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1 **Post-mortem confirmation of fetal brain abnormalities:**
2 **challenges highlighted by the MERIDIAN cohort study**

3 Fetal brain abnormalities - post-mortem assessment

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18

19 **Abstract**

20 **Objectives:** To assess and analyse the concordance between post-mortem findings and *in*
21 *utero* MR imaging in the MERIDIAN cohort.

22 **Design:** Prospective cohort study

23 **Setting:** Fetal medicine units in the United Kingdom

24 **Population:** Pregnant women with a diagnosis of fetal brain abnormality identified on
25 ultrasound at 18 gestational weeks or more

26 **Methods:** All pregnancies from the MERIDIAN study that resulted in abortion were included
27 and the rate of uptake and success of the post-mortem examinations were calculated. In the
28 cases in which diagnostic information about the fetal brain was obtained by post-mortem the
29 results were compared with the diagnoses from iuMRI.

30 **Main Outcome Measures:** Outcome reference diagnosis from post mortem examination

31 **Results:** 155/823 (19%) pregnancies ended in abortion and 71 (46%) had post-mortem brain
32 examinations of which 62 were diagnostically adequate. Hence the overall rate of successful
33 post-mortem investigations was 40% and in those cases there was a concordance rate of 84%
34 between iuMRI and post-mortem. Detailed information is provided when the results of the
35 post-mortem and the iuMRI study were discrepant.

36 **Conclusion:** We have shown tissue-validation of radiological diagnosis is hampered by a low
37 rate of post-mortem studies in fetuses aborted with brain abnormalities, a situation further
38 compounded by a 12% rate of autopsy being technically unsuccessful. The agreement

39 between iuMRI and post-mortem findings is high but analysis of the discrepant cases
40 provided valuable clues to how providing information to parents can be improved.

41 **Funding:** National Institute for Health Research Health Technology Assessment programme

42 **Keywords:** fetus; magnetic resonance imaging, diagnostic accuracy; post mortem

43 **Tweetable abstract**

44 iuMRI should be considered a reliable indicator of fetal brain abnormalities when post-
45 mortem is not performed

46 **Introduction**

47 The magnetic resonance imaging to enhance the diagnosis of fetal developmental brain
48 abnormalities *in utero* (MERIDIAN) study was designed to compare the diagnostic accuracy
49 of *in utero* magnetic resonance imaging (iuMRI) with the established imaging method, ante-
50 natal ultrasonography (USS) in cases of fetal brain pathology detected on USS in UK fetal
51 medicine units.^{1,2} The results of the 570 cases in the primary cohort showed a significant
52 improvement in diagnostic accuracy of 25% when iuMRI was performed following USS (to
53 approximately 93%). The primary cohort came from a larger group of pregnant women who
54 had iuMRI of their fetus and had provided informed consent.

55 The objective was to assess and analyse the concordance between the ante-natal imaging
56 findings from iuMRI and the results of post-mortem autopsy studies in fetuses from the
57 extended MERIDIAN cohort that underwent abortion, either spontaneous or by termination
58 of pregnancy (TOP). Post-mortem studies are exceptionally important in the context of an
59 aborted fetus and can provide information on why the fetus was lost in cases of spontaneous
60 abortion and may provide important information about any increased risk of recurrence in
61 future pregnancies. As discussed below, this is over and above the important role of
62 providing data for quality assurance of the ante-natal imaging programmes.

63 The purpose of this study is to report the uptake and success rate of post mortem studies of
64 the fetal brain in the MERIDIAN cohort and show how frequently discrepancies between the
65 diagnoses made on iuMRI and the post mortem findings occurred. By investigating the
66 source of discrepancies we attempt to make recommendations on how to improve the quality
67 of information given to parents in the future.

68

69 **Methods**

70 **Ethics and participants**

71 The full details concerning ethical approval, recruitment, techniques and analysis of the
72 MERIDIAN study have been reported elsewhere^{1,2} but, in summary, ethical approval was
73 obtained from Yorkshire and the Humber – South Yorkshire ethics committee (11-YH-0006)
74 for a multicenter observational study to recruit pregnant women from 16 fetal medicine units
75 (FMU) in the UK. The main entrance criterion was a brain abnormality of the fetuses
76 recognized on USS at 18 gestational weeks (gw) or more and in this study we will report all
77 of the MERIDIAN cases which resulted in abortion, either spontaneous or TOP.

