USE OF MRI IN THE DIAGNOSIS OF FETAL BRAIN ABNORMALITIES IN UTERO (MERIDIAN): A MULTICENTRE, PROSPECTIVE COHORT STUDY

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OBJECTIVE

- To assess whether the diagnostic accuracy and confidence of the prenatal diagnosis of brain abnormalities is improved with in-utero MRI
- To assess the clinical impact and patient acceptability of in-utero MRI
Ultrasound is the mainstay of antenatal anomaly screening in the UK

High frequency of abnormalities in the fetal brain
- 3/1000 pregnancies
- Wide range of changes/manifestations/morbidities

Prior studies: in-utero MRI (iuMRI) might be a useful adjunct to ultrasonography for detecting fetal brain abnormalities
- Uncertainty about diagnostic and clinical impact

this MERIDIAN study designed to address uncertainty of iuMRI
- Diagnostic performance
- Clinical impact
- Acceptability to patients
STUDY SELECTION

- prospective cohort study
  + 16 fetal medicine centers in UK (28 million population base)

- Inclusion Criteria:
  + Pregnant women ≥ 16yo
  + Fetus with brain abnl by sono ≥ 18wga
  + No contraindications to iuMRI
  + Able to provide consent
  + Able to understand English (or had translation services)
Sample Size:
- Planned recruitment of 750 pregnant women
- Anticipated 504 fetuses to complete outcome reference diagnosis
  - 336 of these evaluated between 18.0 – 23.6 wga

Assumptions:
- 70% accuracy of sono to dx brain abnl
- 70% concordance between sono and iuMRI
- 10+% increase in accuracy (80+%%) with iuMRI adjunct
  - Clinical importance = changes in fetal prognostic info/mgmt in around 5% of all cases
  - n= 336 ensures ruling out improvement in accuracy <5% with 90% power and 95% confidence
**METHODS**

- **Sono evaluation (at one of 16 sites)**

- **Sono interpretation**
  - Women offered iuMRI after having sono suggesting fetal brain abnl
  - Clinicians recorded their certainty of diagnosis on 5-point Likert scale

- **MRI evaluation (at one of 6 sites) – within 14 days of ultrasound**
  - T2-weighted images in three orthogonal planes
  - Ultrafast imaging (maximum slice thickness = 5mm)
  - T1-weighted images in at least one plane, usually axial
  - Other sequences added by radiologists as deemed appropriate

- **MRI interpretation**
  - Radiologist aware of diagnosis and certainty of ultrasound expert
  - Comments on each anatomical diagnosis required (e.g., “diagnosis excluded” or addition of extra anatomical diagnoses)
  - Recorded certainty of diagnosis with same 5-point Likert scale
OUTCOME REFERENCE DIAGNOSIS (ORD)

- Survival: postnatal neuroimaging for clinical purposes up to age 6 mos
- EAB/Stillbirth/Neonatal Death: autopsy, post-mortem MRI, or both

2-level review process to establish agreement between sono/iuMRI/ORD:
- Review by neuroradiologist not associated with MERIDIAN
- Review by Multidisciplinary Independent Expert Panel
  - 3 UK National Health Service specialists (neuroradiology, fetal medicine, pediatric neurology) from one single center not associated with MERIDIAN
- required unless complete/unequivocal agreement between sono, iuMRI, and ORD, or if ventriculomegaly resolved
ANALYSIS: DIAGNOSTIC ACCURACY

- Primary population: participants who underwent iuMRI within 14 days of sono + ORD confirmed
  - Fetal brain rapidly growing/maturing
  - Brain abnormalities easier to detect with larger/mature brains

- Repeat scans were allowed, but only first scans were included for this article

- If multiple abnormalities, all had to be accurate to be classified as correct

- Sensitivity/specificity not applicable measures as a positive sono was requirement for study entry

- Diagnostic Accuracy Defined:
  - $\text{Diagnostic Accuracy} = \frac{\text{TP}}{\text{total (sono)}}$ (equivalent to PPV)
  - $\text{Diagnostic Accuracy} = \frac{\text{TP+TN}}{\text{total (iuMRI)}}$

- Calculated for 2 groups: 18-23.6 wga, ≥24wga
  - McNemar’s paired binomial test
Comparison of level of confidence in diagnosis made by ultrasound/iuMRI with accuracy of diagnosis made by ORD

- Likert Scale 70/90% = “high confidence”
- Likert Scale 10/30/50% = “low confidence”
- Plotted on histogram against whether correct or not by ORD
ANALYSIS: CLINICAL IMPACT

- At the time of sonographic diagnosis:
  - Prognostic info given to patients:
    - Normal (no worse than risk to a fetus w/o abnl)
    - Favourable (normal neuro outcome expected in >90% of cases)
    - Intermediate (normal neuro outcome expected in 50-90% of cases)
    - Poor (normal neuro outcome expected in <50% of cases)
    - Unknown
  - Fetal Medicine specialists asked if they discussed termination of pregnancy

- After iuMRI, updated:
  - Diagnosis: did iuMRI provide additional info
  - Prognosis: did iuMRI change the prognosis/regraded on above scale
  - Management: did Fetal Medicine specialists discuss termination, did iuMRI alter their counseling and mgmt, the extent of change

- Patients were asked to evaluate the acceptability of iuMRI
RESULTS

- Recruitment between 7/29/2011 and 8/31/2014

- Successful iuMRI in 823 of 830 women
  + iuMRI abandoned in 7 cases
    - Maternal claustrophobia (4)
    - Back pain (1)
    - Fetal demise since sono (2)

- Successful ORD confirmation in 638 fetuses
  + 570 (89%) had iuMRI within 2 weeks of ultrasound
    - 502 continued pregnancy
    - 68 terminated pregnancy
RESULTS: DIAGNOSTIC ACCURACY

- Overall diagnostic accuracies:
  - Ultrasound 68%
    - Lower >24 wga compared to 18-23.6 wga
  - iuMRI 93%
    - Similar >24 wga compared to 18-23.6 wga

