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INTRODUCTION

1
2 Recent systematic reviews¹⁻³ and the results from our previous work from the MERIDIAN
3 study⁴ have shown that *in utero* Magnetic Resonance (iuMR) imaging significantly improves
4 the detection of fetal brain abnormalities when compared with antenatal ultrasonography
5 (USS). Specifically, iuMR improves diagnostic accuracy⁴ and diagnostic certainty⁵ when a
6 brain abnormality is shown or suspected on USS and those findings are likely to have
7 substantial implications for clinical practice.⁴ An important limitation of those studies is they
8 have not evaluated the impact of iuMR imaging in cases in which no brain abnormality was
9 detected or suspected on USS. The intrinsic value of a diagnostic test relies not only its
10 ability to identify an abnormality correctly when one is present but also to exclude
11 abnormalities correctly when they are not present. To date, studies of iuMR for fetal brain
12 abnormality have been undertaken among fetuses in which a brain abnormality was suspected
13 (predominantly on the basis of abnormal USS) and, whilst these strongly support the use of
14 iuMR in such cases, the benefit – if any – of iuMR in ostensibly normal pregnancies is
15 unknown.

16
17 In this study we present the results of an extension to the MERIDIAN study in which women
18 with low-risk pregnancies and normal fetuses on USS were recruited in order to have iuMR
19 imaging of the fetal brain (full protocol available at
20 <https://www.sheffield.ac.uk/meridian/studysummary>). This enabled the calculation of
21 negative predictive value (NPV) for both iuMR and USS imaging in order to complement the
22 positive predictive value (PPV) derived from the main MERIDIAN cohort. To our
23 knowledge, no previous study has evaluated the impact of iuMR in this population. We also
24 discuss the problems of measuring diagnostic performance for iuMR and antenatal USS with
25 particular reference to the inherent difficulties in estimating sensitivity and specificity.

26 MATERIALS AND METHODS

27 Participants and Recruitment

28 This work was funded by the NIHR-HTA by way of an extension to the main MERIDIAN
29 study (ISRCTN 27626961) and conducted under the same ethics approval.⁴ We aimed to
30 recruit approximately 200 women carrying a fetus in whom no brain (or somatic) abnormality
31 was detected on the 20-week anomaly USS that is routinely offered to women in the UK.
32 Any subsequent USS examinations (if performed) also had to show normal fetal anatomy. All
33 of the pregnancies were otherwise considered ‘low-risk’ with no known serological or
34 chromosomal/genetic concerns. Potential participants were informed about the study by way
35 of posters and leaflets in 12 of the original 16 fetal medicine referral centres involved in the
36 original MERIDIAN and by press coverage in those regions. Interested pregnant women
37 contacted the central site (Academic Unit of Radiology, University of Sheffield) and were
38 sent a patient information leaflet by email or post, which gave full details of the study. A
39 follow-up telephone call enabled queries to be answered, initial screening questions to be
40 assessed and eligibility for the study confirmed. A copy of the most recent antenatal USS
41 report was then obtained to confirm the normal development of the pregnancy. Other
42 inclusion criteria were: the woman was at least 16 years old and the fetus a minimum of 18
43 gestational weeks (gw) at the time of iuMR imaging was to be performed. Exclusion criteria
44 were inability to give informed consent, contraindications to MR imaging, or
45 inability/unwillingness to travel to Sheffield for iuMR imaging. There were no set
46 requirements for the interval between considered eligible for the study and having the iuMR
47 scan.

48

49 Written informed consent was taken on the day of the study after further explanation of the
50 iuMR procedure, including potential risks and the right to withdraw from the study at any
51 time. The consent procedure also confirmed willingness of the woman to inform her GP that
52 she had been involved in the study and to send them a copy of the iuMR report if no
53 unexpected findings were shown. If a brain abnormality was detected on iuMR imaging the
54 woman agreed that the findings would be discussed verbally with her obstetrician who would
55 subsequently receive a full clinical-style report in accordance with the guidance from the
56 Ethics Committee. Participants were not paid for volunteering for the study but a £10 gift
57 voucher was given, along with travel expenses, for the participant and an accompanying
58 person.