78 **Patient and Public Involvement (PPI)**

79 PPI representatives were included the Trial Steering Committee with the aim to ensure that
80 the design of the study was appropriate and relevant to the participant population and provide
81 oversight of the MERIDIAN study. Representatives from Antenatal Results and Choices
82 (ARC) and the Spina Bifida, Hydrocephalus, Information, Networking, Equality (SHINE)
83 charity were involved in the study oversight throughout the project through the Trial Steering
84 Committee. This included review and development of the study protocol and patient
85 documents; monitoring the study progress; review and discussion of the final results of the
86 study. Feedback from the PPI members informed our approach to potential participants and
87 the content of the Participant Information Sheets. They also had input to the content of the
88 results summary/participant debrief letter and the method for disseminating this to
89 participants.

90 **Imaging and post mortem studies**

91 All of the cases were recruited following USS by appropriately trained consultants working
92 in fetal maternal units in England, Scotland or Northern Ireland, although no further analysis
93 of those USS cases is undertaken in this paper. Two thirds of the iuMRI studies were
94 performed at the central site (Sheffield, England) with the others being performed at one of
95 five other participating sites. The iuMRI protocols were not matched across the sites but
96 involved ultrafast T2-weighted imaging in the three orthogonal planes and T1-weighted
97 imaging in the axial plane as a minimum requirement. Clinicians reporting on the iuMRI
98 studies were asked to provide diagnoses of any structural intracranial abnormalities present
99 and record their certainty of diagnosis on a five-point Likert scale that was used to define
100 low-certainty diagnoses (10-50% certainty) and high-certainty diagnoses (70-90%).³ In cases
101 resulting in abortion the outcome reference diagnosis (ORD) was derived from examination
102 of the brain post-mortem by a pathologist, most frequently one pathologist with
103 fetal/paediatric experience.

104 **Analysis of cases**

105 We determine how frequently post-mortem studies were performed in those cases and the
106 success rate of obtaining a definitive post-mortem diagnosis when a study was performed. In
107 cases in which a successful post-mortem study was performed we will compare those
108 findings with the iuMRI findings in terms of the structural diagnosis and the confidence of
109 the diagnosis (either high certainty – 70% and 90% or low certainty 10%, 30% or 50% as
110 described previously.^{2,3} We will concentrate on the cases in which the iuMRI and post-
111 mortem findings were discrepant and highlight how the discrepant findings were handled
112 during the course of the study (as potential serious adverse events) by describing two cases in
113 depth.

114 **Role of the funding source**

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

118

119 **Results**

120 In total 823 women were recruited into the MERIDIAN study and all had at least one iuMRI
121 examination of the fetal brain after providing written, informed consent. In 155/823 (19%)
122 cases the pregnancy ended in abortion and of 81% of those (125/155) the abortion resulted
123 from TOP and 19% (30/155) from spontaneous abortion. 55% (84/155) of all abortions went
124 without a post-mortem brain examination but the reason/cause (e.g. out-of-hospital loss,
125 refusal of post-mortem) for the lack of a post-mortem examination was not recorded under
126 the remit of the MERIDIAN study. Those cases are summarized in Table S1. Of the 71/155
127 (46%) fetuses that underwent post-mortem brain examination, 60 (84%) came from a TOP
128 procedure and the remainder from spontaneous abortions. Autolysis of the brain tissue
129 precluded diagnostic yield in 9 cases [Table S2] leaving 62/155 (40%) of adequate diagnostic
130 quality.

131 In cases with a successful post-mortem examination, there was complete agreement between
132 the post-mortem and iuMRI findings in 52/62 (84%) fetuses and of those the diagnosis of the
133 brain abnormalities on iuMRI was made with high confidence in 51/52 (98%) as shown in
134 Table S3 and examples in figures 1, 2 and figure S1. The iuMRI report did not agree with the
135 post-mortem findings in 10/62 (16%) cases (Table 1) and a breakdown of the nature of the
136 ten discrepancies between post-mortem and iuMRI findings is presented in Table 2.

