

Magnetic resonance imaging-estimated placental perfusion in fetal growth assessment

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KEYWORDS: intrauterine growth restriction; magnetic resonance imaging; perfusion; perfusion fraction; placenta; small-for-gestational age

ABSTRACT

Objective To evaluate in-vivo placental perfusion fraction, estimated by magnetic resonance imaging (MRI), as a marker of placental function.

Methods A study population of 35 pregnant women, of whom 13 had pre-eclampsia (PE), were examined at 22–40 weeks' gestation. Within a 24-h period, each woman underwent an MRI diffusion-weighted sequence (from which we calculated the placental perfusion fraction), venous blood sampling and an ultrasound examination including estimation of fetal weight, amniotic fluid index and Doppler velocity measurements. The perfusion fractions in pregnancies with and without fetal growth restriction were compared and correlations between the perfusion fraction and ultrasound estimates and plasma markers were estimated using linear regression. The associations between the placental perfusion fraction and ultrasound estimates were modified by the presence of PE ($P < 0.05$) and therefore we included an interaction term between PE and covariates in the models.

Results The median placental perfusion fractions in pregnancies with and without fetal growth restriction were 21% and 32%, respectively ($P = 0.005$). The correlations between placental perfusion fraction and ultrasound estimates and plasma markers were highly significant ($P = 0.002$ and $P = 0.0001$, respectively). The highest coefficient of determination ($R^2 = 0.56$) for placental perfusion fraction was found for a model that included pulsatility index in the ductus venosus, plasma level of soluble fms-like tyrosine kinase-1, estimated fetal weight and presence of PE.

Conclusion The placental perfusion fraction has the potential to contribute to the clinical assessment of cases with placental insufficiency. © 2015 The Authors. *Ultrasound in Obstetrics & Gynecology* published by John Wiley & Sons Ltd on behalf of the International Society of Ultrasound in Obstetrics and Gynecology.

INTRODUCTION

Intrauterine growth restriction (IUGR) is a major cause of perinatal mortality and morbidity^{1–3} and is associated with long-term consequences, including impaired neurological development⁴ and increased risks of developing cardiovascular disease⁵ and metabolic syndrome⁶. There are no effective therapies to reverse IUGR, and antenatal management is aimed at determining the ideal time for delivery, sometimes very prematurely. However, preterm birth is also associated with both short- and long-term consequences for the infant^{7,8}, and therefore good diagnostic tools are needed when evaluating fetal health in cases of IUGR. The major cause of IUGR is placental insufficiency^{9,10}. The fetal response to placental insufficiency, and the resulting fetal hypoxia, is a progressive process, with early signs including stunted growth and minor changes in umbilical or cerebral artery blood flow¹¹. In clinical practice, placental function and fetal health in cases of suspected IUGR are assessed by ultrasound (to estimate fetal growth and the amount of amniotic fluid), Doppler velocimetry measurements and cardiotocography. Of the available methods, Doppler velocimetry has the strongest predictive value regarding fetal morbidity and mortality¹². It enables assessment of the circulation on both sides of the placenta, thereby

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making an indirect assessment of placental function, as well as of the consequent adaptive fetal circulatory changes¹¹.

Magnetic resonance imaging (MRI) is an established method in clinical investigations of fetal and placental anomalies. However, MRI can also provide physiological information such as the perfusion fraction, an *in-vivo* estimate of the volume fraction of perfused tissue^{13–15}, the examination for which can be performed within minutes. Previous studies have investigated the placental perfusion fraction *in vivo*^{16–19}. One study showed that a small placental perfusion fraction in the second trimester was strongly associated with delivering a small-for-gestational age (SGA) neonate¹⁷. The aim of this study was to investigate the placental perfusion fraction as a potential marker for placental function.

METHODS

This study was approved by the Regional Ethical Review Board in Uppsala, Sweden, and informed consent was obtained from each woman participating in the study.

