Magnetic resonance imaging of the placenta identifies placental vascular abnormalities independently of Doppler ultrasound

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KEYWORDS: Doppler; fetal MRI; outcome; placental pathology

ABSTRACT

Objective To evaluate the relationship between placental vascular pathology detected by prenatal magnetic resonance imaging (MRI) and perinatal outcome.

Methods This was a retrospective, hospital-based, cross-sectional study in which all fetal MRI examinations of singleton pregnancies with vascular placental pathology (i.e. infarction without hemorrhage, subchorionic thrombi/hemorrhages, intervillous thrombi/hemorrhages, or retroplacental hematoma) in the last 6 years were included. The extent of the pathology was expressed as a percentage of the total placental volume. Abnormalities of umbilical artery Doppler ultrasound examinations within 7 days between MRI and ultrasound examination were noted. Death in utero or postnatally was the primary outcome. Gestational age at MRI and at birth and the occurrence of intratuterine growth restriction (IUGR) were noted. Logistic regression analysis was performed to assess the impact of gestational age at MRI, extent of the vascular lesion and presence of pathological Doppler ultrasound measurements on the prediction of mortality.

Results Fifty-nine structurally normal singleton pregnancies were included in the analysis. Mortality rate was 36%; among the survivors 87% were born before 37 + 0 gestational weeks, and 50% suffered from IUGR. In 53% of the pregnancies pathological umbilical artery Doppler findings were identified, of which 27% were non-survivors. Mortality was predicted by earlier gestational age at fetal MRI for placental pathology (P < 0.05) and increasing extent of the vascular lesion (P < 0.05), but not by the presence of pathological Doppler ultrasound data. Accuracy of the prediction was 82%, sensitivity was 67% and specificity 89%.

Conclusion MRI-detected vascular placental pathologies may help to identify at-risk pregnancies for adverse outcome and fetal death independently of umbilical artery Doppler status. Copyright © 2011 ISUOG. Published by John Wiley & Sons, Ltd.

INTRODUCTION

Successful placental development is an important prerequisite for normal fetal maturation and perinatal outcome. Understanding the effects of abnormal placental morphology and function can help to understand their prenatal impact on perinatal outcome. Placental morphology is typically assessed by clinicopathological correlation of placental histology following delivery and provides evidence that placental pathology is related to adverse perinatal outcome. However, recent reports have failed to find an association between placental histology in pre-eclampsia and neonatal hematological abnormalities, or between histological chorioamnionitis and neonatal cerebral alterations. Placental histopathology has the disadvantage that it is performed postnatally and that its use may be limited in attempts to fully explain the impact of abnormal placental function on perinatal outcome.

Prenatal ultrasonography is the most widely practiced imaging modality for the evaluation of placental function in the prediction of adverse perinatal outcome. Ultrasound assessment of placental function has evolved over the years. Gray-scale evaluation of placental
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text – which shows only a weak correlation between
villous infarction and intervillous thrombosis8–10 – has
villous infarction and intervillous thrombosis8–10 – has
been replaced by Doppler ultrasound, which provides
been replaced by Doppler ultrasound, which provides
a good correlation with abnormal placental vascular
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disease and therefore is the current standard for
the detection of placental insufficiency with subsequent
the detection of placental insufficiency with subsequent
intrauterine growth restriction (IUGR)11–13.
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Prenatal magnetic resonance imaging (MRI) continues
to evolve as an important imaging modality for
providing additional information on the fetus that is
valuable for prenatal counseling, and optimizing perinatal
management14–16. In our institution, antenatal MRI
has been well established for years as a second-line
imaging technique for more precise information on
the fetus and its environment17,18. In addition to fetal
evaluation prenatal MRI allows visualization of the
normal structure of the placenta and its morphological
changes during gestation19. Hitherto MRI studies on
placental pathologies have focused on the detection of
abnormal placental adherence20,21. Recently we were
able to detect placental vascular pathologies such as
hemorrhages and ischemic lesions by prenatal MRI that
were confirmed by placentomal histology22. Accordingly it
was the aim of this study to evaluate whether vascular
placental pathologies detected by prenatal MRI correlate
with fetal outcome.

