and perfusion quantified by Magnetic Resonance Imaging are markers of human placenta development in normal pregnancy

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ABSTRACT

Purpose: To investigate the potential of bi-exponential model of diffusion-weighted (DW) signal decay to quantify diffusion and perfusion changes in human placenta of normal pregnancies due to its development.
Methods: 26 normal pregnancies at 19–37 weeks of gestation underwent Magnetic Resonance Imaging (MRI) examination at 1.5 T. DW Spin-Echo Echo Planar Imaging with diffusion gradients applied along 3 no-coplanar directions at seven different b-values (0,50,100,150,400,700,1000 s/mm^2) was used.
Apparent diffusion coefficient (ADC), pseudodiffusion (D*) and perfusion fraction (f) were extracted in selected placenta regions: umbilical (U-ROI), central (C-ROI) and peripheral (P-ROI). The relation between ADC, D*, f and mother age, gestational age (GA), Body-Mass Index (BMI), basal Glycaemia (bG), were evaluated. Pearson correlation with Bonferroni correction was used.
Results: A significant negative correlation was found between ADC and GA, for GA≥30w in P-ROI, while no-dependence of ADC on GA was observed in GA range 19–29 weeks. A positive linear correlation was found between f and GA in the C-ROI and between f and GA in P-ROI for GA≥30 week. No significant correlations were found between ADC, D*, f and age, BMI, bG.
Conclusion: ADC measurements in P-ROI of normal placenta reflects tissue changes occurring in the third trimester of gestation. Specifically, ADC decreases with GA increase. Besides, f increases with the GA increase in the C-ROI and during the third trimester of pregnancy in the P-ROI.
These results suggest the potential of diffusion and perfusion parameters extracted by using a biexponential model to provide information about placenta changes during its development.

1. Introduction

Human placenta, comprised of maternal and fetal parts, is the organ dedicated to the metabolic exchange between mother and fetus [1]. To carry out this function, the placenta consists of complex tissue microstructures, with a broad variety of differently structured villi, and perfusion functions. The maternal blood basin, which is supplied by spiral arteries and drained by maternal veins [2], holds villous trees inside which fetal blood goes from umbilical arteries to the umbilical vein through fetal capillaries. Maternal blood percolates through the same arborous structure on the outside [3].

Placental morphological and physiological characteristics are related to health of the newborn and the future adult [4]. Moreover, abnormalities in placentation are responsible for pregnancy complications such as preeclampsia, severe growth restriction, late intrauterine death [5,6].

Due to the limited ability of ultrasound examinations to detect early evidence of placental dysfunction at a macroscopic level [7,8], the search for alternative tools to perform a sensitive and early diagnosis is highly desirable. In this regard, a suitable diagnostic tool should furnish both microstructural and vascular information in a non-invasive manner and without exposing a patient to

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ionizing radiation.

Diffusion-weighted imaging (DWI) is powerful Magnetic Resonance (MR) technique that provides microstructural and physiological information of human tissues without requiring exogenous contrast agents [9]. DWI can measure water proton displacements, within tissues, by probing molecular motion on the micrometer length scale. Therefore, the diffusion and perfusion parameters quantified by DWI techniques are especially sensitive to microscopic tissue changes. The apparent diffusion coefficient (ADC) of water molecules in tissues can be measured from DWI signal decay as a function of the different degrees of diffusion weights [9] through a simple fit of acquired data to a monoexponential function. By using a biexponential decay function and a wider range of degrees of diffusion weights, perfusion parameters such as perfusion fraction (f) and pseudodiffusion coefficient (D*) are also obtainable.

However, studies that address DWI as an adjunct to placenta MRI are limited [10–15]. Moreover, the potential of ADC, f and D* measurements in placenta to detect microstructural and vascular changes remains poorly defined. In particular, the promising role of ADC in detecting microstructural placenta changes is controversial [10,13,14].

Since the definition of biomarkers indicative of normal placenta development is essential to establish the potential of new diagnostic protocols, in this study we quantify both water ADC and blood perfusion in placentas of normal pregnancies as a function of the fetus gestational age (GA), by DWI acquisitions. Toward this goal, we examined the placenta of pregnant women at 1.5T, by using a bi-exponential model of diffusion to quantify both water ADC and blood perfusion parameters in different placental sites and assessing their associations with subjects' clinical data such as: GA, body mass index (BMI), basal glycaemia (bG) and age of pregnant women.

2. Methods

Thirty normal singleton pregnancies (GA range 19–37 weeks), fulfilling the initial study inclusion criteria, underwent MRI examination without maternal-fetal sedation. The maternal position was supine. The study was approved by the local Ethics Committee, and written informed consent was obtained from all women before entering the study.

