

MRI in the diagnosis of fetal developmental brain abnormalities: the MERIDIAN diagnostic accuracy study

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Scientific summary

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Scientific summary

Background

For many years, fetal imaging with ultrasonography has been the mainstay of antenatal screening programmes in the UK. However, no imaging method is perfect and various technical factors and physical limitations may result in suboptimal images. These may lead to incorrect diagnoses of structural abnormalities and inaccurate counselling and prognostic information being given to parents. The fetal brain is a particular area of concern because of the relatively high frequency of developmental abnormalities (approximately 3/1000 pregnancies), many of which are associated with serious clinical morbidities.

Previous studies have suggested that in utero magnetic resonance imaging (iuMRI) may be a powerful adjunct to ultrasonography for detecting fetal brain abnormalities from 18 weeks' gestational age. However, the majority of these studies have a number of key limitations and, most notably, they lack an outcome reference diagnosis (ORD), which means that improvements in diagnostic accuracy could not be assessed accurately. Therefore, the extent of diagnostic improvement and the impact that this has on clinical management and counselling remains unclear.

Aims and objectives

The aim of the research was to assess iuMRI to aid the prenatal diagnosis (PND) of fetal developmental brain abnormalities among fetuses for which ultrasonography had suggested a brain abnormality.

The objectives were to:

- assess the diagnostic accuracy of iuMRI compared with antenatal ultrasonography using ORD as a comparator
- assess the clinical effectiveness of iuMRI through changes in clinical diagnostic confidence before and after iuMRI and the effect on prenatal counselling and management decisions
- assess the acceptability of the clinical care package with the use of magnetic resonance imaging (MRI) included
- conduct a health economics analysis to assess the cost consequences of the use of MRI.

Methods

Design

We conducted a pragmatic, prospective, multicentre, cohort study with a health economics analysis and a qualitative substudy.

Recruitment and imaging examinations

Participants were pregnant women aged > 16 years and carrying a fetus with a suspected brain abnormality on detailed ultrasonography as diagnosed by a fetal medicine consultant. They were recruited by 16 fetal medicine centres and referred for iuMRI. There were no specific requirements made for the ultrasound technique and details of suspected brain abnormalities were recorded along with a confidence rating of the diagnosis. The iuMRI was completed at one of six collaborating centres where radiologists were required to comment on each abnormality suspected by the ultrasonography and their confidence in the diagnosis. The radiologist could add a diagnosis if appropriate, or use 'diagnosis excluded' if they disagreed with an ultrasonography diagnosis. It was not possible to match protocols across all scanning centres because of different MRI manufacturing systems; however, all scans were performed at 1.5 T and an absolute requirement of imaging sequences was defined.

Outcome reference diagnoses

This was defined as postnatal neuroimaging for continued pregnancies with a surviving child and autopsy and/or postmortem MRI in cases of termination of pregnancy, stillbirth or neonatal death. Agreement between ultrasonography, iuMRI and ORD was determined by a two-level review process including a Multidisciplinary Independent Expert Panel.

Diagnostic accuracy

Participants who underwent iuMRI within 14 days of ultrasonography and for whom an ORD was available were included in the primary analysis.

In cases with multiple anatomical diagnoses, all had to be reported accurately to be classified as 'correct'. We estimated the overall diagnostic accuracy, defined as:

$$(\text{true positives})/\text{total for ultrasonography and } (\text{true positives} + \text{true negatives})/\text{total for iuMRI.} \quad (1)$$

This percentage is equivalent to the positive predictive value for ultrasonography. Diagnostic accuracy was calculated for both gestational age groups (i.e. 18–23 weeks and ≥ 24 weeks) and overall using McNemar's paired binomial test.

Diagnostic confidence and clinical impact

Data on diagnostic confidence and the clinical impact of the iuMRI on the counselling and management of pregnancies were also collected for analysis.

Economic evaluation

This determined whether or not the new intervention (iuMRI) represented good value for money compared with current practice (ultrasonography alone). Information on participant resource use and outcomes were analysed to estimate the total additional costs and change in outcomes associated with iuMRI in the diagnosis of fetal brain abnormalities. In the base case, the economic analysis compares the costs and outcomes associated with iuMRI with ultrasonography alone. In scenario analyses, iuMRI is compared with repeat ultrasonography.