PATIENTS AND METHODS

This was a retrospective, hospital-based, cross-sectional
study, carried out at our tertiary perinatal referral cen-
ter. Patients in whom placental vascular lesions were
suspected on antepartum MRI evaluation in the last
6 years were eligible for the study. Antepartum MRI eval-
uation was performed for various fetal and placental
indications, and vascular placental pathologies were diag-
nosed at this first indicated MRI examination. Because it
was our intention to study the role of MRI in assessing
placenta-based risks we excluded potentially confound-
ing conditions. Accordingly, placental adhesion disorders
(placenta accreta, increta and percreta), multiple preg-
nancies and major fetal congenital anomalies with serious
medical or functional consequences were excluded. Local
ethics committee approval was obtained.

Prenatal MRI was performed for various clinical
indications using a 1.5-T superconducting system (Philips
Gyroscope, Best, The Netherlands) with a five-element
surface phased-array coil without sedation or application
of contrast medium. A multistack, steady-state-free-
precession survey (SSFP) (repetition time (TR) 3.13 ms,
echo time (TE) 1.56 ms, slice thickness 3–7 mm) in three
orthogonal planes was obtained to provide a 20 fetal
and placental overview. Single-shot, fast spin echo T2-
weighted sequences (T2-w) (TR infinite, TE 4.6 ms, slice
thickness 5–4 mm, gap 0.3–0.4 mm) were performed.
T1-weighted sequences (T1-w) (TR infinite, TE 4.6 ms,
slice thickness 5 mm, gap 0.5 mm) were performed while
the mother held her breath, to ensure that there were no
motion artifacts. Echo-planar imaging (EPI) (TR 3000 ms,
TE 53 ms, slice thickness 3 mm, gap 0.3 mm) was also
used, as well as diffusion-weighted imaging (DWI) (TR
1470 ms, TE 125 ms, slice thickness 5 mm, gap 0.1 mm, b
value 700). The whole protocol was valid for investigating
the fetus and placenta. The duration of fetal MRI studies
was 30–45 min.

Placental MR images were evaluated for the following
vascular pathologies:

1. Infarction with/without hemorrhage (infarction with
hemorrhage: diffuse/circumscribed intraplacental
pathology, T1-w and DWI (′i) hyperintense, T2-
w, SSFP and EPI/DWI (0) hypointense; ischemic
infarction without hemorrhage: diffuse/circumscribed
intraplacental pathology, T1-w hypointense, T2-
w, SSFP and DWI (′i) hypointense, EPI/DWI
(0) isointense/hyperintense).

2. Subchorionic thrombi/hemorrhages (subchorionic
hemorrhage: circumscribed subchorionic pathology,
T1-w and DWI (′i) hyperintense, T2-w, SSFP
and EPI/DWI (0) hypointense; subchorionic thrombi:
circumscribed subchorionic pathology, T1-w and
EPI/DWI (0) hypointense, T2-w and SSFP hyperin-
tense, DWI (′i) variable).

3. Intervillous thrombi/hemorrhages (intervillous hem-
orrhage: round intraplacental pathology, T1-w and
DWI (′i) hyperintense, T2-w, SSFP and EPI/DWI
(0) hypointense; intervillous thrombi: round/circumscribed
intraplacental pathology, T1-w and EPI/DWI
(0) hypointense, T2-w and SSFP hypointense,
DWI (′i) variable).

4. Retroplacental hematoma (circumscribed retroplacen-
tal pathology, T1-w and DWI (′i) hyperintense, T2-w,
SSFP and EPI/DWI (0) hypointense).

These pathologies have been described as being detectable by MRI22. The extent of the pathology in
relation to the whole placental volume was assessed semi-
quantitatively. In each case the whole placenta was taken
to have a volume of 100% and evaluation of the amount
of pathological change was done by assessing each slice of the
placenta and summarizing the findings as percent affected
by volume (Figure 1). Estimation of the percentage of
placental volume involvement was done using information
from at least two section planes on which the placenta
was completely visualized (Figure 2). The assessment was
carried out by two investigators and the final decision was
achieved by their agreement. In cases with more than one
investigation, the one with the largest extent of vascular
pathology was included.

Additional perinatal variables that were noted were
gestational age at the time of MRI, umbilical artery
Doppler velocimetry within 7 days of MRI, gestational
age at delivery, birth-weight percentile and perinatal
mortality. Abnormal umbilical artery Doppler was defined
as elevation of the pulsatility index above the 95th
centile according to our reference ranges and/or absent or
reversed end-diastolic velocity.