Study population

The study cohort originated from a cross-sectional study of MRI-estimated placental perfusion in pre-eclampsia (PE)¹⁹, but it also included three normotensive pregnancies (both at examination and throughout the pregnancy), with fetuses estimated to be IUGR. A total of 41 women (16 with and 25 without PE) were included. The study was carried out at Uppsala University Hospital, Sweden, during 2008–2013. Only women with a singleton pregnancy of a live fetus and a gestational age between 22 + 0 and 41 + 6 weeks were eligible. Women with chronic hypertension, pre-existing renal disease, diabetes mellitus or severe claustrophobia were not included. For technical reasons related to other MR investigations performed simultaneously (data not presented here), only women with an anterior placenta and a body mass index (BMI) of $\leq 36 \text{ kg/m}^2$ were included. PE was defined as hypertension of $\geq 140/90 \text{ mmHg}$ on two separate occasions $\geq 4 \text{ h}$ apart and proteinuria ($\geq 2+$ on a dipstick or a urine collection showing $\geq 300 \text{ mg}$ in 24 h). IUGR was defined as an estimated fetal weight of more than 2 SD below the mean gestational age-related Swedish reference curve²⁰, in combination with a pathological pulsatility index (PI) in the umbilical artery or ductus venosus.

Gestational age was assessed by an ultrasound examination performed around 18 weeks of gestation. Information on maternal early pregnancy, BMI, age and parity, as well as gestational age at delivery and infant birth weight, was collected from the medical records. Delivery of an SGA neonate was defined as a birth weight below 2 SD from the mean birth weight for gestational age, according to the sex-specific Swedish fetal growth curve²⁰. All medical records were reviewed postpartum and no included women

delivered an infant with a suspected chromosomal abnormality, an intrauterine infection or any major malformation. The study participants all underwent MRI, ultrasound examinations and blood sampling within a 24-h period.

Ultrasound assessment

Study participants underwent an ultrasound examination that included estimation of fetal weight and amniotic fluid index and assessment of blood flow parameters. Each ultrasound examination was performed by an experienced consultant in fetal medicine. All examinations were performed with Voluson E8 ultrasound equipment (GE Medical Systems, Zipf, Austria) using a 4–5-MHz transabdominal transducer. The mechanical and thermal indices were below 1.1 and 0.9, respectively. The presence of normal amniotic fluid index (5.0–25.0 cm), oligohydramnios ($< 5.0 \text{ cm}$) or polyhydramnios ($> 25.0 \text{ cm}$) was recorded.

Color and pulsed-wave Doppler ultrasound were used to record the waveforms from maternal and fetal blood vessels. Both uterine arteries were identified by color Doppler, with the transducer directed to the lateral wall of the uterus in the region of the lower uterine segment. Measurements were performed at the point at which the uterine artery crosses the external iliac artery. The mean of the right and left uterine artery PI ($\text{PI} = \text{peak systolic velocity} - \text{end diastolic velocity}/\text{mean}$) was calculated and the presence of an early diastolic notch was noted. The umbilical artery was assessed in a free loop of the umbilical cord. PI was measured and absence of diastolic flow was recorded. The middle cerebral artery was visualized using color Doppler in a transverse section of the brain and measurements were obtained in the proximal section, at the level of the circle of Willis. The ductus venosus was assessed either in a mid-sagittal longitudinal plane of the fetal trunk or in an oblique transverse plane through the upper abdomen. The sample volume was positioned at its origin from the umbilical vein, at which color Doppler indicated the highest velocities. All Doppler waveforms were traced and the PI was calculated automatically.

Magnetic resonance imaging

MRI was performed with a 1.5-T clinical scanner (Philips Achieva, Best, The Netherlands) using the integrated whole-body transmit–receive 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. Depending on the size of the placenta, three to seven slices, each with a thickness of 6 mm, were collected. Acquisition time for the diffusion-weighted sequence was typically 3 min and 45 s.

Evaluation of the perfusion fraction was performed with research software (PRIDE, Philips Medical Systems, Best, The Netherlands). Calculation of the perfusion fraction is performed with the intravoxel incoherent motion technique, which is based on the fact that

a diffusion-weighted sequence is affected not only by molecular diffusion, but also by tissue perfusion. If the sequence is repeated with different degrees of motion sensitization (different b -values), the perfusion fraction can be calculated¹⁵. In each slice of the diffusion-weighted sequence, regions of interest were selected, including as much of the placenta as possible, but excluding areas with artifactual signal loss. Estimates of the perfusion fraction were obtained using a monoexponential fit for the signal intensities at b -values of 200–800 s/mm². Only estimates with a goodness of fit (R^2) of ≥ 0.9 were accepted for further analysis. The mean perfusion fraction from the different slices was calculated.

