The use of *in utero* MRI to supplement ultrasound in the foetus at high risk of developmental brain or spine abnormality

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Objectives: It is widely accepted that the diagnosis of foetal central nervous system (CNS) abnormalities can be improved by performing MRI examinations *in utero*. Most of the published literature has concentrated on pregnancies in which a developmental abnormality has been detected (or suspected) on ultrasound in an otherwise low-risk pregnancy. In this paper, we test the hypothesis that *in utero* MRI of the foetal brain in high-risk pregnancies will detect abnormalities not shown by ultrasound at a rate that justifies its use in clinical practice.

Methods: 100 females were recruited into the study from foeto-maternal or clinical genetic departments. They all had a foetus/child with a CNS malformation from an earlier pregnancy, which led to an increased risk of recurrence being quoted for the present pregnancy. All *in utero* MRI examinations were performed on 1.5 T clinical MRI systems at 18 weeks gestational age or later.

Results: In 78% of cases, the ultrasound and MRI results agreed and showed no abnormality. In 13%, ultrasound and MRI described identical abnormal findings. In 9%, the ultrasound and MRI examinations had discrepant findings; in all these cases the MRI findings described more serious CNS pathology. The effects on management were judged to be major, by at least one assessor, in 7/9 of those cases.

Conclusion: As in many other situations involving antenatal detection of CNS abnormalities, *in utero* MRI should be considered in females with increased risk of foetal CNS malformation based on the results of an earlier pregnancy.

Advances in knowledge: *In utero* MRI of the foetus has an important role in antenatal diagnosis of females carrying a foetus with an increased risk of a brain abnormality.

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Central nervous system (CNS) malformations are among the commonest types of structural abnormalities diagnosed *in utero* and often have significant clinical sequelae post-natally. Many CNS malformations have been shown to have an increased recurrence risk in future pregnancies based on either a known genetic mechanism or, more commonly, by empirical observation. Females who have had such a foetus/child usually have detailed ultrasound examinations during the course of subsequent pregnancies, usually in the hope of reassuring parents that the current foetus is not affected. Many CNS pathologies present a diagnostic challenge for ultrasound in the second trimester and a search for improved methods of antenatal detection is a justifiable goal.

In utero MRI (iuMRI) is used increasingly to detect CNS abnormalities in the foetus from 18 weeks gestational age onwards. iuMRI has several theoretical advantages over ultrasound, many of which are realisable in clinical practice. One of the most significant advantages is the improved contrast resolution of iuMRI, which is particularly pertinent for CNS imaging in order to define fluid, grey matter and developing white matter structures. There are several publications that indicate advantages in including iuMRI in the diagnostic pathway to define foetal neuropathology, in cases when an abnormality has been shown or is suspected on ultrasound [1–6]. It should be appreciated, however, that the relative strengths and weaknesses of the two examinations are dependent on the anatomical location of the pathology and the gestational age at the time of examination.

In this paper we report a group of pregnant females who were at higher than normal risk of having a foetus with a CNS malformation based on the result of a previous pregnancy. We wish to test the hypothesis that iuMRI imaging in the foetal brain will detect abnormalities not shown by ultrasound at a rate that justifies its use in clinical practice.

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Methods

Recruitment

Most of the females involved in this study were recruited as research cases under the guidance of the South Sheffield Research Ethics Committee and provided written consent after full explanation, in line with the requirement at the time of recruitment. The participants were not paid for their involvement in the study but travel expenses were offered for themselves and a companion. From 2004 iuMRI examinations were also offered as a clinical service to the referring hospitals and a minority of cases in the study came from that source. Relevant review and approval was sought and obtained from the Institutional Clinical Effectiveness Unit and Research Department to include those cases in this report.

The cases in this study consist of 100 pregnant females with singleton pregnancies recruited consecutively from 10 different foetal assessment units in Britain. The antenatal ultrasound examinations were performed by an appropriately trained consultant with a responsibility for looking after foetal medicine problems in the referring hospital. Entrance criteria for the study were: a documented CNS abnormality in a foetus in an earlier pregnancy, higher than base level risk of recurrence of that pathology in the index pregnancy and no contra-indications to MRI. Females were eligible to come into this study if the antenatal ultrasound was either normal or abnormal for the index pregnancy. All of the iuMRI examinations were performed at the MRI facilities of the University of Sheffield. The majority of iuMRI examinations (over 80%) were planned and performed between 18 and 24 weeks gestational age (we do not perform iuMRI routinely before 18 weeks gestational age). Females who were scanned between 18 and 24 weeks were invited back for a second iuMRI examination at 30–32 weeks gestational age. The remaining females, referred after 24 weeks gestational age, were scanned within 4 working days.