59 **Sample size and reference diagnoses**

60 Starting from the assumption that no USS false negatives will be found, the study aimed to
61 recruit 200 fetuses on the basis of the 3/n rule,⁶ a large sample approximation of the upper
62 95% confidence interval for very rare events. This allowed the negative predictive value of
63 USS to be estimated to an upper confidence limit of 1.5% in the absence of any abnormal
64 scans, and to within a standard error of $\leq 2\%$ for an incidence of $< 10\%$.

65 The brain of the fetus was assumed to be normal if both USS and iuMR were normal, an
66 approach supported by the low rate of false positive finding for iuMR in the main MERIDAN
67 study ($1/570 = 0.18\%$). These became the True Negatives for USS and iuMR used in this
68 study. Additional tests were undertaken in the event of a brain abnormality reported on iuMR,
69 and these were intended to be the reference against which USS and iuMR were compared,
70 although this approach was found to be too simplistic for practical cases as discussed below.

71

72 **iuMR scanning procedures and protocols**

73 All of the iuMR examinations were performed at the Academic Unit of Radiology, University
74 of Sheffield on either a 1.5T whole body scanner (HDx, GE Healthcare, Milwaukee) or a 3T
75 whole body scanner (Ingenia, Philips, Netherlands). The 3T scanner was used only when the
76 1.5T was not available (e.g. breakdowns) and this occurred in two cases only. The iuMR
77 imaging targeted the fetal brain only and the woman was on the scanner for maximum of 30
78 minutes. The imaging protocol performed at 1.5T consisted of ultrafast imaging in the three
79 orthogonal planes (T2 weighted ssFSE and 2D-FIESTA), T1 weighted, FLAIR, Diffusion
80 weighted in the axial plane and T2-weighted volume acquisitions and MR cine using 3D-
81 FIESTA. After the scan the woman and her companion(s) were shown some of the iuMR
82 images and given the opportunity to take some images on their phone or camera. The formal
83 report on the study was issued the following day after review by a paediatric neuroradiologist
84 with extensive experience of fetal neuroimaging (PDG).

85 **Statistical methods for assessing diagnostic performance**

86 The accuracy of a negative USS was quantified by the NPV, the percentage of fetuses in
87 whom no abnormality was subsequently detected. For iuMR, NPV agreement was derived
88 separately for fetuses whose initial USS was normal and abnormal USS (i.e. USS+, iuMR-
89 and USS-, iuMR-). The PPV of USS and iuMR were derived analogously. PPVs and NPVs
90 were presented alongside 95% binomial confidence intervals. No attempt was made to
91 combine the PPV and NPV of iuMR with those from the main MERIDIAN study, or to
92 estimate the sensitivity and specificity for reasons explained in the discussion.

93

94

95

96 **RESULTS**

97 Recruitment and scanning took place between November 2013 and May 2017 during which
98 time 225 pregnant women enquired about the study but three women did not meet the
99 inclusion criteria because of pregnancy complications. Appointments for iuMR were made
100 for the other 222 women who did meet the entrance criteria but of those 23 did not attend.
101 One woman underwent the iuMR study but the procedure was abandoned due to the
102 participant feeling unwell before any relevant data was obtained and three women withdrew
103 from the study after iuMR imaging was performed. In total, therefore, 198 participants with
104 205 fetuses (14 twin pregnancies) were scanned successfully as shown in Figure 1. The
105 pregnant women recruited were from a wide geographical area, with 68 (34%) participants
106 living within 18 miles of the Sheffield MR unit and the remaining 137 from further afield
107 (maximum 189 miles). The age range of the pregnant women was 20 – 46 years (mean 31.5
108 years) and the gestational age at the time of iuMR is shown in Figure 2 (26% between 18 and
109 23 gw, 74% \geq 24 gw). There were no reportable adverse events during the iuMR scanning of
110 these pregnant women. IuMR studies were reported as normal for 203 cases and brain
111 abnormalities were reported in two fetuses (from separate pregnancies) as described below.