Blood sampling

At the time of the examinations, venous blood samples were collected from each participant. The samples were immediately placed in a refrigerator where they were kept for 20 min to 2 h before being centrifuged for 10 min at 1500 g. Plasma samples were obtained and stored at -70°C until analyzed. Levels of pentraxin-3, placental growth factor (PlGF), soluble fms-like tyrosine kinase-1 (sFlt-1), tumor necrosis factor receptor-1 and tumor necrosis factor receptor-2 were analyzed using commercial sandwich enzyme-linked immunosorbent assays (DY1826, DY264, DY321B, DY225 and DY726, R&D Systems, Minneapolis, MN, USA), according to the recommendations from the manufacturer. The total coefficients of variation (CV) for the assays were 5–7%.

Statistical analysis

Maternal and fetal characteristics are presented as mean \pm SD or n (%). Correlations between placental perfusion fraction and estimated fetal weight, amniotic fluid index, Doppler velocity measurements, infant birth weight and plasma markers were estimated by multiple linear regression. Compared to normal pregnancy, perfusion fraction is affected in PE, with lower perfusion in early PE (≤ 34 weeks) and higher perfusion in late PE (> 34 weeks)¹⁹. We investigated a possible effect measure modification by the presence of PE. We introduced a cross product for presence of PE (yes/no) and the explanatory variable when estimating the associations, and we found significant interactions ($P < 0.05$). Therefore, we included the cross product as an interaction term in the models. In normal pregnancy, placental perfusion fraction decreases with increasing gestational age¹⁹, and for that reason we adjusted for gestational age at examination in the models. However, gestational age and estimated fetal weight at examination were highly correlated and therefore either gestational age or estimated fetal weight was used in the models. Some of the plasma marker levels had a skewed distribution. All regression models were validated using residual plots, and variables were log-transformed prior to statistical analyses unless the residuals of the model were normally distributed. PlGF levels were not normally distributed, even after

Table 1 Maternal and fetal characteristics of 35 pregnancies that underwent placental perfusion assessment by magnetic resonance imaging

Characteristic	Value
Maternal age at examination (years)	30 \pm 5
BMI at first antenatal visit (kg/m ²)	23 \pm 3
Nulliparous	23 (66)
Daily smoking in early pregnancy	0 (0)
At examination	
Gestational age (weeks)	33 \pm 5
Pre-eclampsia	13 (37)
Intrauterine growth restriction*	5 (14)
Oligohydramnios†	1 (3)
At delivery	
Gestational age (weeks)	37 \pm 5
Birth weight (g)	3031 \pm 1182
Small-for-gestational age‡	5 (14)

Values are presented as mean \pm SD or n (%). *Estimated fetal weight below 2 SD compared to mean gestational age-related Swedish reference curve²⁰ and pathological umbilical artery or ductus venosus pulsatility index. †Amniotic fluid index < 5.0 cm. ‡Birth weight below 2 SD compared to gestational age-related Swedish sex-specific reference curve²⁰. BMI, body mass index.

log-transformation, probably due to the fact that more than one-third of the women (all women with PE) had a PlGF value below the detection limit. Therefore, PlGF levels were not included in the models. P -values < 0.05 were considered statistically significant. All analyses were performed using IBM SPSS Statistics version 20 (IBM, Armonk, NY, USA) or RStudio version 0.98.1062 (2009–2013; RStudio, Inc., Boston, MA, USA).

RESULTS

Of the 41 pregnant women originally included in the study, six were excluded because of severe artifacts prohibiting perfusion fraction calculations. Thus, 35 pregnant women remained in the analyses, of whom 13 had PE. Table 1 presents maternal and fetal characteristics of the study population. The mean gestational age at examination was 33 (range, 22–40) weeks. Five pregnancies had fetuses with IUGR; three in normotensive women and two in women with PE. These fetuses were later delivered as SGA neonates.

The placental perfusion fraction was smaller in the five pregnancies with IUGR, all examined before 34 weeks, than in six gestational age-matched normal pregnancies (median perfusion, 21% vs 32%; $P = 0.005$, after adjusting for presence of PE) (Figure 1).