- Sono/iuMRI both correct: n=385 (68%)
- Sono/iuMRI both incorrect: n=39 (7%)
- Sono incorrect, iuMRI correct: n=144 (25%)
- Sono correct, iuMRI incorrect: n=2 (<1%)

Most common diagnoses:
- ventriculomegaly (n=306, 54%),
- posterior fossa abnormalities (n=83, 15%),
- agenesis/hypogenesis of the corpus callosum (n=79, 14%)

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Ultrasound correct (%)</th>
<th>iuMRI correct (%)</th>
<th>Percentage difference (95% CI)</th>
<th>p value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>18 to &lt;24 weeks</td>
<td>258 (70%)</td>
<td>341 (92%)</td>
<td>23% (18-27)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>≥24 weeks</td>
<td>129 (64%)</td>
<td>188 (94%)</td>
<td>29% (23-36)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Combined</td>
<td>387 (68%)</td>
<td>529 (93%)</td>
<td>25% (21-29)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

Data are n (%) unless otherwise stated. iuMRI=in-utero MRI. *McNemar’s test between ultrasound and iuMRI correct diagnoses.

Table 1: Diagnostic accuracy of ultrasound and iuMRI by age of fetus in the 570 cases constituting the primary group
**RESULTS: DIAGNOSTIC ACCURACY**

- **Potential sources of bias:**
  - Large number of scans undertaken at the host institution (which could favor iuMRI)
  - Possibility of non-random sample with missing ORD (which could favor either sono or iuMRI)
    - More likely to be <24wga, poor prognosis, EAB

<table>
<thead>
<tr>
<th>Gestational age at iuMRI (weeks)</th>
<th>ORD available (n=570)</th>
<th>ORD unavailable (n=176)</th>
<th>Excluded (n=81)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age</td>
<td>24.5 (4.5)</td>
<td>23.9 (4.2)</td>
<td>25.7 (3.6)</td>
</tr>
<tr>
<td>&lt;24 weeks</td>
<td>369 (65%)</td>
<td>127 (72%)</td>
<td>35 (43%)</td>
</tr>
<tr>
<td>≥24 weeks</td>
<td>201 (35%)</td>
<td>49 (28%)</td>
<td>46 (57%)</td>
</tr>
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<table>
<thead>
<tr>
<th>Time from ultrasound to iuMRI (days)</th>
<th>Mean time</th>
<th>ORD available (n=570)</th>
<th>ORD unavailable (n=176)</th>
<th>Excluded (n=81)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean time</td>
<td>5.8 (3.5)</td>
<td>5.3 (3.3)</td>
<td>22.6 (8.6)</td>
<td></td>
</tr>
<tr>
<td>&lt;1 week</td>
<td>403 (71%)</td>
<td>134 (76%)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>1-2 weeks</td>
<td>167 (29%)</td>
<td>42 (24%)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>≥2 weeks</td>
<td>0</td>
<td>0</td>
<td>81 (100%)</td>
<td></td>
</tr>
</tbody>
</table>

| iuMRI site                           |            |                       |                         |                 |
|--------------------------------------|------------|-----------------------|-------------------------|
| Sheffield                            | 380 (67%)  | 121 (69%)             | 31 (38%)                |
| Birmingham                           | 75 (13%)   | 34 (19%)              | 15 (19%)                |
| Newcastle                            | 66 (12%)   | 6 (3%)                | 9 (11%)                 |
| Leeds                                | 34 (6%)    | 12 (7%)               | 11 (14%)                |
| Nottingham                           | 12 (2%)    | 3 (2%)                | 1 (1%)                  |
| Belfast                              | 3 (1%)     | 0 (0%)                | 14 (17%)                |

| Pregnancy type                       |            |                       |                         |                 |
|--------------------------------------|------------|-----------------------|-------------------------|
| Singleton                            | 539 (95%)  | 166 (94%)             | 78 (96%)                |
| Multiple                             | 31 (5%)    | 10 (6%)               | 3 (4%)                  |

| Previous iuMRI for pregnancy        |            |                       |                         |                 |
|--------------------------------------|------------|-----------------------|-------------------------|
| No                                   | 7 (1%)     | 3 (2%)                | 2 (2%)                  |
| Yes                                  | 563 (99%)  | 173 (98%)             | 79 (98%)                |

Data are mean (SD) or n (%). iuMRI=in-utero MRI, ORD=outcome reference diagnoses.

Table 2: Participant characteristics in the primary cohort and in those excluded.
RESULTS: DIAGNOSTIC CONFIDENCE

- **High Confidence**
  - Sono: $n=465$ (82%);
    - incorrect $n=124$ (22%)
  - iuMRI: $n=544$ (95%);
    - incorrect $n=32$ (6%)

- **Low Confidence**
  - Sono: $n=105$ (18%);
    - correct $n=46$ (8%)
  - iuMRI: $n=26$ (5%);
    - correct $n=17$ (3%)

*Figure 2: The proportion of diagnoses made with high and low confidence on antenatal ultrasound and iuMRI in the 570 patients with complete outcome data and who had iuMRI within 2 weeks of the ultrasound. Diagnoses were compared with the outcome reference diagnoses. iuMRI=in-utero MRI.*
RESULTS: CLINICAL IMPACT

- New/changed diagnosis with iuMRI
  + n=387 (49%) of 783 cases
  + Of these, the new abnormalities were obvious on repeat ultrasound in 201 (52%) of 387 cases

- New/changed prognosis with iuMRI - PERCEIVED
  + n=189 (24%) of 783 cases
  + Of these, 138 (73%) had additional non-neuro imaging (karyotype, fetal echo, infection screening)
    - 32 had non-neuro findings to change prognosis
  + n=189-32=157 (20%) prognostic change based on iuMRI itself (estimated)
RESULTS: CLINICAL IMPACT

