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Placental perfusion in normal pregnancy and early and late preeclampsia: A magnetic resonance imaging study

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ABSTRACT

Objective: Our primary aim was to investigate if women with early or late preeclampsia have different placental perfusion compared with normal pregnancies. A secondary aim was to investigate if placental perfusion changes with increasing gestational age in normal pregnancy.
Methods: The study population included thirteen women with preeclampsia (five with early and eight with late preeclampsia) and nineteen women with normal pregnancy (ten with early and nine with late pregnancy). Early was defined as <34 weeks and late as ≥34 weeks gestation. All women underwent a magnetic resonance imaging (MRI) examination including a diffusion weighted sequence at 1.5 T. The perfusion fraction was calculated.
Results: Women with early preeclampsia had a smaller placental perfusion fraction ($p = 0.001$) and women with late preeclampsia had a larger placental perfusion fraction ($p = 0.011$), compared to women with normal pregnancies at the corresponding gestational age. The placental perfusion fraction decreased with increasing gestational age in normal pregnancies ($p = 0.001$).
Conclusion: Both early and late preeclampsia differ in placental perfusion from normal pregnant women. Observed differences are however in the opposite direction, suggesting differences in pathophysiology. Placental perfusion decreases with increasing gestational age in normal pregnancy.

1. Introduction

Previous studies have suggested that placental hypoxia is an important factor in the development of preeclampsia, especially of early onset [1,2], which is considered to be more related to an abnormal placentation than late onset disease [1–3]. Most previous knowledge on placental function originates from animal studies [4–6], histopathological placental studies [2], *in-vivo* studies with invasive techniques with very few study subjects [7,8], or from studies using Doppler blood flow measurements in the uterine or umbilical arteries [9,10]. There is limited data on visualizing actual *in-vivo* placental perfusion in preeclampsia, as well as in normal pregnancy.

Magnetic resonance imaging (MRI) is a technique with high soft tissue contrast, with no known side effects during pregnancy [11–13]. In addition to information on morphology, it can also provide physiological information. One of these measures is the perfusion fraction, which is an estimate of the volume fraction of perfused tissue [14,15]. This is obtained with the intravoxel incoherent motion (IVIM) technique, which is based on the acquisition of a diffusion weighted sequence with multiple degrees of diffusion weighting (*b*-values). By comparing the signal intensity at the different *b*-values, the perfusion fraction can be calculated. The technique does not require any contrast agent administration, and can be performed in a few minutes. It has been shown to correlate with established, contrast agent based measurements of perfusion [16], which cannot be used in pregnant women for safety reasons.

In a few small previous studies, placental perfusion in normal pregnancy has been studied using the IVIM-technique [17–19]. One of these studies showed a trend toward a decrease in the placental perfusion fraction with increasing gestational age [19]. In pregnancies affected by intrauterine growth restriction with or without preeclampsia the perfusion fraction was smaller than in normal pregnancy [18]. The perfusion fraction in the basal plate of the

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placenta has been shown to be reduced in preeclampsia with and without intrauterine growth restriction [17]. It has not been studied whether differences in placental perfusion fraction between preeclampsia and normal pregnancy depend on time of preeclampsia onset.

Based on existing theories concerning differences in pathophysiology between early and late preeclampsia, we hypothesized that the placental perfusion would be reduced in early preeclampsia compared with early normal pregnancy but not affected in late preeclampsia compared with late normal pregnancy. The primary aim of this study was to compare the placental perfusion fraction in early preeclampsia with early normal pregnancy and to compare the placental perfusion fraction in late preeclampsia with late normal pregnancy. We aimed also to assess the possible relation between perfusion fraction and gestational age in normal pregnancy.

2. Materials and methods

The regional ethical review board in Uppsala, Sweden, approved the study and informed consent was obtained from each woman participating in the study.

Study participants were recruited at Uppsala University Hospital, Sweden, during 2008–2013. Only single pregnancies with a living fetus and a gestational length between 22 + 0 and 41 + 6 weeks were included. Gestational age was assessed by an early second trimester ultrasound examination. Women with chronic hypertension, diabetes mellitus or pre-existing renal disease were not included in the study.

Women suffering from severe claustrophobia were not included. For technical reasons related to other MR investigations performed simultaneously (not presented here), only women with an anterior placenta and a body mass index (BMI) of 36 or less were included.

Sixteen women with preeclampsia were recruited from the obstetric ward or outpatient clinic. Preeclampsia was defined as hypertension of ≥140/90 at two separate occasions ≥4 h apart and proteinuria (≥2 + on a dipstick or a urine collection showing ≥ 300 mg/24 h).

Twenty-two women with normal pregnancies were recruited with the help of information posters at antenatal outpatient clinics in Uppsala, or during a visit to the clinic. A normal pregnancy was defined as a healthy, single pregnancy in a woman who gave birth at term (≥37 weeks of gestation) to a child appropriate for the gestational age (birth weight within ±2 standard deviations of the Swedish reference standard for newborns [20]).

Both women with preeclampsia and normal pregnancy were categorized into early (gestational age of <34 + 0 weeks at the time of examination) and late (≥34 weeks). There were six women with preeclampsia and ten with normal pregnancy in the early groups. The corresponding numbers in the late groups were ten and twelve.

Information on early pregnancy BMI, maternal age and parity was obtained from the women's medical records.