112

113 Case 1 (Figure 3).

114 *iuMR imaging for this study was performed at 35gw following normal USS examinations in*
115 *the second trimester (3a-3c). There was focal abnormal high signal on T2-weighted images*
116 *in the right inferior/sub-central gyri with broadening of the gyri. The diagnostic confidence*
117 *of abnormality was quoted as 70% (certain) and pathology such as a focal cortical dysplasia*
118 *or cortical tuber was suggested, although the possibility of an artefact was considered. Post-*
119 *natal MR imaging performed at 3 weeks (3d-3f) confirmed the antenatal findings but its*
120 *nature remained uncertain. Developmental assessment at 6 months showed plagiocephaly*

121 *and reduced central tone but otherwise a normal repertoire of movements. The Bayley Infant*
122 *Neurodevelopmental Screener (a developmental tool across four domains) put the baby in the*
123 *'middle risk' group. Genetic testing for Tuberous Sclerosis Complex was negative. The infant*
124 *remains under clinical review and a further MR examination is planned at 3 years.*

125

126 Case 2. (figure 4)

127 *Routine anomaly USS was performed at 20gw and showed no abnormalities. iuMR imaging*
128 *for this study was undertaken at 26gw and showed mild ventriculomegaly (trigones*
129 *measurements between 10-11mm. The rest of the brain was normal although the fetus had*
130 *macrocephaly (bi-parietal diameter >97th centile and occipito-frontal on the 97th centile).*
131 *Normal sized ventricles were confirmed on review of the USS performed at 20gw but follow*
132 *up USS confirmed non-progressive ventriculomegaly at 30gw. The child was developing*
133 *normally in all domains at 14 months.*

134 **Analysis**

135 Case 1 is treated as a true brain abnormality, although the nature of the abnormality is still not
136 known, so is considered to be a False Negative for USS and a True Positive for iuMR. In
137 contrast, the appearance of VM on iuMR imaging in case 2 after retrospective confirmation
138 of normality at 20 weeks is interpreted as an evolving feature that could not be recognised at
139 20 weeks because it wasn't present. However, the confirmation of ventriculomegaly (VM) on
140 third trimester USS confirm the iuMR finding. This is taken as a True Negative for USS and
141 a True Positive for iuMR imaging. Table 1 shows the number and characteristics of correct
142 and incorrect diagnoses made by USS and iuMR using data from both this study and the
143 MERIDIAN study. Both USS and iuMR have high NPV for the normal risk pregnancies,
144 being 99.5% (95% CI 97.3 to 100.0%) for USS and 100% (98.2 to 100%).

145 In the main MERIDIAN cohort, 388/570 fetuses were correctly diagnosed by USS giving a
146 PPV of 68.1% (64.1 to 71.9%). Of these, iuMR found abnormalities in 513 fetuses of whom
147 39 were incorrect diagnoses giving a PPV of 92.4% (90.0 to 94.5%). The remaining 57 were
148 recorded as normal on iuMR, one of whom was subsequently found to have a brain
149 abnormality matching the original USS diagnosis, giving an NPV in this population of 98.2%
150 (90.6%-100.0%).

151

152 .

153

154 **DISCUSSION**

155 The MERIDIAN study, along with published systematic reviews, demonstrate a significant
156 improvement in diagnostic accuracy when iuMR imaging is used in the diagnostic pathway.¹⁻

157 ⁴ One important implication of this finding is USS might fail to detect some brain
158 abnormalities during screening. This study shows that does not occur at high frequency and
159 supports USS being the primary screening method for brain imaging. IuMR should be used as
160 an adjunct to USS only when brain abnormalities are suspected on USS in low risk
161 pregnancies. There were two abnormalities noted on iuMR following a normal USS in 205
162 fetuses, one of which was a case of mild VM that was confidently described as an evolving
163 pathology and the original USS report was correct at the time of scanning. As such, USS has
164 a NPV of 99.5% (95% CI 97.3% to 100%), supporting the contention that a normal USS can
165 safely be assumed to rule out fetal brain abnormality with very high certainty in fetuses with
166 no other risk factor.

