Placenta 31 (2010) 491–498

Contents lists available at ScienceDirect

Placenta

journal homepage: www.elsevier.com/locate/placenta

Placental MRI in Intrauterine Fetal Growth Restriction

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ARTICLE INFO

Article history:
Accepted 1 March 2010

MeSH Keywords:
Magnetic resonance imaging
Fetal growth retardation
Placenta
Infant
Small for gestational age

ABSTRACT

Objective: Our objectives were to determine if MR imaging of the placenta could demonstrate a specific placental phenotype in small for gestational age fetuses with increasing severity of fetal growth restriction, and if MRI findings at the time of scan could be used to predict fetal or neonatal mortality.
Method: We included singleton growth restricted fetuses with increasing severity of fetal growth restriction secondary to placental insufficiency. 20 growth restricted fetuses and 28 normal fetuses were scanned once during pregnancy at varying gestations. MRI scans were performed on a 1.5T system using ssFSE sequences through the uterus. Data was collected on the severity of fetal growth restriction and pregnancy outcome, including clinical neonatal details, perinatal mortality, and birthweight and centile. Placental volume, maximal placental thickness, the placental thickness to volume ratio, the placenta to amniotic fluid signal intensity ratio, and the presence of abnormal signal intensity consistent with placental pathology were noted. In a subset of patients, histopathological diagnosis was compared with the MRI appearance of the placenta.
Results: There was a significant increase in the placental volume affected by pathology in growth restricted fetuses ($p < 0.001$). The placental appearance was also thickened and globular, with an increase in the placental thickness to volume ratio ($p < 0.001$). Although placental volume increased with increasing gestation, it remained reduced in the growth restricted fetuses ($p = 0.003$). There was a significant correlation between the severity of fetal growth restriction and the placental volume affected by pathology, the placental thickness to volume ratio, and the placental volume. ROC analysis showed that fetal or neonatal death was predicted by the percentage of abnormal signal intensity consistent with placental pathology ($p = 0.002$). The presence of a thickened, globular placenta and a maximal placental thickness to volume ratio above the 95% confidence limit for gestation was significantly associated with an increased incidence of fetal or neonatal mortality (relative risk = 1.615, $p = 0.001$ and relative risk = 7, $p < 0.001$).
Conclusions: The MRI appearance of the placenta provides an indication of the severity and underlying disease process in fetal growth restriction. In units where MRI imaging of the growth restricted fetus occurs, we suggest that the assessment of the placenta should also occur as it may contribute to management decisions in cases at the threshold of viability. It may have a role to play in monitoring disease severity, and the effect of future interventions designed to improve placental function.

Abbreviations: UA, umbilical artery; MCA, middle cerebral artery; AEDF, absent end diastolic flow; REDF, reversed end diastolic flow; DV, ductus venosus; UV, umbilical vein.

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0143-4004/$ – see front matter
doi:10.1016/j.placenta.2010.03.001

1. Introduction

First trimester trophoblastic invasion has far reaching consequences for the fetus; failure at this stage may result in fetal growth restriction with morbidity both in the immediate perinatal period, as well as throughout development into adulthood. Pregnancies complicated by fetal growth restriction are characterised by shallow invasion of the trophoblast into maternal tissue, and inadequate conversion of the spiral arterioles, leading to placental ischaemia [1,2]. Histological examinations of these malperfused placentae demonstrate a thickened, globular placenta with gross areas of infarct and abruption [3], as well as microscopic evidence of chronic inflammation and villitis [1,4]. This increases uteroplacental impedance in both the fetal and maternal compartment as evidenced by an increase in the Doppler velocimetry of the umbilical and the uterine arteries respectively on ultrasonography [5,6].

Growth restricted fetuses are at increased risk of perinatal demise, and of neonatal complications such as intraventricular haemorrhage, periventricular leucomalacia, respiratory distress syndrome, and necrotising enterocolitis [7–9]. In the longer term, these children are at further risk of developmental delay and behavioural problems [10], and in adulthood, there is also an increased incidence of hypertension and diabetes as part of the metabolic syndrome [11].