- New/changed prognosis with iuMRI – ACTUAL
  - n=342 (44%) of 783 cases
    - (despite MFM's answering it only happened in 24% of cases as above)
  - When “Unknown” prognosis after sono, prognosis:
    - became known in n=113 (14%) after iuMRI
    - Most frequent change was out of “Unknown” category – 55% fewer cases
  - When quotable prognosis after sono, prognosis:
    - improved in n=102 (13%) after iuMRI
    - worsened in n=94 (12%) after iuMRI
    - 30% fewer cases in “Intermediate” category
    - became unknown in n=33 (4%) after iuMRI
RESULTS: CLINICAL IMPACT

- iuMRI influence on counseling:
  + None: n=172 (22%)
  + Minor: n=496 (63%)
  + Major: n=115 (15%)

- iuMRI contribution to final choice in mgmt:
  + No value: n=95 (12%)
  + Minor: n=419 (53%)
  + Significant: n=201 (26%)
  + Major: n=49 (6%)
  + Decisive: n=19 (3%)

Acceptability of iuMRI:
- 95% would have an iuMRI if a future pregnancy were complicated by a brain abnl
- 90% thought the care they received iuMRI was “very good” or “excellent”
- 80% strongly agreed or agreed that iuMRI helped them to understand problem
- 70% strongly agreed or agreed that iuMRI helped them to understand how their baby's brain pathology could affect future quality of life
DISCUSSION: KEY FINDINGS

**DIAGNOSTIC ACCURACY**
- sono/iuMRI significantly increases diagnostic accuracy of fetal brain diagnosis compared to ultrasound alone
- Ultrasound accurate in 70% between 18-23.6 wga
  - Less accurate 24+ due to ossification of skull, increased pt size, descent into pelvis
- With iuMRI, accuracy 92% between 18-23.6 wga, 94% 24+wga
  - Larger increase after 24wga because ultrasound less accurate after that time

**CONFIDENCE**
- Proportion of high-confidence diagnoses increased after iuMRI (from 82% to 95%)
- Incorrect diagnosis + high-confidence = inappropriate mgmt (e.g., EAB)
- iuMRI gave fewer incorrect high-confidence diagnoses than ultrasound (6% vs. 22%)
- Correct diagnosis + low-confidence = withholding intervention
- iuMRI gave fewer low-confidence diagnoses (5% vs. 18%) and fewer correct low-confidence diagnoses (3% vs. 8%) than ultrasound

**CLINICAL IMPACT**
- iuMRI as an adjunct to ultrasound brings about additional diagnostic information in 49%, change in prognosis in 44%, change in counseling in 15% of cases
- Change in mgmt “significant” in 26%, “major”/”decisive” in 9%
- Impact objectively more substantial (44%) than subjectively appreciated (24%)
DISCUSSION: STRENGTHS

- No previous studies concerning diagnostic performance of iuMRI (with robust protocol) have been done
- No previous studies concerning diagnostic confidence of iuMRI to diagnose brain abnormalities
- Prospective study
- Appropriately powered
- Does not exclude any type of fetal brain pathology
DISCUSSION: LIMITATIONS

- Experience in iuMRI is limited
- 2/3 of iuMRIs in this study were done at host institution w/ experienced radiologist
- Did not utilize sensitivity/specificity since abnormality was required entrance criteria
- Possible bias from self-reporting confidence
DISCUSSION: CONSIDERATIONS

- A fetus with a suspected brain abnormality on ultrasound should have iuMRI as part of the routine diagnostic evaluation.

- Future articles by this group/others:
  - Formal assessment of changes of diagnostic confidence
  - Detailed analysis of 3 most common diagnoses
  - Qualitative assessment of pregnant women’s views of iuMRI
  - Health economic analysis of adjunctive iuMRI
  - Detailed analysis of diagnostic errors made in iuMRI in relation to experience of reporter
THANK YOU!
Use of MRI in the diagnosis of fetal brain abnormalities in utero (MERIDIAN): a multicentre, prospective cohort study

Paul D Griffiths, Michael Bradburn, Michael J Campbell, Cindy L Cooper, Ruth Graham, Deborah Jarvis, Mark D Kilby, Gerald Mason, Cara Mooney, Stephen C Robson, Allan Wailoo, on behalf of the MERIDIAN collaborative group*

Summary

Background In-utero MRI (iuMRI) has shown promise as an adjunct to ultrasound but the comparative diagnostic performance has been poorly defined. We aimed to assess whether the diagnostic accuracy and confidence of the prenatal diagnosis of fetal brain abnormalities is improved with iuMRI and assess the clinical impact and patient acceptability of iuMRI.

Methods We did a multicentre, prospective, cohort study in the UK, at 16 fetal medicine centres, of pregnant women aged 16 years or older whose fetus had a brain abnormality detected by ultrasound at a gestational age of 18 weeks or more, had no contraindications to iuMRI, and consented to enter the study. Women carrying a fetus suspected of having a brain abnormality on ultrasound had iuMRI done within 14 days of ultrasound. The findings were reviewed by two independent panels and used to estimate diagnostic accuracy and confidence by comparison with outcome diagnoses. Changes in diagnosis, prognosis, and clinical management brought about by iuMRI and patient acceptability were assessed.

Findings Participants were recruited between July 29, 2011, and Aug 31, 2014. The cohort was subdivided by gestation into the 18 weeks to less than 24 weeks fetus cohort (n=369) and into the 24 weeks or older fetus cohort (n=201). Diagnostic accuracy was improved by 23% (95% CI 18–27) in the 18 weeks to less than 24 weeks group and 29% (23–36) in the 24 weeks and older group (p<0·0001 for both groups). The overall diagnostic accuracy was 68% for ultrasound and 93% for iuMRI (difference 25%, 95% CI 21–29). Dominant diagnoses were reported with high confidence on ultrasound in 465 (82%) of 570 cases compared with 544 (95%) of 570 cases on iuMRI. IuMRI provided additional diagnostic information in 387 (49%) of 783 cases, changed diagnostic information in at least 157 (20%), and led to changes in clinical management in more than one in three cases. IuMRI also had high patient acceptability with at least 95% of women saying they would have an iuMRI study if a future pregnancy were complicated by a fetal brain abnormality.