Sociological substudy

The aim of the patient and health professional perspectives substudy was to assess the acceptability of the clinical care package including iuMRI using qualitative and quantitative methods. This substudy drew on quantitative data from patients and qualitative data from patients and health professionals to assess the acceptability of iuMRI in the PND for fetal brain abnormality. This mixed-method approach provided an in-depth analysis of key issues and experiences that matter to those with first-hand knowledge of iuMRI in practice.

Three data sets (i.e. women's survey responses, women's interviews and professionals' interviews) were used to explore service user and health professional experiences of engaging with the clinical study. Survey 1 was administered after the fetal medicine consultation following iuMRI (when a management plan had been made), and survey 2 was administered 3–6 months after the pregnancy outcome. Participants who responded to survey 2 formed the sampling frame for the qualitative interviews with women, and purposive sampling identified the pool for health professional interviews.

Add-on study

Recruitment into the MERIDIAN study included only women with fetuses thought to have had brain abnormalities on ultrasonography, which allowed us to assess the diagnostic accuracy of ultrasonography and iuMRI in terms of the false-positive rate of detecting a fetal brain abnormality; however, the false-negative rate cannot be estimated. The add-on study addressed this by recruiting pregnant women carrying a fetus without any form of abnormality detected on detailed ultrasonography.

Participants were recruited via the MERIDIAN study fetal medicine centres and local media advertisement. Participants could either be referred directly or self-refer. Potential participants were initially screened by telephone and, if deemed eligible, attended the unit for the iuMRI study where further screening took place prior to obtaining written informed consent.

The 2- to 3-year follow-up study

Surviving infants were followed up at 2–3 years of age in order to assess three aims: (1) whether or not additional diagnoses had become apparent, (2) what impact their diagnosis had on their neurodevelopment (i.e. the accuracy of the prognosis following ultrasonography or iuMRI) and (3) the extent to which these matter in the specific subgroup of isolated, mild ventriculomegaly (VM), which is the most frequent single diagnosis. The issue of prognosis is particularly relevant because it is the functional significance of the diagnosis that matters most to parents rather than the brain abnormality per se. Research has shown that following the diagnosis of a fetal abnormality, parents want to hear all possible outcomes. Preparation for the potential outcomes allows families to build a picture of what those difficulties would be like to live with and helps them consider other aspects, such as the emotional impact and the implications for family life.

The surviving infants who underwent ultrasonography and iuMRI as part of the original study, and whose families gave consent to be approached about future studies, were screened and the family was approached to participate in the follow-up study. The first aim involved a review of the child's medical case notes. This review allowed us to refine our estimates of diagnostic accuracy based on more recent imaging of the infant's brain. We also collected information about follow-up care and life events that may have had an impact on the child's development.

For the second aim, parents were asked to complete the Ages and Stages Questionnaire and their children were invited to participate in a developmental assessment, the Bayley Scales of Infant Development, Third Edition (BSID3). The assessments were completed either in the local recruiting hospital or, when possible, in the child's home. The cognitive, language and motor components were completed.

In addition to the BSID3, or when a face-to-face appointment could not be arranged, a further two questionnaires were completed: the Strengths and Difficulties Questionnaire and the MERIDIAN Gross Motor Skills Questionnaire. Following these assessments, each child's neurodevelopment was classified as 'normal', 'at risk' or 'abnormal'.

The third objective was to assess outcomes of children diagnosed with an isolated, mild VM on either ultrasonography or iuMRI.

Results

Between July 2011 and August 2014, 903 participants (911 fetuses) were recruited to the study. A total of 823 participants (829 fetuses) successfully underwent iuMRI. In total, 64% of all participants attended the Academic Unit of Radiology at the University of Sheffield for their iuMRI, whereas the remaining 36% of participants attended one of the five collaborating centres. An ORD was available for 638 out of 829 (77%) fetuses; of these 638, 570 (89%) had the iuMRI performed within 2 weeks of the referral ultrasonography. A total of 369 fetuses (65%) were in the 18–23 weeks group (110% of required participants) and 201 fetuses (35%) were in the ≥ 24 weeks group (120% of required participants). The three commonest ultrasonography diagnoses were isolated VM (306/570, 54%), an abnormality restricted to the contents of the posterior fossa (83/570, 15%) and failed commissuration (79/570, 14%).