167

168 A review of the literature has not shown any other studies of iuMR imaging in normal
169 pregnancies as identified by USS, so there are no other comparative estimates of NPV and
170 PPV for these modalities. Our study has addressed that knowledge gap by recruiting 205
171 fetuses considered to be developing normally on USS; these were combined with the
172 MERIDIAN results to estimate NPV and PPV. Predictive values indicate the precision of a
173 diagnostic test, i.e. how likely the test is to find an abnormality when it actually exists (PPV)
174 or how likely a test is to be negative if no abnormality exists (NPV) and are arguably more
175 relevant to clinicians when making decisions on the basis of diagnostic tests.^{7,8} Traditionally,
176 sensitivity and specificity have been the preferred measures of diagnostic performance, since
177 the PPV and NPV depend on prevalence,⁹ indeed, the STARD checklist for diagnostic
178 accuracy studies made only cursory mention of predictive values until the 2015 update.^{10,11} In

179 this study we have not attempted to estimate the sensitivity and specificity, since our two
180 studies have (deliberately) not recruited random samples of pregnant women. The main
181 MERIDIAN study evaluated iuMR in pregnancies where an abnormality was found on USS,
182 with 570 fetuses included in the primary analysis. Since abnormal brain USS occurs in less
183 than 1% of fetuses, a prospective study of all pregnancies would have needed more than
184 57000 participants in order to recruit this number of brain abnormalities. By conducting two
185 parallel studies we were able to study fetuses with normal and abnormal USS, but combining
186 the two into one data set is inappropriate as doing so vastly over-represents by comparison to
187 the general population, resulting in a biased estimate of both sensitivity and specificity.
188 Although the sensitivity could - in theory - be derived by re-weighting the two studies to
189 match population incidence, this would entail allocating a weight of less than 1% to the
190 original MERIDIAN study with the remainder being allocated to the two cases identified in
191 this study. A similar (though less extreme) situation applies to the specificity, and clearly this
192 results in instable estimates which are best avoided.

193 USS is offered to all women in the UK (and taken by >95%) so sensitivity and specificity of
194 USS may be derived from routine patient notes.¹² The diagnostic capability of USS has
195 previously been quantified using sensitivity and specificity analysis by reviewing clinical
196 cases that have been scanned as part of the routine screening process during pregnancy. A
197 report by the National Institute for Health and Care Excellence (NICE)¹³ described the
198 findings from those studies, showing that whilst the sensitivity of USS was variable (15% to
199 85%) the specificity was consistently very high (99.4% to 100%). Rossi and Perfumo¹
200 attempted to define the diagnostic capability of iuMR using similar sensitivity and specificity
201 measures but, as the vast majority of fetuses were initially suspected of being abnormal by
202 USS, the truly normal pregnancies were again greatly under-represented and their findings do
203 not adequately generalise to the wider population of pregnancies. Perhaps more importantly,

204 it is questionable whether the diagnostic ability of iuMR imaging needs to be evaluated
205 among all pregnancies. Whilst neonatal screening relies heavily on USS, constraints on
206 resource mean it is likely that iuMR will be used more selectively as a second-line screen for
207 high risk pregnancies, most likely a suspected abnormality on USS— a position backed by the
208 data from our study. There are more than 800,000 pregnancies in the UK each year,¹⁴ the
209 majority of which undergo at least one USS, and the resource implications (trained expertise
210 and financial) of providing iuMR routinely is prohibitive. It is interesting to note that the
211 results of the adequately powered study reported by NICE¹³ were comparable to the NPV
212 reported here.

213 There are several possible limitations to our study, which primarily stem from recruiting
214 ‘normal’ participants. Firstly, there may be an element of bias within the recruitment process
215 as it was reliant on volunteers. It is unclear if the women in our sample were fully
216 representative of the obstetric population as, although recruited from a wide geographical
217 area within the UK, we did not record demographics such as ethnicity. Secondly, it was not
218 possible to restrict recruitment to women who could attend for iuMR shortly after USS as we
219 were reliant on participants’ availability. In theory the longer time period between USS and
220 iuMR, the greater the possibility of abnormalities evolving and hence being visible on MR
221 which would therefore biased the findings in favour of iuMR; in reality, the two modalities
222 agreed in all bar two cases. The advantage to not restricting the time between USS and iuMR
223 was that a wider age range of fetuses were scanned, and allowed a greater range of
224 gestational age to be assessed since pregnant women are offered an anomaly screening USS
225 between 18 and 21 weeks’ gestation in the UK. Thirdly, the diagnostic accuracy of USS for
226 this study was based on routine USS screening rather than USS by a fetal-maternal expert,
227 which was a requirement of MERIDIAN. The availability of suitably qualified staff and the
228 cost implications made this unattainable. It is impossible to ascertain whether the 2 cases with