Ultrasound assessment of the placenta typically includes an assessment of placental location and maturity, and the presence of placental haemorrhages or intervillous lakes [12]. Although volumetric assessment of the placenta may be performed using 3D ultrasound in the first trimester, it becomes increasingly difficult to perform as gestation progresses due to limitations in the field of view.

Fetal MRI is now established as an adjunct to ultrasonography in the diagnosis of fetal abnormalities [13,14]. MRI assessment of the placenta was first used in cases of suspected placenta praevia in 1986 [15]. Its role has since expanded and now ranges from the assessment of placental invasion in cases of suspected placenta accreta/increta/percreta in the clinical setting [16–18] to studies on spectroscopy and perfusion of the placenta in the research setting [19,20]. Research on the use of MRI in the diagnosis of placental pathology in fetal growth restriction however has been limited to research analysing placental function [21]. We hypothesised that MRI imaging of the placenta could demonstrate a specific placental phenotype in growth restricted fetuses that correlates with the severity of fetal growth restriction, and that specific MRI findings at the time of scan may be used to predict perinatal mortality.

2. Materials and methods

Ethical approval for in utero fetal MR imaging was obtained from the Hammersmith Hospital Research Ethics Committee (Rec No: 2003/6375 and 07/H0707/105) and written maternal consent was sought in all cases. Two groups of women were recruited from Queen Charlotte's and Chelsea Hospital between May 2007 and September 2009.

Women with fetal growth restriction secondary to placental insufficiency were approached upon referral to the Center for Fetal Care at Queen Charlotte's and Chelsea Hospital. Fetal growth restriction was defined as an estimated fetal weight below the 5th centile. Exclusion criteria were (1) multiple pregnancy, (2) aneuploidy, (3) the presence of in utero infection, (4) the presence of additional structural abnormalities, and (5) suspected genetic syndromes. The severity of fetal growth restriction was graded in order of increasing severity as (1) a Pulsatility Index above the 95th centile in the Umbilical Artery (UA) (2) a Pulsatility Index above the 95th centile in the UA as well as a Pulsatility Index in the Middle Cerebral Artery (MCA) below the 5th centile (cerebral redistribution) (3) absent end diastolic flow (AEDF) in the UA (4) reversed end diastolic flow (REDF) in the UA and (5) absent or reversed 'a' wave in the Ductus Venosus (DV) and/or pulsatility in the Umbilical Vein (UV) (venous Doppler changes).

Assessment of placental location, Grannum classification, and of fetal growth, liquor volume and Dopplers were obtained transabdominally using a 6 MHz curvilinear 6C2 transducer on a Siemens ultrasound system (Siemens Acuson Sequoia 512; Siemens, Germany).

Fetal MRI was performed according to our standard protocol for fetuses, using a 1.5T Philips MRI system (Philips Achieva; Philips Medical Systems, Best, the Netherlands) with a SENSE wrap-around 5 channel cardiac coil. A T2 weighted single shot turbo spin echo sequence through the entire uterus (TE: 98, TR: 1000, NSA: 2, matrix: 400 × 178, FOV: 36 × 40 cm, slice thickness: 4 mm; slice gap: 0.4 mm; acquisition time: 20 s) was the standard protocol used until May 2008, after which an alternative sequence (TE : 98 TR : 1000 NSA: 2, matrix: 400 × 512 FOV: 430, slice thickness: 4 mm; slice gap: 0 mm; acquisition time: 40 s) was used. The fetal MRI examination was conducted with the mother in a left lateral tilt position and the entire examination was limited to one hour. No fetal or maternal sedation was used for the examination, and specific absorption rate (SAR) limits were adhered to, as per departmental protocols.