Interpretation iuMRI improves diagnostic accuracy and confidence for fetal brain anomalies and leads to management changes in a high proportion of cases. This finding, along with the high patient acceptability, leads us to propose that any fetus with a suspected brain abnormality on ultrasound should have iuMRI to better inform counselling and management decisions.

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Introduction

Fetal imaging with ultrasonography has been the mainstay of antenatal screening programmes and detailed anomaly scanning in the UK for many years. The fetal brain is particularly important because of the high frequency of abnormalities (approximately 3 in 1000 pregnancies). A wide range of neuropathological changes occur, many associated with serious clinical morbidities. Previous studies have suggested that in-utero MRI (iuMRI) imaging might be a useful adjunct to ultrasonography for detecting fetal brain abnormalities but uncertainty remains about the extent of diagnostic and clinical impact. The magnetic resonance imaging to enhance the diagnosis of fetal developmental brain abnormalities in utero (MERIDIAN) study was designed to address those uncertainties.

In this Article, we report the results of MERIDIAN in terms of diagnostic performance, clinical impact, and acceptability of iuMRI to pregnant women to provide holistic conclusions about the value of iuMRI. We deliver findings capable of informing best clinical practice in women whose fetus has a possible brain abnormality detected on ultrasound.

Methods Ethics and participants

MERIDIAN was undertaken in accordance with the Medicines for Human Use (Clinical Trials) Regulations 2004, through adherence to the Sheffield Clinical Trials Research Unit’s standard operating procedures. Three committees were established to govern the conduct of the study: a Trial Steering Committee (independent), a Data Monitoring and Ethics Committee (independent), and a Trial Management Group (researchers associated with the study). We obtained ethical approval for a multicentre study through the Integrated Research Application System
Research in context

Evidence before this study
The ultrafast imaging methods required to do in-utero MRI (iuMRI) have been available for approximately 20 years. There is good evidence relating to the safety of the procedure and to the ability to obtain high quality anatomical images of the fetal brain. No formal systematic review was done before this study was started. There have been several fairly small studies (n=15–185) looking at diagnostic performance, all with substantial methodological weaknesses. Those studies have been the subject of three published systematic reviews, the most recent in 2015, which reported 1184 fetuses from 27 studies. A reference standard diagnosis was available in only 454 fetuses and showed that ultrasonography agreed with the reference diagnosis in 54% of cases whilst iuMRI agreed in 80% of cases. There have been no large prospective studies of changes of diagnostic confidence brought about by doing iuMRI to diagnose brain abnormalities; similarly the published evidence relating to clinical impact and patient acceptability is sparse. We aimed to fill this knowledge gap with MERIDIAN.

Sample size calculation
We planned to recruit 750 pregnant women from whom we anticipated complete outcome reference diagnoses (ORD) in 504 fetuses, 336 of whom would be of 18 weeks to less than 24 weeks gestational age at the time that the iuMRI was done, the subgroup of specific interest and on whom the sample size calculation was based. We assumed ultrasonography would achieve an accurate and complete diagnosis of brain abnormalities in 70% of cases and would increase to at least 80% with iuMRI, with iuMRI and ultrasound being concordant (correctly and incorrectly) in 70% of cases overall. If the “true” increase is only 10%, a sample size of 336 patients ensures that we can rule out any improvement in diagnostic accuracy less than 5% with 90% power and 95% confidence. We predicted that a change of that magnitude would be of clinical importance, as it would lead to changes in fetal prognostic information and management intent in around 5% of all cases. On the basis of our experience from earlier research studies, we envisaged that we would scan one woman with a fetus aged 24 weeks gestation or older for every two fetuses scanned in the 18 weeks to less than 24 weeks group, hence the total recruitment target was 504 fetuses with complete ORD.

Added value of this study
MERIDIAN is a prospective, multicentre cohort study recruiting from 16 fetal medicine centres in the UK, designed to provide information on diagnostic and clinical impact of iuMRI as well as the opinions of pregnant women about having iuMRI as an adjunct investigation. Our results show clear diagnostic advantages in doing iuMRI in fetuses with brain abnormalities at gestational age of 18 weeks or older in terms of diagnostic accuracy and confidence, change in prognosis, and changes in clinical management. There is also high acceptability for iuMRI in women whose unborn babies are thought to have a brain abnormality.

Implications of all available evidence
Our data suggest that a fetus with a suspected brain abnormality on ultrasound should have iuMRI as part of the routine diagnostic pathway and this procedure will provide robust information on which formal counselling can be based.

(62734). Inclusion criteria were pregnant women aged 16 years or older whose fetus had a brain abnormality detected by ultrasound at a gestational age of 18 weeks or more, had no contraindications to iuMRI, and gave written informed consent to enter the study. Pregnant women were not recruited into the study if they were unable to give informed consent, had any contraindications to iuMRI, were unable to understand English (except where translation services were available), or if they were under the age of 16 years old.

Recruitment and imaging examinations
Recruitment was from 16 fetal medicine units in the UK (appendix), which covers a population of 28 million people. Women were recruited into the study by being offered an iuMRI scan after a having had a detailed ultrasound scan suggesting a brain abnormality in the fetus. No specific requirements were made for the ultrasound technique and brain abnormalities were recorded with nomenclature used in the most up-to-date version of ViewPoint antenatal ultrasound reporting software (GE Healthcare, Chalfont St Giles, UK) at the time of the study. Clinicians were also asked to record their certainty of diagnosis for each brain abnormality with a five-point Likert scale namely: “Very unsure” (10% certain), “Unsure” (30% certain), “Equivocal” (50% certain), “Confident” (70% certain), and “Highly confident” (90% certain). Afterwards, ultrasound participants underwent iuMRI at one of six sites all performed at 1·5 T. It was not possible to match protocols exactly across the sites because different manufacturers’ MRI systems were used but there was an absolute requirement to obtain T2-weighted images of the fetal brain in the three orthogonal planes with the best ultrafast method available (maximum slice thickness 5 mm) and a T1-weighted ultrafast sequence in at least one plane (usually axial). Other sequences could be added by the attending radiologist as appropriate to the case. The radiologist was aware of the diagnoses and the level of certainty made by the ultrasound expert before the iuMRI study was done and had access to the full clinical ultrasound report. The radiologist was required
to comment on each anatomical diagnosis made with the ultrasound (using “diagnosis excluded” if they disagreed with a finding) and added extra anatomical diagnoses where appropriate. Each entry was accompanied by an indicator of confidence with the same Likert scale as the ultrasound assessment.