IUGR pregnancies were subdivided into normotensive and PE pregnancies for further analysis, and gestational age-matched pregnancies with PE but without IUGR were also included. The respective median placental perfusion fractions in normal pregnancies, normotensive with IUGR, PE without IUGR and PE with IUGR were 32% (range, 26–42%), 23% (range, 21–26%), 20% (range, 19–23%) and 14% (range, 11–16%). Compared to normal pregnancy, both normotensive pregnancies with IUGR and PE pregnancies without IUGR had a

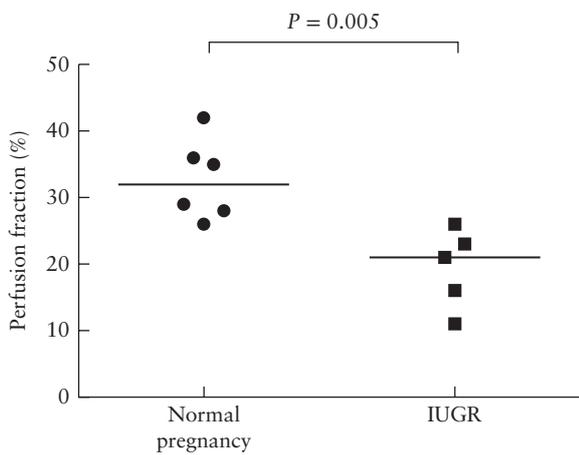


Figure 1 Scatterplot showing placental perfusion fraction, assessed by magnetic resonance imaging before 34 weeks' gestation, in five pregnancies with intrauterine growth restriction (IUGR) and in six gestational-age matched normal pregnancies. Horizontal lines represent median values.

smaller perfusion fraction ($P = 0.02$ for both), while PE pregnancies with IUGR had a borderline significantly reduced perfusion fraction ($P = 0.07$) (Figure 2).

In Table 2 different models of explanatory variables for placental perfusion are shown with calculated coefficients of determination (R^2). All models include presence of PE, gestational age or estimated weight at examination, and an interaction term between PE and gestational age or estimated weight at examination. We added the different ultrasound estimates to the model, one at a time, and in every model the R^2 -value increased. The highest R^2 (0.54) was found in the model that included PI in the ductus venosus. In addition, when plasma markers sFlt-1 or pentraxin-3 were added to the model, the R^2 also increased. Finally, we estimated whether inclusion of both

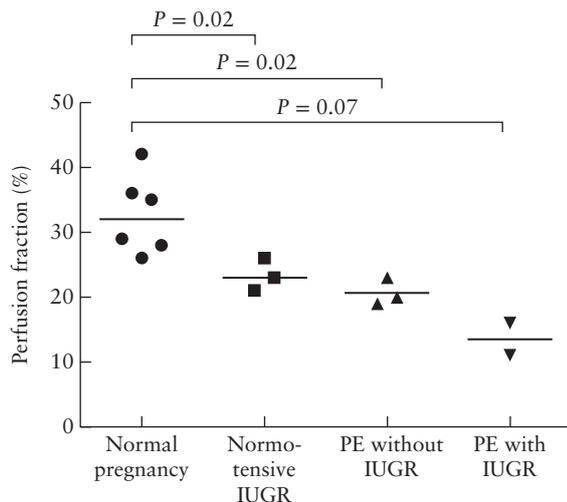


Figure 2 Scatterplot showing placental perfusion fraction, assessed by magnetic resonance imaging before 34 weeks' gestation, in normal pregnancy, normotensive pregnancy with intrauterine growth restriction (IUGR), pre-eclamptic (PE) pregnancy without IUGR and PE pregnancy with IUGR. Horizontal lines represent median values.

Table 2 Different explanatory models for placental perfusion assessed by magnetic resonance imaging

Explanatory variable in model	Adjusted R^2	P
Estimated weight at examination	0.39	0.0004
GA at examination	0.36	0.0007
GA at examination and:		
Amniotic fluid index	0.41	0.0010
Uterine artery PI (mean)	0.40	0.0007
Umbilical artery PI	0.46	0.0001
Middle cerebral artery PI	0.42	0.0020
Ductus venosus PI	0.54	0.0002
Infant birth weight	0.47	0.0001
Plasma level of:		
sFlt-1	0.43	0.0006
Pentraxin-3	0.42	0.0004
TNF receptor-1	0.38	0.0010
TNF receptor-2	0.36	0.0010

All models include presence of pre-eclampsia (yes/no) and interaction term between pre-eclampsia and estimated weight or gestational age (GA) at examination. PI, pulsatility index; sFlt-1, soluble fms-like tyrosine kinase 1; TNF, tumor necrosis factor.

an ultrasound estimate and a plasma marker in the same model further increased the coefficient of determination for placental perfusion fraction. The best R^2 -value (0.56) was found in a model including PI in the ductus venosus, the mean level of sFlt-1 or pentraxin-3, estimated fetal weight and presence of PE.