The primary outcome parameter was mortality, defined
as death in utero or postnatally before discharge from
Fetal MRI identifies placental vascular abnormalities

Figure 1 Axial T2-weighted magnetic resonance image (repetition time (TR) infinite, echo time (TE) 100 ms, slice thickness 3–4 mm, gap 0.3–0.4 mm) of a placenta at 28 weeks’ gestation, showing intra-placental hyperintensive lesions (hemorrhagic infarctions). For semi-quantitative estimation, each slice of the placenta was divided into four parts, pathological changes were assessed in each quarter and the findings were summarized (about 50% of the placenta is affected).

hospital. Prematurity was defined as birth before 37 + 0 weeks’ gestation. IUGR was defined as birth weight < 10th centile according to gestational age.

Statistical analysis

Statistical analysis was performed using SPSS® Version 15.0 for Windows (SPSS, Chicago, IL, USA). Nominal data were presented by using percentages. Dependent on the cell size Fisher’s exact test or the chi-square test was used to compare categorical variables. Logistic regression analysis was performed to assess the impact of gestational age at MRI, extent of the vascular lesion and presence of pathological Doppler ultrasound measurements on the prediction of mortality. P < 0.05 was considered statistically significant.

RESULTS

One hundred and thirty-three MRI investigations with vascular placental pathologies, excluding placental adhesion disorders, were reviewed retrospectively. Four investigations were excluded for technical reasons and 49

Figure 2 Axial T2-weighted magnetic resonance images of a placenta at 24 weeks’ gestation, showing hyperintense lesions (arrows) representing cotyledon infarction extending to 75% of the placental volume.
because of twin or triplet pregnancies. Of the 80 singleton pregnancies left 21 were excluded owing to major congenital abnormalities. Therefore 59 structurally normal singleton pregnancies with placental vascular abnormalities on MRI were included in the final analysis. Including multiple indications for patients the primary referral indications for prenatal MRI were: placental dysfunction (IUGR \( n = 20 \)), preterm, placental insufficiency \( n = 11 \), abnormal Doppler results \( n = 6 \), abnormal placental texture \( n = 6 \), premature rupture of membranes and/or amniotic fluid abnormalities (premature rupture of membranes \( n = 19 \), oligo/anhydramnios \( n = 5 \)), in-utero fetal death \( n = 2 \), suspected fetal anomalies \( n = 10 \), fetal hydrops \( n = 2 \) or maternal conditions \( n = 3 \).

The mean gestational age at MRI was 26 ± 3 weeks (median 26 (range, 20–35) weeks). The vascular abnormalities identified included infarction ± hemorrhage in 49 pregnancies, subchorionic thrombi ± hemorrhage in 21 pregnancies, intervillus thrombi ± hemorrhage in eight pregnancies and retroplacental hematoma in six pregnancies.

Umbilical artery Doppler results obtained within 7 days of the MRI investigation were available for 55/59 pregnancies (93%). Thirty of these 55 examinations had an abnormal umbilical artery Doppler finding (elevated index and/or absent end-diastolic velocity).

In this cohort of high-risk pregnancies there were 21 perinatal deaths (36% mortality rate; Figure 3). Fetuses that survived until birth were delivered at a median gestational age of 29 (range, 21–39) weeks. Preterm delivery before 37 weeks’ gestation occurred in 33 of the 38 survivors (87% prematurity rate) and fetal growth restriction was present in 19 of them (50%).

In the 25 women with normal umbilical artery Doppler only four developed IUGR (16%) and 10 had a perinatal death (40%). Among the 30 patients with abnormal Doppler parameters 24 (80%) had IUGR and there were eight perinatal deaths (27%). Doppler parameters were significant predictors of IUGR (\( P < 0.01 \)), while perinatal death was not predicted (\( P = 0.294 \)).

The association between perinatal mortality and MRI findings was further explored using logistic regression analysis. In this model perinatal death was used as the dependent variable and gestational age at MRI, extent of MRI-detected vascular lesions and umbilical artery Doppler abnormality were independent variables. This analysis showed that gestational age at MRI (\( P < 0.05 \); odds ratio (OR) 0.894) and the extent of the vascular lesion (\( P < 0.05 \); OR 1.032) were significant determinants of perinatal mortality, whereas abnormal umbilical artery Doppler had no independent impact (\( P = 0.38 \); OR 0.466). Accuracy of the prediction was 82%, sensitivity was 67% and specificity was 89%.