Outcome reference diagnoses
In cases where pregnancy continued and the child survived, the ORD was the neuroanatomical diagnosis from post natal neuroimaging studies done for clinical purposes up to the age of 6 months (term corrected). In cases of termination of pregnancy (TOP), stillbirth, or neonatal death the ORD was based on autopsy or post-mortem MRI, or both.

A two-level review process was used to establish agreement between ultrasonography, iuMRI, and ORD. The first level review was carried out by one of two neuroradiologists, not associated with MERIDIAN. Their role was to determine, on the basis of ORD, whether full review by the Multidisciplinary Independent Expert Panel (MIEP) described below was required. Full review was required unless there was complete and unequivocal agreement between the anatomical findings on ultrasound, iuMRI, and the ORD; or ventriculomegaly was the only finding described on both ultrasound and iuMRI examinations but the size of the ventricles had returned to normal as shown on ultrasound later in pregnancy or on neonatal imaging. Ventricle reduction was counted as agreement because enlargement of ventricles can often resolve spontaneously during pregnancy.

The MIEP consisted of three UK National Health Service consultants (neuroradiology, fetal medicine, paediatric neurology) from a single centre (University Hospitals Southampton NHS Foundation Trust, Southampton, UK) that did not recruit into MERIDIAN. The MIEP were given tabulated diagnostic results for each fetus in such a way that they were masked to whether it was an ultrasound or an iuMRI report. They were asked whether each report agreed with the ORD completely (all listed diagnoses correct) and, in the case of ultrasonography and iuMRI disagreeing, which one indicated the more severe pathology. The results were subsequently unblinded by staff at the Sheffield Clinical Trials Research Unit. In a small number of cases, the MIEP required more information and had access to the full clinical reports and imaging, if necessary, at which point blinding was no longer possible.

Diagnostic accuracy
The primary analysis population comprised participants who underwent iuMRI within 14 days of ultrasound and for whom ORD was available. The time difference between the ultrasound and iuMRI examinations is an important confounding factor for diagnostic accuracy of pathology of the fetal brain as it is growing and maturing rapidly in the late second to third trimester. Most brain abnormalities will be easier to detect in larger, more mature fetal brains, particularly for iuMRI. To reduce potential biased to show improvements in the diagnostic accuracy of iuMRI, the time between ultrasound and iuMRI should be as short as reasonably possible. The choice of 2 weeks as the cutoff for the primary analysis was made to balance between these issues and the expected ease of access to MRI facilities.

Although repeat scans were allowed, only the results of the first scans are reported in this Article. In cases with multiple anatomical diagnoses, all had to be reported accurately on the imaging study to be classified as correct. Because a positive ultrasound scan was a requirement for study entry, neither sensitivity nor specificity could be used as summary measures; instead, we estimated the overall diagnostic accuracy, defined as (true positives) divided by total for ultrasound and (true positives + true negatives) divided by total for iuMRI. This percentage is equivalent to the positive predictive value for ultrasound. Diagnostic accuracy was calculated for both gestational age groups (18 weeks to <24 weeks and ≥24 weeks) and overall with McNemar’s paired binomial test.

Diagnostic confidence
Assessment of diagnostic confidence in this Article is purely descriptive, comparing the level of confidence of diagnosis made by ultrasound and iuMRI with the accuracy of diagnosis obtained from the ORD. A more detailed assessment of change in diagnostic confidence on a case by case basis will be published elsewhere. Diagnostic confidence of the dominant diagnosis (the one most likely to influence prognostication as assessed by the independent panels) on the Likert scale was converted to high confidence (70% and 90%) or low confidence (10%, 30%, and 50%) diagnoses for both ultrasound and iuMRI. This information was plotted on a histogram along with the information about whether the diagnosis was correct or not compared with the ORD.

Clinical impact
The prognostic information given to participants after ultrasound was categorised as either: normal (no worse than the risk to a fetus without a demonstrable brain abnormality), favourable (normal neurological outcome expected in >90% of cases), intermediate (normal neurological outcome expected in 50–90% of cases), poor (normal neurological outcome expected in <50% of cases), or unknown.

The fetal medicine specialists were also asked if TOP had been discussed or offered if the abnormalities on ultrasound were sufficient to consider that option under Ground E of the Abortion Act (1967, section 1(1)d substantial risk of serious mental or physical handicap). At the next consultation with the woman, where the iuMRI report was available, the fetal medicine specialist
recorded the updated diagnostic and prognostic information, and management plan. From a diagnostic perspective, the clinicians were asked if iuMRI had provided additional information and, if so, could the new imaging features be confirmed on follow-up ultrasound. For prognosis, they were asked if iuMRI had changed the prognostic information given to the woman and to regrade the prognosis with the same five categories used previously (subsequently referred to as the tabulated prognostic information). The fetal medicine specialists also recorded whether or not TOP had been either discussed or offered. They were also requested to consider if iuMRI had altered counselling and management and if so, what was the extent of change. This analysis does not require ORD, so all 823 cases with successful iuMRI studies are included.

The acceptability of iuMRI to pregnant women is presented in the appendix. The protocol for this study was peer-reviewed and accepted by The Lancet; a summary of the protocol was published on the journal’s website, and the journal then made a commitment to peer-review the primary clinical manuscript. This trial was registered with ISRCTN, number ISRCTN27626961.