In utero MRI

The iuMRI technique used in this study has been described in detail elsewhere [2]; nonetheless, it is summarised here. All images were acquired on a 1.5-T

scanner, which was either Infinion (Philips Medical Systems, Cleveland, OH) or HDx (General Electric Healthcare, Waukesha, WI). A flexible phased-array body coil was placed around the lower abdomen and a series of three plane scout views made. Once the anatomical target was located, single shot fast spin echo sequences were run using the following typical parameters: repetition time 20000 ms, echo time (effective) 75 ms, echo train length 132, field of view 25 cm and matrix size 248×256 , number of excitations=1, flip angle 120° . Twenty 5 mm-thick slices of the foetal brain were obtained (approximately 20 s acquisitions) in the three, natural orthogonal planes. After those were judged to be of diagnostic quality, similar acquisitions were performed using 3-mm-thick sections with repetition time 31416 ms, echo time (effective) 92 ms, echo train length 136, field of view 25 cm and matrix size 183×256 , number of excitations=1, refocusing angle 120° . In cases when a foetal spine abnormality was known or suspected, the 3 and 5 mm single shot fast spin echo sequences were repeated for the whole spine. Clinical reports of the iuMRI examinations were produced at the time of the iuMRI examination but were later reviewed by a neuroradiologist experienced in iuMRI brain studies (PDG). The iuMRI reviewer had access to the referral information, including the nature of the abnormality in the earlier pregnancy and the ultrasound report, but not the ultrasound images per se. Results for diagnostic agreement between ultrasound and iuMRI, and the proportion of cases where discrepant diagnostic information was found, are expressed as percentages, with 95% confidence intervals estimated using the binomial method.

Clinical relevance of the findings

We did not study the clinical significance of the iuMRI results directly; instead we made a retrospective assessment of possible effects on clinical management using a method that has been described previously [1], but is summarised here. The cases with discrepant ultrasound and iuMRI findings were presented to two foeto-maternal experts involved in the study (SR and GM) in an anonymised, hypothetical fashion. Any changes in management were discussed, and “effects on management” were classified as one of five categories as shown in Table 1.

Table 1. A summary of the grades used for classifying changes in clinical management brought about by the introduction of *in utero* MRI

Group	Criteria
1	iuMRI provided information that did not change the management or the information given to the female
2	iuMRI provided additional information about the foetal brain that was discussed with the female but did not alter management
3	iuMRI gave additional information that affected either management/treatment and/or prognosis, but not to a degree to warrant offering termination of pregnancy
4a	iuMRI gave additional information that significantly altered prognosis to a degree that termination of pregnancy was offered
4b	iuMRI gave additional information that significantly altered prognosis to a degree that termination of pregnancy was not offered

iuMRI, *in utero* MRI.

Table 2. A summary of the CNS malformations in 78 females whose foetal ultrasound and iuMRI examinations were concordant and showed no structural CNS abnormality

Condition	Cases
Supratentorial brain malformation	56
Primary neurulation	
Cranial neural tube defect	2
Spinal neural tube defect	2
Failed commissuration	
Agenesis of the corpus callosum	9
Agenesis of the corpus callosum and migration abnormality	2
Cortical formation abnormalities	
Abnormal proliferation	
Primary microcephaly	3
Hemimegalencephaly	1
Abnormal migration	
Lissencephaly	17
Heterotopia	2
Abnormal organisation	
Polymicrogyria	6
Polymicrogyria with schizencephaly	3
Other	
Septo-optic dysplasia	3
Isolated ventriculomegaly	4
Cerebral arteriovenous malformation	2
Infratentorial brain malformation	14
Dandy-Walker spectrum	10
Ponto-cerebellar hypoplasia	3
Joubert's syndrome	1
Miscellaneous genetic syndromes	8

CNS, central nervous system; iuMRI, *in utero* MRI.

Results

The ultrasound examinations were reported as normal in 81/100 examinations, and in 78 of those cases (78%; 95% confidence intervals, 69–86%) the ultrasound and the iuMRI examinations were concordant in revealing no CNS abnormality. The developmental pathologies of the fetuses from an earlier pregnancy that warranted entry into this study are shown in Table 2. These have been grouped according to the classification used in a modern

textbook of paediatric neuroimaging [7]. Of those 78 cases, 66 had the iuMRI between 18 and 24 weeks gestational age and were invited to return for a further iuMRI between 30–32 weeks gestational age. 36/66 (55%) agreed to return for the second iuMRI examination and in all but one case the second iuMRI examination was also reported as normal. One foetus had developed mild ventriculomegaly (VM) on the second study, in a case of a sibling with a cerebral arteriovenous malformation.