137 In accordance with the study protocol, a full case review was instigated in all cases where the
138 iuMRI and post-mortem findings were at variance in a case that underwent TOP. This
139 accounted for eight cases as the review was considered to be unnecessary for spontaneous
140 losses (cases 199 and 889). The first stage of the review was performed by a fetal medicine
141 specialist (GM), whose role throughout the study was to assess a) if the overall rate of
142 discrepancy was too high and to degree that might close the study prematurely (there were no

143 such concerns at any stage) and b) to judge if further action was required in individual cases.
144 Those opinions were passed to the Data Monitoring Committee. In six cases the offer of TOP
145 was judged to have been appropriate due to either the severity of the confirmed brain
146 abnormalities and/or other abnormalities not related to the study diagnosis (e.g. a
147 cardiac/somatic abnormalities or chromosomal abnormalities). Only two cases of
148 discrepancy between iuMRI and post-mortem findings obliged close review by the Trial
149 Steering Committee both of which were referred back to the original recruiting centre for a
150 full multidisciplinary team review and investigation. Those two cases are described in detail
151 below for their instructive value:

152 **Case 236** (Figure S2)

153 USS performed at 20gw had shown agenesis of the corpus callosum (CC) and an associated
154 cyst with low certainty and no other somatic abnormality of the fetus. iuMRI at 20gw agreed
155 with the USS findings, although the diagnosis of agenesis of the CC was made with high
156 certainty. The interhemispheric cyst was not thought to be in continuity with the ventricular
157 system (therefore described as a Barkovich type 2 cyst). In addition, a dysplastic frontal lobe
158 was also reported on iuMR imaging albeit with low certainty.

159 TOP at 20gw macroscopically confirmed the midline cystic structure but considered the CC
160 to be present and made no comment on the frontal lobes and no microscopical assessment
161 was made of those regions. The Data Monitoring Committee was concerned that TOP had
162 been performed inappropriately because the CC was reported as being present on the post-
163 mortem study. At local multidisciplinary review the post-mortem procedure was described as
164 difficult and under such circumstances the findings of the ante-natal imaging studies should
165 be considered as reliable.

166 **Case 453** (figure 3)

167 USS performed at 21gw had shown hydranencephaly with high certainty as well as multiple
168 somatic abnormalities. iuMRI performed the next day showed severe ventriculomegaly (high
169 certainty rather than hydranencephaly) on the basis of a preserved albeit thin cortical mantle.
170 The fetus had a relatively large head size and other features indicating obstructive
171 hydrocephalus (effaced sulci and extra-axial CSF spaces) due to a Dandy-Walker
172 malformation (DWM - high certainty). TOP was performed at 22gw and the post-mortem
173 examination confirmed severe hydrocephalus possibly due to aqueduct stenosis without
174 mentioning a DWM. Multidisciplinary review determined that the brain-removal was
175 performed by a routine" supra-tentorial approach because the iuMRI report of posterior fossa
176 abnormality was concurrently unavailable. As a result, the cerebral hemispheres were intact
177 but there was severe mechanical disruption to the brainstem and cerebellum and an autopsy-
178 based exclusion of DWM should be considered unreliable, and the radiological diagnosis
179 should be favoured. Also, the severe hydrocephalus and extensive extra-cranial abnormalities
180 were sufficient justification for TOP, independent of the brain-state.

181 **Discussion**

182 **Main Findings**

183 USS is offered to all pregnant women in the UK at 18-21gw and >95% accept the procedure⁴.
184 If an abnormality is suspected, a second opinion is sought from a fetal maternal medicine
185 specialist. This is often the first opportunity for a pregnant woman to see her baby and in the
186 excitement the chance and consequences of an abnormality can be overlooked, highlighted by
187 ‘Ultrasound scans in pregnancy’⁵. Fetal abnormalities are looked for in all body regions,
188 however, brain abnormalities are amongst the most common and are important clinically
189 because of the relatively high risk of adverse outcomes. Approximately 3/1000 fetuses have
190 structural brain abnormalities detected on anomaly scans⁶ and some have such a high risk of
191 poor prognosis that discussion about TOP is warranted under Ground E of the Abortion Act
192 (1967, section 1[1]d, substantial risk of serious mental or physical handicap).