Role of the funding source
The funders had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results
The recruitment, which took place between July 29, 2011, and Aug 31, 2014, scanning, and follow-up process is summarised in figure 1. Most iuMRI procedures (64% of all procedures) were done at the University of Sheffield’s MRI facility (Sheffield, UK), whilst the others were done at one of the five collaborating centres and reported by local radiologists. In five cases, iuMRI was abandoned without useful information being obtained: four because of the mother’s claustrophobia and one for physical discomfort arising from backache. Two iuMRI examinations were stopped before completion when it was realised that the fetus had died since referral from ultrasound. Successful iuMRI studies were done, therefore, in 823 (99%) of 830 women. ORD was collected in 638 fetuses of which 570 (89%) had iuMRI within 2 weeks of the ultrasound; 502 fetuses were continued pregnancies and 68 fetuses resulted in a TOP. Of the 570 fetuses, 369 (65%) were in the 18 weeks to less than 24 weeks group (110% of required) and 201 (35%) in the 24 weeks and older group (120% of required).

The overall diagnostic accuracies of ultrasound was 68% and of iuMRI was 93% (difference 25%, 95% CI 21–29; see table 1). Ultrasound and iuMRI reports were both correct in 385 [68%] of 570 cases, and both incorrect in 39 (7%). Incorrect ultrasound reports were corrected by iuMRI in 144 (25%) of 570 cases, and two fetuses (<1%) were diagnosed correctly by ultrasound and incorrectly by iuMRI. The diagnostic accuracy of ultrasound was lower in fetuses 24 weeks or older gestational age compared with those aged 18 weeks to 24 weeks whilst iuMRI remained similar (table 1).

The three most common ultrasound diagnoses were ventriculomegaly as the only intracranial abnormality (306 [54%] of 570 fetuses), an abnormality restricted to contents of the posterior fossa (83 [15%] of 570 fetuses), and failed commissuration (ie, agenesis or hypogenesis of the corpus callosum; 79 [14%] of 570 fetuses). These anatomical subgroups will be described fully in subsequent publications.

Two potential sources of bias were the proportionately large number of scans undertaken at the host institution (which could favour iuMRI) and the possible non-random sample of cases with missing ORD (which could favour either modality). A number of sensitivity analyses were
undertaken that confirmed the robustness of the findings (appendix). Cases for which no ORD was available were more likely to be fetuses that were younger than 24 weeks of gestational age (table 2), had poor prognosis, and had TOP (appendix); upweighting cases with these characteristics with imputation methods gave similar findings to the overall cohort. Cases referred into the host institution showed a marginally higher diagnostic accuracy on both modalities compared with other centres, with the difference between the two therefore being similar in host and other centres.

The dominant diagnosis (as defined by the independent panels) was reported with high confidence on ultrasound in 465 (82%) of 570 cases compared with 544 (95%) of 570 cases on iuMRI, an absolute difference of 13% (figure 2). High confidence diagnoses were subsequently found to be incorrect in 124 patients after ultrasound (22% of overall population) compared with 32 (6%) of 570 patients who had iuMRI. IuMRI made fewer diagnoses with low confidence than ultrasound (5% vs 18%), of which 17 (3% of all cases) were found to be correct compared with 46 (8%) of cases correct on ultrasound.

Complete data for clinical impact was available in 783 (95%) of 823 cases, the higher figure being because ORD was not required for this analysis. The 40 missing or excluded forms resulted from: no follow-up (n=26), incomplete clinical feedback form (n=13), and withdrawal from the study (n=1).

IuMRI was considered to provide additional diagnostic information in 387 (49%) of 783 cases by the referring fetal medicine expert. In 201 (52%) of 387 patients, the apparent new anatomical abnormalities described on iuMRI were obvious on repeat ultrasound.

Fetal medicine clinicians answered yes to the question “did iuMRI imaging change your prognosis?” in 189 (24%) of 783 cases. Additional non-neuroimaging investigations (eg, karyotyping, fetal cardiac echo, and infection screening) were done in tandem with the iuMRI in 138 (73%) of 189 cases, 32 of which were considered to have a major influence on prognosis. We estimate, therefore, that iuMRI itself changed the prognostic information in at least 157 (20%) of 783 cases.

When the tabulated regrading of prognostic information was analysed, changes in prognosis were recorded in 342 (44%) of 783 cases despite the fact that the clinicians had answered yes to the direct question in only 24% of cases. After iuMRI, there were 30% fewer cases in the “Intermediate” category and 55% fewer cases in the “Unknown” category with correspondingly more cases in the “Normal”, “Favourable”, and “Poor” categories (table 3). In the 342 cases in which a change of prognosis was recorded, the most frequent change was from “Unknown” to “Normal”, “Favourable”, and “Poor” categories (table 3). In the 342 cases in which a change of prognosis was recorded, the most frequent change was from “Unknown” to “Normal”, “Favourable”, and “Poor” categories (table 3).
“major influence” in 49 (6%) cases, and “decisive” in 19 (3%) cases.

As shown in the appendix, the overall acceptability of iuMRI was high; at least 95% of women said they would have an iuMRI study if a future pregnancy were complicated by a fetal brain abnormality. Additionally, approximately 90% of women considered that the care they received after referral for iuMRI was either “very good” or “excellent”. Overall, around 80% of women strongly agreed or agreed that information from iuMRI helped them to understand their baby’s problem, while around 70% strongly agreed or agreed that the information had helped them to understand how their baby’s brain pathology could affect his or her future quality of life.

**Discussion**

The accuracy of a positive ultrasound in diagnosing fetal brain abnormalities has been the subject of several previous studies. Our finding that ultrasound was accurate in 70% of fetuses of gestational age below 24 weeks and 64% in 24 weeks and older gestation is consistent with those reports. The reduced accuracy of ultrasound in older gestational age fetuses can be attributed to several factors including difficulties caused by the ongoing ossification of the fetal skull, the increased physical size of the woman, and the descent of the fetal head into the maternal pelvis. We found that adding iuMRI to the diagnostic pathway increased the diagnostic accuracy to 92% for fetuses younger than 24 weeks and 94% thereafter (p<0·0001 for both comparisons). This, together with the encouraging findings of other studies described later, suggests that iuMRI significantly increases the accuracy of fetal brain diagnoses compared to ultrasound alone in all fetuses 18 weeks and older.2–4

![Figure 2](https://example.com/figure2.png)

**Figure 2:** The proportion of diagnoses made with high and low confidence on antenatal ultrasound and iuMRI in the 570 patients with complete outcome data and who had iuMRI within 2 weeks of the ultrasound. Diagnoses were compared with the outcome reference diagnoses. iuMRI=in-utero MRI.