The presence of placental pathology was assessed by the signal intensity, localisation, and morphology of the lesions using the T2 weighted MRI specific appearance of placental lesions as characterised by Linduska et al. [22]. We documented the presence of placental infarct in cases where there was an intraplacental lesion with a core region of increased signal intensity surrounded by a diffuse region of reduced signal intensity, or where there were diffuse regions of reduced signal intensity on T2 weighted images (Fig. 1a). We recorded the presence of a retroplacental haemorrhage in cases where there was a retroplacental circumscribed lesion with reduced signal intensity on T2 weighted images (Fig. 1b). We recorded the presence of subchorionic haemorrhage in cases where there was a subchorionic circumscribed lesion demonstrating reduced signal intensity (Fig. 1c). The MRI images were assessed for the presence of placental infarct, retroplacental haemorrhage, and subchorionic haemorrhage with the observer (MD) blinded to the histopathological diagnosis of placental pathology.

Placental signal intensity was assessed in relation to the amniotic fluid signal intensity by measuring the signal intensity in the largest possible region of interest on the slice that contained the maximal area of both placenta and amniotic fluid with no image artefact present (Fig. 2a and b). In the case of growth restricted fetuses, where there was a region of obvious placental pathology, this was not included within the region of interest, or if no regions of normal signal intensity could be identified, regions with an appearance closest to normal was used. The placenta to amniotic fluid signal intensity ratio in normal fetuses has previously been investigated by Blaicher et al. [23], however a description of the signal intensity ratio in growth restricted fetuses has not previously been undertaken.

Maximal placental thickness was taken as the thickness of the placental parenchyma at the point of central umbilical cord insertion as the placental parenchyma is thickest at this point (Fig. 2c). The images were viewed in rView (Image Registration Toolkit, ver 1, Ixico Ltd) which enabled images to be viewed in the three orthogonal planes. In cases where the cord insertion was eccentric, the placental thickness was taken at the thickest portion visualised.

Placental volume was assessed by manually drawing the region of interest on each slice with placental tissue present using ImageJ (ImageJ, ver 1.41o. NIH: Bethesda, MD). The area of the region of interest in each slice was measured automatically by counting the number of pixels covering the region of interest and multiplying this number by the area corresponding to a pixel. This was then multiplied by the sum of the slice thickness and slice gap (if present) to give the volume. The observers (MD and EE) were blinded to the patient's identity, gestation at scan, and patient group. In each case, regions of placental tissue with abnormal signal intensity that were identified as indicating regions of placental pathology were delineated and the percentage of abnormal placental volume was calculated. The accuracy of volumetric estimation was limited by the error in delineating the area of interest in each slice. Intra and inter observer variability (MD and EE) in calculating placental volume resulted in an interclass correlation coefficient of 0.99 and 0.98 respectively ($p < 0.001$). Inter and intra observer variability (MD and EE) in calculating the percentage of placental volume affected by apparent pathology resulted in an interclass correlation coefficient of 0.99 and 0.93 respectively ($p < 0.001$). The maximal placental thickness to placental volume ratio was calculated by dividing the maximal placental thickness by placental volume. This was interpreted as a surrogate marker of the inverse of placental surface area.

As a secondary aim of this study, where available, results of histological examination of the placenta were obtained. Placentae were examined at the Wigglesworth Perinatal-Paediatric Pathology Service based at Imperial College Healthcare NHS Trust (JWA). At least 21 macroscopic factors including weight, infarcts, subchorionic haemorrhage, and retroplacental haemorrhage were checked and recorded. From each placenta, a minimum of 12 areas were sampled, fixed in 10% buffered formalin, and embedded in paraffin. Paraffin embedded tissue sections were cut into four micron sections, deparaffinized, and stained with haematoxylin and eosin prior to histologic examination.

MRI assessment of placental appearance was taken to be accurate if the histopathology report demonstrated evidence of placental infarct, retroplacental haemorrhage, or subchorionic haemorrhage. The placental MRI findings were not used to decide on optimal timing for delivery in either group.

Fetal mortality was defined as an intrauterine death or an iatrogenic termination of pregnancy for severe fetal growth restriction from 20 weeks gestation. Early neonatal death was defined as neonatal death in the first week of life.