193 The MERIDIAN study^{1,2} assessed the diagnostic impact of iuMR imaging in detecting fetal
194 brain abnormalities and showed a 25% improvement in diagnostic accuracy when compared
195 with USS and influenced clinical management in a substantial proportion of cases.
196 MERIDIAN, a large, prospective study, had broadly inclusive entrance criteria so we believe
197 its results are a fair representation of clinical activity in UK FMUs during the recruitment
198 period (2011-14). We have described the cases which resulted in abortion, 80% were TOP
199 and 20% spontaneous losses. Approximately 1/80 pregnancies in the UK result in TOP when
200 all fetal abnormalities considered⁷. The Royal College of Obstetricians and Gynaecologists
201 and Royal College of Pathologists recommended a post-mortem rate of 75%.⁸ UK data
202 indicates only 44% of spontaneous losses result in post-mortem.⁹ Examination of the fetal
203 brain is probably lower as clinicians report parents consenting for post-mortem but exclude
204 the brain.

205 The post-mortem rate was 46% with 37% in spontaneous losses and 48% following TOP.
206 Some hospitals only request consent for autopsy when legally required, despite
207 recommendation that it should be requested in all abortions⁹. A further feature identified,
208 compounding the low rate of post-mortem studies is the relatively high rate of not obtaining
209 diagnostic quality information. Tissue autolysis accounted for a failure to obtain information
210 in 9 cases, therefore information about the brain was only available in 40%. One major
211 contributory factor is the number of late TOP, involving injection of potassium chloride into
212 the fetal heart. There is often a delay between fetal death and delivery which is associated
213 with a high rate of autolysis.

214 **Strengths and Limitations**

215 We have shown a good concordance between iuMRI and post-mortem (when successful)
216 with agreement in 84%. IuMR diagnoses were made with high confidence in 98% of cases,
217 which is important as low confidence diagnoses may result in TOP not being
218 discussed/performed when appropriate.³ Cases in which iuMRI and post-mortem were
219 inconsistent have been analysed. Many disagreements occurred in cases of abnormalities of
220 the CC and cerebellum, indicating that there are specific anomalies that are difficult to
221 corroborate on post-mortem examination because of: friable structures (e.g. septum
222 pellucidum, CC) or structural integrity defined in the sagittal plane, which imaging can
223 access, but is poorly-assessed by conventional coronal slicing of fixed-brains. In such cases it
224 is difficult to agree which study provides the 'ground truth', highlighted by cases 236 and 453
225 and the MERIDIAN independent review panels concluded the post-mortem results were
226 incorrect.

227 Post-mortem results are potentially compromised if the pathologist is unaware of ante-natal
228 diagnoses. Case 453 has an obvious DWM on iuMRI but because the pathologist was

229 unaware of this the specific approach to avoid disruption of the brainstem and cerebellum
230 was not performed and the diagnosis missed. This is a highly likely reason for abnormalities
231 of the cerebellum featuring frequently in the discrepancies between post-mortem and iuMRI.
232 Another factor that may contribute to the incomplete assessment of the brainstem and
233 cerebellum is failure to weigh those structures separately from the whole brain, which will
234 resolve dispute about reduced volume. The other anatomical source of major disagreement
235 between post-mortem and iuMRI involved malformations of the CC (5/9 cases). IuMRI
236 overcalled a callosal abnormality in three cases and missed it in two. At least two factors are
237 likely contributing to those discrepancies. Absence of the radiological report during the brain
238 examination and, callosal dysmorphology/integrity is necessarily defined in the sagittal plane,
239 which is readily accessible on iuMRI but poorly-appreciated in the coronal-plane brain-slices
240 of routine post-mortem studies – especially when the brain is small. Factors that increase the
241 likelihood of discrepancies in all types of fetal brain abnormality, include: examining and
242 histologically sampling of the brain without prior fixation; external examination of the brain
243 without immersion in a water-bath to mitigate gravitational deformation and tissue-rupture;
244 not sampling appropriate sites for microscopy; and even minor degrees of autolysis are likely
245 to increase these problems. This points to a requirement for closer collaboration and
246 information sharing between fetal medicine, radiology and pathology specialists.