**DISCUSSION**

Prenatal evaluation of the placenta and its function is currently almost exclusively based on ultrasonographic techniques. Specifically, the documentation of vascular abnormalities requires Doppler ultrasound of maternal or fetal compartments of the placenta. The ability to accurately characterize a variety of placental abnormalities by prenatal MRI opens up the possibility of applying this imaging technique for prognostic placental evaluation. To date, pathologies of the placenta have not been considered a ‘classic’ indication for fetal MRI. As we have included imaging of the placenta in our standard MRI protocol, our experience in this field has grown over recent years. This study evaluated the predictive value of prenatal placental MRI-detected vascular placental pathology on perinatal outcome in patients with known umbilical artery Doppler status.

We studied a selected high-risk population with a high rate of perinatal mortality, prematurity and fetal growth delay. In these patients the finding of vascular placental pathologies was associated with adverse outcome that was not predicted by their umbilical artery Doppler status. The specific adverse outcomes included mortality, prematurity and significant placental dysfunction. In addition to the early onset of the underlying condition that required prenatal evaluation, the size of the vascular pathology on placental MRI was a major predictor of outcome. These findings are consistent with a synergistic negative impact of gestational age and extent of placental vascular abnormality on perinatal outcome.

Ultrasound evaluation of placental vascular function is based on Doppler examination of the maternal uterine arteries and the fetal umbilical arteries. Uterine artery Doppler provides an estimate of successful trophoblastic transformation of the spiral arteries and accordingly is predictive of maternal hypertensive disorders and to a lesser degree of fetal growth restriction. Umbilical artery

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*Figure 3* Outcome of the fetuses included in the study in relation to gestational age at magnetic resonance imaging (MRI) and extent of the vascular placental pathology. ▲, Survivor; ●, non-survivor.
Doppler evaluates the integrity of the villous circulation and becomes abnormal when villous occlusive disease exceeds a certain threshold\(^1\). This study suggests that significant placental vascular disease that remains below the threshold of detection of umbilical artery Doppler can be predicted by prenatal MRI. This appears plausible since many significant placental vascular pathologies may not cause sufficient disruption of the villous circulation to elevate umbilical artery blood flow resistance but may still have a clinically significant effect.

Ischemic infarctions result in villous necrosis as a result of deficient intervillous maternal circulation and may be associated with pregnancy-induced hypertension, lupus anticoagulant, low-lying placentas and placental abruption as well as viral infections such as varicella and rubella\(^4\). Naeye\(^24\) investigated the relationship of infarctions to perinatal outcome, and showed fatal infarcts to be associated with pre-eclampsia, placental abruption, older age and overweight. Vessel thrombosis has diverse etiologies including diabetes, cytomegalovirus infection, toxoplasmosis and other acute inflammatory processes\(^25\). Thrombotic vascular obliteration results in villous atrophy and eventually reduces functional exchange area due to avascular hyalinized villi in the affected area\(^8\). Placental hemorrhage is frequently associated with deficient placental implantation associated with placenta previa and placental abruption, but can also occur spontaneously or after trauma. The degree and rate of feto–maternal hemorrhage determine the degree of fetal anemia and risk for stillbirth\(^9\).

Gray-scale ultrasound examination of the placental echotexture can be graded according to the Grannum classification\(^26\). However, it has been established that this ultrasound evaluation of the placental parenchyma bears little relationship to outcome\(^27\). When placental integrity is assessed by Doppler ultrasound, detection of placental dysfunction is possible when the underlying pathology produces a sufficient increase in blood flow resistance to elevate the Doppler index above the gestational age limits. Accordingly, placental infarcts and decreased trophoblast invasion may be suspected when uterine artery Doppler is abnormal, and these findings can predict maternal hypertensive disorders and to a lesser degree IUGR\(^28,29\). Deficient peripheral villous development and accelerated trophoblast apoptosis increase umbilical artery blood flow resistance, producing Doppler-index elevation, absence of end-diastolic velocities and even reversal if villous involvement involves 30–70% of the placenta, respectively\(^29,30\). However, it has been shown previously that significant villous abnormality may be missed by traditional umbilical artery Doppler\(^31\) and that MRI can detect villous flow abnormalities in this setting\(^32\). These previous studies further support the concept that prenatal MRI evaluation of the placenta can offer significant information on placental pathology that is at least complementary to Doppler ultrasound.