DISCUSSION

In this study, we found that the placental perfusion fraction was smaller in women with IUGR than in women with normal pregnancy. Furthermore, we found correlations between the placental perfusion fraction and fetal growth, Doppler blood flow in maternal and fetal vessels, infant birth weight and plasma markers of placental function. Our results indicate that the measurement of placental perfusion fraction could be an additive technique when assessing the degree of placental insufficiency.

Earlier studies have shown that pregnancies affected by IUGR have smaller placental perfusion compared with normal pregnancies, using *in-vivo* scintigraphy²¹, Doppler²² and histology²³. In a recent study, Brunelli *et al.* investigated placental perfusion with contrast-enhanced MRI²⁴. Their results were similar to ours, with a reduced placental perfusion in women with normotensive IUGR compared with normal pregnancy. Furthermore, among pregnancies with IUGR, those with a pathological ductus venosus PI had a smaller placental perfusion than those with a normal ductus venosus PI. In our study, we found the highest correlation between placental perfusion fraction and ultrasound estimates for Doppler blood flow in the ductus venosus. Both the present study and that of Brunelli support a strong association between Doppler blood flow in the ductus venosus and perfusion in the placenta.

Compared with normal pregnancy, we found an indication that placental perfusion is least affected in

pregnancies with normotensive IUGR, more affected in PE without IUGR and most affected in PE with IUGR (Figure 2). This would be in line with previous histological studies, which indicate an increasing degree of compromised vascular remodeling and obstructive occlusions in the spiral arteries in pregnancies with normotensive IUGR, PE without IUGR, and PE with IUGR²⁵. In addition, in studies that used *in-vivo* scintigraphy, reduced placental perfusion compared with normal pregnancy was seen both in pregnancies with IUGR and in those with PE^{21,26}. The latter studies did not compare normotensive IUGR pregnancies and PE pregnancies with IUGR. *In-vivo* scintigraphy studies are no longer performed, due to the risks associated with radiation exposure.

To our knowledge, only one study, that of Derwig *et al.*, has investigated possible correlations between placental perfusion fraction and Doppler blood flow in the uterine artery and infant birth weight¹⁷. Their results are in accordance with ours, with correlations between the placental perfusion fraction and infant birth-weight percentile ($R = 0.40$) and the mean uterine artery PI ($R = 0.48$). However, Derwig's study had a somewhat different approach from ours, with a main objective of predicting delivery of an SGA infant, by estimating the correlation between perfusion fraction at 24–29 weeks' gestation and delivery of an SGA infant.

A major limitation of our study is the small sample size, which increases the risk of random bias. The diffusion sequence used to estimate the perfusion fraction is sensitive to motion and this limitation led to the exclusion of six study subjects. However, the examination technique has improved in recent years and, with an average examination time of 3 min and 45 s in a clinical setting, it would be possible to repeat the examination if substantial motion artifacts arose.

In comparison with ultrasound examinations, the diffusion sequence has strengths, such as its independence of maternal obesity. Another strength of our study is that we were able to correlate the perfusion fraction to different indirect measurements of placental function. We could also correlate the perfusion fraction to infant birth weight, in some cases several weeks after the MRI examination. However, to establish whether the placental perfusion fraction offers additional information to the clinical management of pregnancies with IUGR and suspected placental insufficiency, larger studies are required.

During the last few decades, several large studies have been performed to determine which surveillance technique and signs should be used to determine the optimal timing of delivery of a fetus with IUGR in order to achieve the best short-term outcome^{27–29}. Recently, studies in which the outcome also includes long-term neurodevelopment have been performed^{30–33}. We speculate that the optimal timing for delivery could be determined by a combined test including several techniques, such as the combined ultrasound and biochemical test used to screen for chromosomal abnormalities. We endorse the inclusion of presence of PE in such a combined test. Our study

indicates the presence of an effect on placental perfusion in cases of PE, which can have a short- and long-term effect on the child. The existence of such a long-term effect is also supported by a recent study on cognitive abilities in children born preterm, in which it was found that children who had IUGR during pregnancy, complicated by PE, had the worst cognitive outcome, even when compared with normotensive IUGR³⁴. We further suggest that placental perfusion on MRI could be part of a combined test for determining the optimal time point for delivery in cases of IUGR.

In conclusion, we found correlations between the placental perfusion fraction and estimated fetal growth, Doppler velocity measurements in maternal and fetal vessels, birth weight, and plasma markers of placental function. Our findings show that the placental perfusion fraction has the potential to contribute to the clinical assessment of cases with IUGR, by providing a direct measurement of placental function.

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