247 **Interpretation**

248 We must place these findings in the wider context of the purpose of post-mortem studies for
249 fetal abnormalities. The loss of a fetus is a difficult time for parents and requesting
250 permission for a post-mortem is a delicate task. Obtaining consent has become increasingly
251 complicated and there may be reluctance to ask parents, as well as reduced approval.^{10,11} The
252 value of the information gained from post-mortem studies may not be fully appreciated. They

253 provide a cause of death but may also confirm or refute the ante-mortem diagnoses; providing
254 quality control. The recurrence risk in future pregnancies is exceptionally important and
255 requires accurate diagnosis of the anomaly in the index pregnancy to be presented robustly.
256 This is particularly true when the results from gross anatomical studies are supplemented by
257 histological, chromosomal and genetic investigations, which may include whole-exome
258 sequencing.¹² Those investigations can refine, or fundamentally change the ante-natal
259 diagnosis, changing the future risk substantially. For example, cortical formation
260 abnormalities may have a high recurrence rate. If, however, the post-mortem identifies an
261 acquired cause the recurrence risk is often negligible. In other cases post-mortem studies may
262 provide information that can help resolve the pathogenicity of findings of “unknown or
263 uncertain clinical significance”.

264 There can be little doubt that the experience of the person undertaking the procedure impacts
265 the quality of information obtained. An audit of pathology services reporting between 1994-
266 1995 found; marked variability in standards, poor or missing histology in 56% of cases, an
267 ‘adequate commentary’ in only 35% of cases and a need to improve observational, diagnostic
268 and interpretative skills for pathologists undertaking perinatal postmortem examinations.¹³
269 The situation could be improved in a number of ways and some processes have been
270 implemented. Recent guidelines^{14,15} has led to most procedures being performed in tertiary
271 centres, which appears to have led to improvements but the lack of experienced perinatal
272 pathologists remains a concern.^{16,17}

273 The value of post-mortem MRI of the fetal brain has been discussed at length in the published
274 literature¹⁸⁻²¹ and although the results are generally good many authors have concluded that
275 post-mortem MR should be an adjunct to post-mortem not a replacement. This is a difficult
276 position to justify if there is only a 40% successful performance of post-mortem examination

277 of the brain. There is no doubt, however, that post-mortem MR suffers from some, but not all,
278 of the problems associated with autolysis and brain distortion arising from fetal demise,
279 which may limit its value. Izzo *et al.*²² suggests a close concordance between post-mortem
280 MR and iuMRI for fetal brain pathology, which in conjunction with our results suggest that
281 iuMRI should be considered a reliable indicator of brain abnormalities in the fetus when
282 formal post-mortem is not performed or unsuccessful.

283 **Conclusion**

284 We have highlighted the low rate of post-mortem examination of the fetal brain after the
285 ante-natal detection of brain abnormalities and a relatively high rate of failure to get
286 diagnostic information at post-mortem. We have described some of the limitations of post
287 mortem studies even when they are technically successful and we have suggested ways in
288 which further improvements can be made.

289

290 **Ethics Statement**

291 Ethical approval was obtained from Yorkshire and the Humber – South Yorkshire ethics
292 committee, date of approval 04th April 2011, reference number 11-YH-0006).

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298 Health.

299 **Disclosure of interest**

300 The authors have declared that no potential conflicts of interest exist.

301 **Author contributions**

302 PDG and GM contributed to the concept and design of the study. Data collection and trial
303 management were coordinated by CM; data analysis and interpretations was by PDG, DJ, AD
304 and GM. PDG and CM drafted the manuscript and all authors performed a critical revision of
305 the manuscript. PDG and CM had full access to all of the data in the study and take
306 responsibility for the integrity of the data and the accuracy of the data analysis.

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312

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