The main study group in MERIDIAN was 18 weeks to younger than 24 weeks fetuses because of the need to respond to problems raised at the mid-pregnancy (18–21 weeks) anomaly ultrasound programme in the UK. There are many institutions worldwide that do not do iuMRI before 24 weeks gestation and although MERIDIAN was not powered for fetuses of that age, they were recruited into the study. We have shown significant improvements in diagnostic accuracy in the 24 weeks and older group and the absolute difference in diagnostic accuracy was greater in that age group when compared with 18 weeks to younger than 24 weeks fetuses, mainly because of reduced accuracy of ultrasonography. Although we believe that the diagnostic impact data are generalisable, further studies are needed to assess clinical impact in countries that have, for example, different laws on termination of pregnancy.

The relevance of diagnostic accuracy in assessing an imaging technology is self-evident but the importance of the diagnostic confidence in imaging examinations is often overlooked and less well studied, although Ng and Palmer17 have explained its relevance. Our data show the proportion of high confidence diagnoses increased by 13% after iuMRI (from 82% to 95%) but there are other considerations that highlight the advantages of iuMRI further. As highlighted by Ng and Palmer, an incorrect diagnosis made with high confidence can result in an inappropriate change in management (in this case an inappropriate TOP). We found iuMRI gave fewer high confidence but incorrect diagnoses than ultrasound (6% vs 22% of the total number of cases). Alternatively, TOP might not be offered if an imaging diagnosis is made with low confidence. This situation again can bring about medical errors if the diagnosis is found to be correct, as withholding an intervention might have detrimental effects. The MERIDIAN data show that the iuMRI resulted in fewer low-confidence diagnoses (5% vs 18%) and fewer correct low-confidence diagnoses (3% vs 8%). Subsequent publications with the MERIDIAN cohort will explore this issue further.

There was a wide range of previous experience of reporting iuMRI examinations for the radiologists

![Table 3](https://example.com/table3.png)

**Table 3:** The tabulated results of prognostic grade given to pregnant women before and after iuMRI assessments
contributing to MERIDIAN at the start of the study. The most experienced radiologist (PDG) was from the host site (Sheffield, UK) where approximately two thirds of the cases in the study were done. Previous experience of iuMRI is probably related to improvement in diagnostic accuracy and this subject will be analysed in the future with MERIDIAN data.

As far as we are aware, there are no published studies concerning diagnostic confidence in the field of iuMRI but other indicators of diagnostic performance have been the source of three systematic reviews. One published before the start of MERIDIAN (Mundy and colleagues\(^3\)) was produced as a technology report for the Australian Government in 2007 about iuMRI and combined both brain and somatic fetal pathology. Fifteen studies were analysed (nine prospective and six retrospective) but cumulative diagnostic accuracy was not reported although discordant diagnoses between ultrasound and MRI were found in 6% to 58% of cases. That review concluded that iuMRI changed the diagnosis in 6% to 32% of cases and provided additional information in 18–85% of cases. Rossi and Prefumo\(^4\) reviewed only CNS anomalies from 13 studies of 710 fetuses and showed that iuMRI agreed with ORD in 670 (94%) of 710 cases, including 40 (6%) of 710 cases in which both showed normal brains. Brain abnormalities were over-diagnosed on iuMRI in 31 (4%) of 710 cases, including 18 (3%) cases in which the ORD was normal and abnormalities were missed on iuMRI in 13 (2%) cases. More recently, in 2015, Van Doorn and colleagues\(^5\) analysed 27 studies with 1184 fetuses. In 65% of cases ultrasound and iuMRI agreed, in 23% iuMRI gave different or additional pathology to ultrasound, and in 8% iuMRI excluded the ultrasound diagnosis. The postnatal diagnosis was available in 454 cases only, but when comparison was made with the reference standard, ultrasound was correct in 54% of cases and iuMRI correct in 80% of cases.

These systematic reviews highlight consistent methodological weaknesses that compromise their validity. Many included studies had no reference standards to confirm or refute the imaging findings. Only half of the studies reported the level of expertise of the clinicians doing the ultrasound and iuMRI and the time difference between the examinations was rarely reported. Rossi and Prefumo\(^4\) reported a pooled sensitivity and specificity for iuMRI but acknowledged the flaw in doing so without true negatives and false negatives (an inevitable effect in studies that have abnormal ultrasound findings as an entrance criterion). We have not attempted to report sensitivity or specificity in this study for those reasons. It is notable that the reported diagnostic accuracy for ultrasound of 54% in the most recent review\(^6\) is significantly lower than the 70% widely accepted in the published literature, used in our power calculation, and close to that observed in our study. It is highly likely that the low figure reflects substantial selection bias in many of the earlier iuMRI studies which, for example, might not have included cases of isolated ventriculomegaly. We believe that MERIDIAN has major advantages over the previous studies and systematic reviews because it is a prospective study, appropriately powered, and does not exclude any type of fetal brain pathology.

This study was designed to be pragmatic, to evaluate the diagnostic and clinical impact of the use of iuMRI as an adjunct to, as opposed to a replacement for, ultrasound, reflecting how the service would be implemented in clinical practice. The limitations of the study design include potential for investigators to bias reporting of diagnostic and prognostic outcomes as well as information about their confidence in the outputs. However, changes in prognosis were under-reported by clinicians, suggesting that they were not systematically going back to review their initial decisions at the time of reviewing the iuMRI results.

Two sensitivity analyses were undertaken to address the potential impact of missing ORD (which occurred in 24% of cases) and the high proportion (67%) of iuMRI scans undertaken at the host institution. The details are provided in the appendix and confirm the robustness of the difference in favour of iuMRI.