The weaknesses of our study that need to be taken into consideration are the retrospective design, which led to a significant ascertainment bias. We studied a very high-risk population of patients that does not represent the entire spectrum of patients at risk for adverse outcome due to placental disease. Although placental dysfunction is the predominant clinical picture in this patient population we also included other conditions in which outcome is unrelated to umbilical artery Doppler. Similarly, venous Doppler parameters that are more predictive of outcome in IUGR were not considered in our analysis. The MRI technique employed only allowed for a semi-quantitative assessment of the degree of placental involvement. Finally, we do not have histologic correlates to the MRI-based placental pathologies.

The strengths of the study include the relatively large patient group with a high level of adverse outcome that allowed a statistical comparison of the primary placental function test (umbilical artery Doppler) and the MRI-based placental assessment.

Our observations provide an important basis for future studies. Ultimately we will require a better understanding of the causes of vascular placental pathologies and their clinical evolution. Evolving placental vascular pathology may limit placental and fetal reserves for repair and therefore lower the threshold for injury. The strong associations between placental pathology and neurodevelopment suggest that these effects occur before overt clinical deterioration. From the imaging standpoint, vascular placental pathologies detected by MRI may help to identify at-risk pregnancies where short term re-evaluation is necessary. T2-weighted imaging may be recommended, as most pathological changes can readily be detected on this sequence. While the new technique of placental perfusion scan appears to be most promising for the measurement of placental perfusion and permeability\(^33,34\), it currently remains some distance away from clinical applicability.

In summary, our retrospective study demonstrates that fetal MRI investigation of vascular placental pathologies may be a useful tool for the prediction of adverse fetal outcome. Future prospective studies including placental volumetry and placental perfusion scan are required.

ACKNOWLEDGMENT

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REFERENCES


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AQ3 “… in the last 6 years were included.”, could you give the exact period considered?

AQ4 “intrauterine growth retardation” changed to ‘intrauterine growth restriction’ in line with usual Journal style, ok?

AQ5 “Mortality was predicted by placental abnormalities at earlier gestational age at the performance of fetal MRI…” changed to ‘Mortality was predicted by earlier gestational age at fetal MRI for placental pathology…’, is that correct?

AQ6 Are you happy with the change to the layout of Figure 2?

AQ7 “… and that it may have limitations to fully explain impacts of abnormal placental function on perinatal outcome” reworded to ‘and that its use may be limited in attempts to fully explain the impact of abnormal placental function on perinatal outcome’, ok?

AQ8 “… MRI evaluation in the last 6 years were eligible…”, again, could you provide the exact time period considered?

AQ9 “… to provide a 20 fetal and placental overview”, the meaning here does not seem clear, could you check your wording?

AQ10 In each case the whole placenta was estimated as a volume of 100%. The evaluation of the respective part of pathological changes was done by assessing each slice of the placenta and summarizing the findings’ changed to: ‘In each case the whole placenta was taken to have a volume of 100% and evaluation of the amount of pathological change was done by assessing each slice of the placenta and summarizing the findings as percent affected by volume’; does that convey the intended sense?

AQ11 “Estimation of the percentage of placental volume involvement was done using information from at least two section planes on which the placenta was completely visualized”, does this mean that the placenta was analyzed in sections in at least two different planes? Or that it was assessed in at least two sections in any plane?

AQ12 Figure 1 caption ‘(about 50% of the placenta is affected)’, does this mean that the extent of the lesion is around 50% of the placenta as a whole in this case?

AQ13 “Nominal data were presented by using percentages”, this does not seem quite right, as in statistics ‘nominal data’ refers to unordered categories. Could we change this to something along the lines of ‘Data on the extent of placental pathologies were presented using percentages’?

AQ14 “… absence of end-diastolic velocities and even reversal if villous involvement involves 30–70% of the placenta, respectively”, this statement does not seem completely clear. Is a lower proportion of villous involvement associated with more severe Doppler abnormalities? If so, could something along the lines of ‘absence of end-diastolic velocities and even reversal if villous involvement is as low as 70% or 30% of the placenta, respectively’ be better here?

AQ15 ‘concentrated [adverse outcome]’ changed to ‘a high level of [adverse outcome]’; is that OK?

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