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

Fetal brain abnormalities - post-mortem assessment

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Abstract

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

Design: Prospective cohort study

Setting: Fetal medicine units in the United Kingdom

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

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

Main Outcome Measures: Outcome reference diagnosis from post mortem examination

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

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

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

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

Tweetable abstract

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

Introduction

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

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

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

Methods

Ethics and participants

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

Patient and Public Involvement (PPI)

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

Imaging and post mortem studies

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

Analysis of cases

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

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 author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

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

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

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

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

Case 236 (Figure S2)

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

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

Case 453 (figure 3)

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

Discussion

Main Findings

USS is offered to all pregnant women in the UK at 18-21gw and >95% accept the procedure[4]. If an abnormality is suspected, a second opinion is sought from a fetal maternal medicine specialist. This is often the first opportunity for a pregnant woman to see her baby and in the excitement the chance and consequences of an abnormality can be overlooked, highlighted by 'Ultrasound scans in pregnancy'[5]. Fetal abnormalities are looked for in all body regions, however, brain abnormalities are amongst the most common and are important clinically because of the relatively high risk of adverse outcomes. Approximately 3/1000 fetuses have structural brain abnormalities detected on anomaly scans[6] and some have such a high risk of poor prognosis that discussion about TOP is warranted under Ground E of the Abortion Act (1967, section 1[1]d, substantial risk of serious mental or physical handicap).

The MERIDIAN study[1,2] assessed the diagnostic impact of iuMR imaging in detecting fetal brain abnormalities and showed a 25% improvement in diagnostic accuracy when compared with USS and influenced clinical management in a substantial proportion of cases. MERIDIAN, a large, prospective study, had broadly inclusive entrance criteria so we believe its results are a fair representation of clinical activity in UK FMUs during the recruitment period (2011-14). We have described the cases which resulted in abortion, 80% were TOP and 20% spontaneous losses. Approximately 1/80 pregnancies in the UK result in TOP when all fetal abnormalities considered[7]. The Royal College of Obstetricians and Gynaecologists and Royal College of Pathologists recommended a post-mortem rate of 75%.[8] UK data indicates only 44% of spontaneous losses result in post-mortem.[9] Examination of the fetal brain is probably lower as clinicians report parents consenting for post-mortem but exclude the brain.

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

Strengths and Limitations

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

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

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

Interpretation

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

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

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

The value of post-mortem MRI of the fetal brain has been discussed at length in the published literature[18-21] and although the results are generally good many authors have concluded that post-mortem MR should be an adjunct to post-mortem not a replacement. This is a difficult 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

Ethics Statement

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

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Disclosure of interest

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

Author contributions

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

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