229 abnormalities detected by iuMR were not present at USS or if they were missed. In the fetus
230 with VM, there was 6 weeks between USS and iuMR, and in the second abnormal case there
231 was 16 weeks. It was therefore possible that the abnormality was not present at the time of
232 the USS and even if it was, it is impossible to say whether a fetal-maternal expert could have
233 identified the abnormality.

234

235 The consequences of abnormalities being missed on ante-natal USS are variable. Detecting
236 abnormalities allows further investigations and additional monitoring of the pregnancy, or, if
237 the abnormality is severe and detrimental to long term outcome allows the option of
238 termination of pregnancy. Isolated mild VM is a common finding during pregnancy and a
239 very high proportion have a favourable outcome, but iuMR is necessary to identify additional
240 abnormalities.¹⁵⁻¹⁷ This finding therefore is perhaps less significant than the cortical
241 abnormality diagnosed by iuMR in a fetus of 35 gw. Cortical dysplasia (or cortical tubers) is
242 exceptionally difficult to identify by USS prenatally¹⁸ and can have a range of causes and
243 outcomes. Earlier identification of this abnormality may not have changed the outcome in
244 terms of health of the fetus, but would have provided vital information and allowed the
245 parents to make an informed choice regarding its management.

246

247 In conclusion, our results confirm the ability of both USS and iuMR to confirm when brain
248 development of the fetus is normal. This highlights the validity of USS remaining as the
249 primary screening imaging method for pregnancy, and further supports the need for
250 additional iuMR imaging when abnormalities are detected on USS. **However further research**
251 **on fetuses at an increased risk of brain abnormality may be appropriate.**¹⁹

252

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302 specific findings? *Clin Radiol* 2018; 73(2):123-134

303

TABLE LEGENDS

304 Table 1. Data showing the agreement between ultrasonography (table 1a) and iuMR imaging
305 (table 1b) when compared with outcome reference data.

306

307

308 Table 1a:

Test finding	Agreement with ORD		
	USS correct	USS incorrect	
USS abnormal*	388	182	PPV=68.1% (CI 64.1%-71.9%)
USS normal	204	1	NPV=99.5% (CI 97.3%-100.0%)

309

310

311

312 Table 1b:

Test finding	Agreement with ORD		
	iuMR correct	iuMR incorrect	
Following abnormal USS*			
iuMR abnormal	474	39	PPV=92.4% (CI 90.0%-94.5%)
iuMR normal	56	1	NPV=98.2% (CI 90.6%-100.0%)
Following normal USS			
iuMR abnormal	2	0	PPV=100% (CI 15.9%-100%)
iuMR normal	203	0	NPV=100% (CI 98.2%-100%)

313

314 * taken from original MERIDIAN cohort of fetuses with brain abnormality on USS

315

316

317

FIGURE LEGENDS

318 Figure 1. Flow of participants through the study.

319

320 Figure 2. Chart showing the number of fetuses scanned by gestational age.

321

322 Figure 3. Single shot FSE image (3a), coronal (3b) and sagittal (3c) reconstruction from T2-
323 weighted 3D datasets show broadening of the right inferior frontal gyrus and abnormal white
324 matter signal extending into the sub-central gyrus. These features were confirmed on post-
325 natal imaging (3d-3f). See text for details.

326

327 Figure 4. Single shot FSE images (4a sagittal, 4b axial) show mild ventriculomegaly and
328 macrocephaly (trigones of the lateral ventricles measured an axial reconstruction from a 3D
329 dataset – 4c). See text for details.

330