Much work has already been undertaken and published about the safety of iuMRI. The general risks of MRI apply and include scanning people with contraindications (eg, pacemakers) and the risks of taking ferromagnetic objects into the scan room, which become a projectile threat. These risks are mitigated by rigorous screening procedures by appropriately trained MRI radiographers and no adverse events of this type occurred during the course of MERIDIAN. The expertise of the MRI radiographers doing the examinations in the MERIDIAN study is highly likely to have contributed to the high completion rate of iuMRI in this study (more than 99% of patients).

The specific risks to the fetus have been discussed in detail elsewhere but the consensus of opinion is that iuMRI is a safe procedure\(^18–21\) provided that it is done within the energy deposition limits set by the International Electrotechnical Commission.\(^19\) The main concern is about raising the temperature of the fetus during a study, which cannot be measured directly and has to be modelled. No assessments in MERIDIAN were abandoned because of subjective warming of the pregnant woman but core temperatures were not measured. Additionally, the theoretical risk of hearing impairment in a child who had iuMRI brought about by the high acoustic noise (around 100 dB) has not been supported by any measurable harmful effects on hearing postnatally.\(^20\)

To our knowledge, this prospective analysis of clinical impact of iuMRI in fetuses with brain abnormalities is the first and in this Article we have shown that iuMRI brings about changes in counselling and management in a high percentage of cases. Specifically, iuMRI provided additional diagnostic information in 49% of cases, caused...
a documented change in prognosis in 44%, and had major effects on counselling in 15% of cases. The contribution of iuMRI to overall clinical management was judged to be “significant” in 26% of cases and had either a “decisive” or “major influence” in a further 9% of cases. This effect is considerably larger than the 5% change in management anticipated at the design stage, an increase that can be attributed to the greater than predicted improvement in diagnostic accuracy.

One important contributory factor to the change in management was that fetal medicine specialists gave more decisive prognoses after iuMRI compared with results from the ultrasound alone because there was a move away from “Intermediate” and “Unknown” prognosis groups (30% fewer cases in the “Intermediate” category and 55% fewer in the “Unknown” category) with a move towards “Normal”, “Favourable”, and “Poor” prognoses. This finding is important because parents are likely to find “Intermediate” and “Unknown” prognosis groups the hardest to resolve. Additionally, iuMRI provided increased certainty that the indication for TOP (where offered) was based on a greater probability of risk of substantial handicap. We have considered the possibility that other non-neuroimaging investigations done in parallel might have contributed to the 24% change in prognosis, but our data indicate that iuMRI alone was responsible for the change in at least 20% of cases. One aspect of our assessment of prognostic information warrants further discussion. On direct questioning, the fetal medicine specialists stated that prognosis was changed by iuMRI in 24% of cases, whereas the tabulated regrading of prognosis data indicate changes in 44% of cases. The most likely explanation is referring clinicians did not refer back to their earlier post-ultrasound prognosis when describing the findings of iuMRI, or felt the change in prognostic category was qualitatively unimportant. It is also important to point out that iuMRI did not always worsen the prognosis; in 26 cases where the prognosis was described as “Poor” on ultrasound this improved to “Normal” in four cases and “Favourable” in six cases after iuMRI. These data suggest that a prognosis based on only ultrasound results could result in offers of TOP on the basis of predictions from inaccurate diagnoses.

We have described a high completion rate for iuMRI in MERIDIAN (more than 99% of patients) and in the appendix we have presented a more detailed analysis of acceptability.

In conclusion, our results indicate a 23% absolute increase in diagnostic accuracy when iuMRI is used to supplement ultrasound imaging in the 18 weeks to younger than 24 weeks gestational age group of fetuses and a 29% increase in the 24 weeks or older fetuses. Diagnostic confidence is also improved when iuMRI is used to assess prenatal fetal neuropathology as an adjunct to ultrasound. The increased diagnostic accuracy and confidence results in changes in counselling and clinical management in a high proportion of cases. These factors, in conjunction with high patient acceptability, lead us to propose that any fetus with a suspected brain abnormality on ultrasound should have iuMRI before definitive counselling.

We predict the publication of several further papers based on the MERIDIAN cohort to cover aspects of the published protocol that have either not been covered or only partly covered in this Article. Those papers will include but are not limited to: a formal assessment of changes in diagnostic confidence brought about by using iuMRI; a detailed analysis of the three commonest anatomical subgroups of abnormalities referred from ultrasound, ventriculomegaly, agenesis of the corpus callosum, and abnormalities confined to the posterior fossa; qualitative assessment of pregnant women’s views of iuMRI; health economic analysis; a detailed analysis of diagnostic errors made on iuMRI in relation to experience of the reporter.

Contributors
PDG (Chief Investigator) oversaw all study conduct; helped to develop the study design and all study materials including the study protocol; assessed participant eligibility and was the reporting radiologist for MRI scans completed at the Sheffield site; participated in data analysis and interpretation of the results; and drafted and revised the manuscript. MB and MJC were the study statisticians, assisting with the study design and providing advice and input to all statistical issues; completed the data analysis and data interpretation and revised the manuscript. CLC provided oversight to the trial design, helped to develop study materials including the trial protocol, provided oversight to trial conduct, and revised the manuscript. RG led the substudy and led the design of the substudy components; provided advice and input into all the substudy components, supervised the qualitative data collection and analysis of the data relating to parent perspectives; contributed to the analysis and interpretation of the data relating to parent perspectives; and revised the manuscript. DJ was a radiographer on the study, assisted with data analysis, completed literature searching and revised the manuscript. MDK was a principal investigator at the Birmingham research site, referred and actively recruited participants, assessed participant eligibility, and assisted with data collection; interpreted results; and revised the manuscript. GM and SCR were collaborators and principal investigators at sites; assisted with development of the protocol and other study materials; referred and actively recruited participants, assessed participant eligibility, and assisted with data collection; interpreted results; and revised the manuscript. CM was the study manager who coordinated study activities, provided training for research sites, assisted with and facilitated data collection; participated in data analysis and revised the manuscript. AW was the health economist for the study, contributed to the study design, completed data analysis and interpretation and revised the manuscript.

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References