Study participants were recruited at Policlinico of Sapienza University of Rome, Italy, during March–October 2016. All women in our cohort had at least two ultrasound measures (including umbilical and uterine artery Doppler) obtained at different gestational age to assess normal pregnancies.

Patients with suspected utero-placental insufficiency or placental anomalies were excluded.

Women with chronic hypertension, diabetes mellitus or pre-existing renal disease and women with contraindications to the use of MRI were not included in the study. A normal pregnancy was finally defined as single pregnancy in a woman who gave birth at term (>37 weeks of gestation) to a newborn appropriate for the gestational age (birth weighted within ±2 standard deviation of the standard reference for newborns) [16] (post-delivery criteria).

Information on maternal age, BMI and bG at the GA was obtained from the women's medical records. GA was assessed by an early second trimester ultrasound examination and by last menstrual period (LMP) dating.

Characteristics of the study population are described in Table 1.

The MRI protocol performed with a 1.5T scanner (Siemens Avanto, Erlangen, Germany), included a Diffusion-weighted Spin Echo Echo Planar Imaging with repetition time/echo time, TR/TE = 4000ms/79ms; bandwidth = 1628 Hz/px; matrix size = 192 × 192. The number of slices was from 18 to 30. The in-plane resolution was 2.0 × 2.0 mm^2 and the slice thickness, STK = 4 mm. The diffusion encoding gradients were applied along 3 no-coplanar directions using seven different b-values (0,50,100,150,400,700,1000 s/mm^2). The number of averaged signal (NS) for each b value was NS = 4 and the total acquisition time of DW protocol was 6 min.

Table 1
Demographic and clinical data of the investigated women cohort.

	Average	Max	Min
Gestational age at MRI (weeks)	28	37	19
Maternal Age	33	52	22
Basal Glycaemia (mg/dL)	75	95	60
Blood Pressure (mmHg)	110/70	120/80	90/60
Body Mass Index (BMI)	25	36	18

Adequate anatomical visualization of the uterus and the placentary tissue were obtained in all cases by using T2-weighted MRI in coronal and transversal view with TE/TR = 118/1100ms and 149/1000ms, respectively.

DICOM images of DWI acquisitions were elaborated off line with suitable software and homemade scripts in MATLAB (MathWorks 8.1, R2013a, 1994–2017 The MathWorks, Inc.) were used. The preprocessing of data was performed with the use of FMRIB Software Library, v5.0 (FSL,Oxford, UK). The DWIs were realigned with respect to the b = 0 image using FLIRT tool with six degree of freedom. Even though FSL is optimized for brain environment, good quality results were obtained. The images were carefully examined to exclude miss-registrations. Since low Signal to Noise Ratio (SNR) of DWIs is an obvious drawback for diffusion techniques, we assessed SNR of DW image acquired at each b value. In order to estimate the SNR, we selected an area in the placenta to compute the signal, and an area placed outside the subject's body to compute the background noise, and took the ratio between the mean of the signal and the standard deviation (SD) of the noise times 0.655. The 0.655 factor is due to the Rician distribution of the background noise in a magnitude MRI image. The average value of SNR over a cohort of five subjects was then computed.

To investigate the potential of biexponential model to quantify both water ADC and blood perfusion in placenta we choose to investigate placental areas with different relative contribution of perfusion and diffusion. Therefore, after a careful examination of the literature concerning placental tissue microstructural features [17] we chose three rois depending on distance from lateral distance across uterine wall. Specifically, three volumetric Regions of Interest (ROIs) were identified in each placenta by an expert radiologist: Central ROI (C-ROI), Peripheral ROI (P-ROI) and Umbilical ROI (U-ROI) were bordered as shown in Fig. 1. Placentones (a placentone is a one villous tree plus the related part of the intravillous space) in peripheral placenta are more clearly separated from each other. In the thicker, more central regions of the placenta, most villous trees overlap causing less distinct differences between maternal inflow and outflow areas in placentone [17]. In the Umbilical region, due to the massive presence of vessels, we expect a greater contribution from perfusion.

Each volumetric ROI was obtained by joining two-dimensional masks, which were identified on different slices. The number of slices varied from one to four, depending on the gestational age. Data were spatially smoothed using a Gaussian filter with full-width-half-maximum of 3.2 mm. Signal intensity in each ROI was averaged and data was fitted to the bi-exponential function [18–20]:

$$S(b)/S(0) = f\exp(-b\cdot D^*)+(1-f)\cdot\exp(-b\cdot ADC) \quad (1)$$