The overall diagnostic accuracies of ultrasonography and iuMRI were 68% and 93%, respectively, with a difference of 25% [95% confidence interval (CI) 21% to 29%]. The difference between ultrasonography and iuMRI increased with gestational age. In the 18–23 weeks group, the figures were 70% for ultrasonography and 92% for iuMRI (difference of 23%, 95% CI 18% to 27%); in the ≥ 24 weeks group, the figures were 65% for ultrasonography and 94% for iuMRI (difference of 29%, 95% CI 23% to 36%).

In 386 out of 570 cases (67.7%) both ultrasonography and iuMRI reports were correct, and in 144 out of 570 cases (25.3%), the ultrasonography report was incorrect but the iuMRI report was correct. There were two fetuses (0.4%) in whose cases the ultrasonography was correct and the iuMRI was incorrect, and 38 fetuses (6.8%) in whose cases both the ultrasonography and iuMRI were incorrect.

In total, 198 participants (205 fetuses) were recruited to the add-on study and underwent iuMRI. Although the results confirm the ability of both ultrasonography and iuMRI to correctly confirm when brain development of the fetus is normal, there was one instance of a brain abnormality that ultrasonography had not detected but which was apparent on iuMRI. This highlights the validity of ultrasonography as the primary screening imaging method for pregnancy.

The 2- to 3-year follow-up study recruited 238 participants, 10 of whom had a new ORD available (five previously had no ORD and another five had a diagnosis that differed from the original ORD). The overall difference in diagnostic accuracy was revised to 24.8% (95% CI 21.0% to 28.5%; $p < 0.0001$), which was very similar to the original difference of 24.9% and still statistically significant. Analysis of the developmental data showed minimal difference between ultrasonography and iuMRI in prognosticating abnormal development. However, iuMRI demonstrated a higher number of correct prognoses in surviving infants who were developmentally assessed as 'normal' or 'at risk'.

In total, 19 (22%) participants diagnosed with isolated, mild VM on ultrasonography had abnormal neurodevelopment, with a further 12 (14%) participants being considered 'at risk'. Among those with a diagnosis of isolated, mild VM on iuMRI, the incidences were 18% (13/71 of patients) among those with abnormal neurodevelopment and 13% (9/71 of patients) among those 'at risk'. None of the children had received a poor prognosis on either modality. The higher than expected incidence of abnormal neurodevelopment in some of the children could be attributed to additional brain diagnoses (some of which the iuMRI detected correctly) other (non-brain) diagnoses and life events (e.g. accidents) leading to delayed development.

Health economic evaluation

The use of iuMRI resulted in additional costs compared with ultrasonography alone, owing to the cost of iuMRI itself and the costs from the resulting management decisions. Across a range of scenarios, the incremental cost was consistently $< \pounds 600$ per participant and the cost per management decision appropriately changed was always $< \pounds 3000$.

Sociological substudy

Patient acceptability was high, with 97% of questionnaire 1 and 95% of questionnaire 2 respondents stating that they would have iuMRI as part of their care if they were ever in a similar situation again. In response to the question about whether or not iuMRI was undertaken at an acceptable time and place, 73% of questionnaire 1 and 68% of questionnaire 2 respondents strongly agreed or agreed. Interviews suggested that participants were usually 'information hungry' and prepared to tolerate significant discomfort to maximise information prior to decision-making about their pregnancy. Health professional interviews suggested that iuMRI was broadly acceptable to clinicians and it was consistently noted that iuMRI was useful as an adjunct to ultrasonography, but not as a replacement.

Conclusions

Implications for health care

Our study provides robust data indicating that there would be significant benefits from the routine use of iuMRI as an adjunct to ultrasonography in the diagnostic pathway for identifying fetal brain abnormalities.

The development of a service that includes iuMRI in the diagnostic pathway may consider providing the service at a small number of supraregional centres and/or promoting collaboration between radiologists to form expert panels for cases, provide formal training to improve radiologists' knowledge base and having the iuMRI study supervised by the radiologist and the images double reported.

Recommendations for research

- Evaluate the use of iuMRI for cases of isolated microcephaly identified on ultrasonography, as this is often associated with other brain abnormalities and the severity correlates with the risk of poor outcome.
- Evaluate the use of iuMRI in the diagnosis of fetal spine abnormalities that, to date, have not been well studied; however, there is a small body of research that suggests that iuMRI may have a role in the diagnosis of these abnormalities.
- Longer-term follow-up studies of children diagnosed with fetal brain abnormalities to fully assess the functional significance of the diagnoses.

Trial registration

This trial is registered as ISRCTN27626961.

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