All study participants underwent blood pressure measurement, urine sampling, ultrasound assessment including an estimation of fetal weight and MRI examinations within a 24 h period. Systolic and diastolic blood pressures were measured in the right arm, in the supine position, after approximately 15 min rest, using a manual sphygmomanometer (Umedico CE) with a cuff size appropriate for the arm circumference. The mean arterial pressure was calculated ([(2 × diastolic) + systolic]/3). Fresh midstream urine samples were collected and analyzed with dipsticks for the presence of proteinuria (Roche Diagnostics GmbH, Mannheim, Germany). The ultrasound examinations included estimations of fetal weight, amniotic fluid index and Doppler blood flows in the umbilical and uterine arteries. All examinations were performed with Voluson E8 ultrasound equipment (GE Healthcare, Kretz Ultrasound, Zipf, Austria) using a 4–5 MHz transabdominal transducer. The ultrasound examinations were performed by six physicians all specialized in fetal medicine. Fetal weight deviation was based on the mean gestational age-related Scandinavian reference curve [21], and expressed as a percentage. Fetal growth was categorized into 1) appropriate for gestational age (−22% to +22%), 2) large for gestational age (>22%), 3) small for gestational age (<−22% and a normal umbilical artery pulsatility index) and 4) intrauterine growth restriction (<−22% and pathological umbilical artery pulsatility index). Oligohydramnios was defined as amniotic fluid index less than 5 cm.

MR imaging was performed with a 1.5 T scanner (Gyroscan ACS Intera, Philips Medical Systems, Best, the Netherlands) using the integrated body coil. An echo-planar imaging diffusion weighted sequence with five different *b*-values (0, 200, 400, 600, and 800 s/mm^2) was obtained perpendicular to the placenta, in order to avoid partial volume averaging. Depending on the size of the placenta, three to seven slices of six mm thickness were collected. Imaging time for the diffusion weighted sequence was typically 3:45 min.

Measurements of the perfusion fraction were performed with research software (PRIDE, Philips Medical Systems, Best, The Netherlands). In each slice from the diffusion weighted sequence, regions of interest were placed including as large parts of the placenta as possible, excluding areas with infarcts, hemorrhages or other artifactual signal loss. An example of a diffusion weighted image with measurement region is given in Fig. 1. The median, minimum and maximum volume of the examined part for all women was 97.1, 22.0 and 369.1 cm^3. Table 1 presents this information by study group. Estimates of the perfusion fraction were obtained using a mono-exponential fit for the signal intensities at *b*-values of 200–800 s/mm^2. Only estimates with a goodness of fit (R^2) of 0.9 or more were accepted for further analysis. The mean perfusion fraction from the different slices was calculated.

Differences in maternal characteristics and perfusion fraction between early preeclampsia and early normal pregnancy and late preeclampsia and late normal pregnancy were assessed with the Mann–Whitney *U* test. Proportions were compared using the Fisher's exact test. *p*-Values <0.05 were considered statistically significant. The relation between gestational age and perfusion fraction in normal pregnancy was estimated using simple linear regression. All analyses were performed using IBM SPSS Statistics 20 (IBM SPSS, Inc., Chicago, IL).

3. Results

Of the 38 included subjects, six were excluded because of severe artefacts prohibiting perfusion fraction calculations. All women with normal pregnancies gave birth at term (≥37 + 0 weeks) to an infant appropriate for gestational age.

Table 2 presents the maternal characteristics of the study participants. Women with preeclampsia did not differ in maternal age, early pregnancy BMI, proportion of primiparous women or in gestational length at examination compared to normal pregnancy. However, as expected they had higher systolic, diastolic and mean arterial blood pressures at examination. Moreover, 80% of the women with early and 62.5% of the women with late preeclampsia were taking blood pressure medication; all used Labetalol and one woman had a supplement of Nifedipine. In early preeclampsia the median estimated fetal weight deviation was −18% and of the five fetuses included in the group, two were estimated to be growth restricted and one of these also had oligohydramnios. Further, the mean pulsatility index in the uterine arteries was higher in women with early preeclampsia than in early normal pregnancies. Women with late preeclampsia did not differ regarding estimated fetal weight deviation, intrauterine growth restriction, oligohydramnios or mean pulsatility index in the uterine arteries parameters compared to late normal pregnancies.

Fig. 2 shows a comparison of the placental perfusion fraction between women with early preeclampsia and women with early

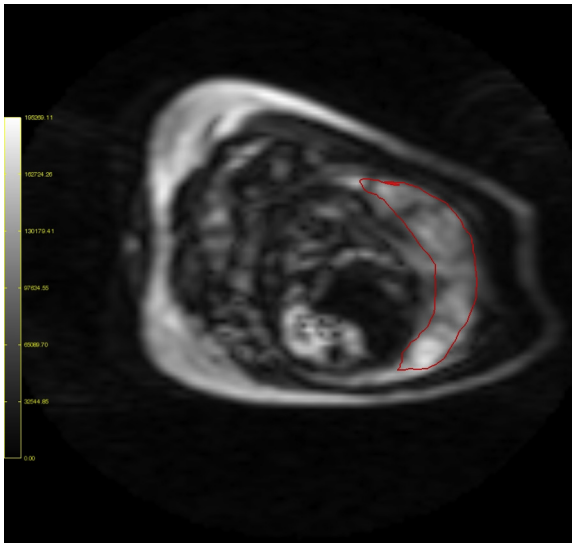

Fig. 1. Diffusion weighted image illustrating the region of interest (ROI) in the placenta. The perfusion fraction was calculated from measurements using the same ROI with different degrees of diffusion weighting.