The ultrasound examinations were reported as abnormal in 19/100 examinations, and in 13 cases (13%; 95% confidence intervals 7–21%) there were congruent, abnormal findings on ultrasound and on the initial iuMRI, details of which are listed in Table 3. 11 females in this group had iuMRI between 18 and 24 weeks gestational age, and were invited to return for an iuMRI examination at 30–32 weeks gestational age. Of those, eight declined, one had terminated the pregnancy and two had the second iuMRI. In one case the same iuMRI findings were shown, but in the other a foetus previously described as having VM on ultrasound and on the iuMRI at 22 weeks gestational age showed hypogenesis of the corpus callosum (absent splenium) at 30 weeks gestational age. An example from this group is shown in Figure 1.

In 9/100 cases (9%; 95% confidence intervals 4–16%) the results of ultrasound and iuMRI were discrepant, as shown in Table 4. In 3/9 cases the ultrasound examination was normal and 6/9 cases the ultrasound examination was abnormal (showing apparent isolated VM in five and cerebellar hypoplasia in one case). iuMRI showed more severe abnormalities in all cases. Six of these females were eligible to return for a second iuMRI study in the third trimester: three declined, one underwent termination of pregnancy and one went into premature labour at 28 weeks, with subsequent death of the neonate. One female in this group was reimaged with iuMRI (Case 98). This female had had a previous foetus with VM and ultrasound of the current pregnancy had shown VM as well. That finding was confirmed on iuMRI at 23 weeks, but also raised the possibility of lissencephaly based on poor sulcation and that diagnosis

Table 3. A summary of the CNS malformations in previous pregnancies in 13 females whose foetal ultrasound and iuMRI examinations were concordant and showed CNS abnormalities

Study number	Case number	Gestation at iuMRI (weeks)	History of previous pregnancy	Ultrasound and initial iuMRI brain findings	Outcome of pregnancy
1	14	21	Heterotopia	Microcephaly	Delivered at term
2	16	22	VM	VM	Delivered at term
3	28	21	DWS	DWS	Stillbirth
4	35	32	Curarino triad	Curarino triad	Delivered at term
5	37	21	DWS	DWS	Neonatal death
6	41	24	VM	VM	Delivered at term
7	54	22	X-linked hydrocephalus	VM	TOP
8	55	22	Septo-optic dysplasia	VM	Premature 34 weeks
9	58	34	Zellweger syndrome	VM	Delivered at term
10	61	23	DWS	DWS	TOP
11	72 ^a	20	Micro-lissencephaly, ACC	Micro-lissencephaly, ACC	TOP
12	86	23	Kallmann syndrome	Cleft lip/palate	Delivered at term
13	89	20	VM	VM	Delivered at term

ACC, agenesis of corpus callosum; DWS, Dandy-Walker spectrum; iuMRI, *in utero* MRI; PMG, polymicrogyria; TOP, termination of pregnancy; VM, ventriculomegaly.

^aConsanguinity.

Table 4. A summary of the CNS malformations in previous pregnancies in nine females whose fetal ultrasound and iuMRI examinations showed discrepant results.

Study number	Case number	History of previous pregnancy	Ultrasound findings	iuMRI: gestation (weeks): findings	Outcome	Effect of iuMRI
1	4	VM	Moderate VM	18: DWS	TOP	1, 1
2	13	PMG	Mild VM	27: Mild VM, PMG	TOP	2, 4a
3	17	Walker-Walburg syndrome	Small cerebellum	25: Lissencephaly, hypogenetic corpus callosum, brainstem and cerebellum	Delivered at term	2, 4a
4	30	Lissencephaly	Normal	28: Lissencephaly	TOP	4a, 4a
5	43	Spinal neural tube defect	Mild VM	18: Myelocoele Chiari 2	TOP	3, 4a
6	60 ^a	VM	Severe VM	21: ACC	TOP	2, 2
7	88	DWS, semilobar HPE	Normal	20: DWS	Neonatal death (delivery at 28 weeks)	4a, 4a
8	98	VM	Mild VM	23: VM, lissencephaly	Stillbirth 29 weeks	2, 4a
9	100	Baraitser-Winter syndrome	Normal	22: VM	Delivered at term	4a, 4a

ACC, agenesis of corpus callosum; DWS, Dandy-Walker spectrum; HPE, holoprosencephaly; iuMRI, *in utero* MRI; PMG, polymicrogyria; TOP, termination of pregnancy; VM, ventriculomegaly.

The rightmost column represents the opinions of two foeto-maternal experts about the effects on clinical management that would have been brought about by including iuMRI in the diagnostic pathway as described in Table 1.

^aConsanguinity.

was confirmed on the third trimester iuMRI. Two examples from this group are shown in Figures 2 and 3. Assessment of the potential effects on clinical management made retrospectively showed that in 2/9 cases of

discrepant findings the iuMRI had minor effects (Grade 1 or 2) as judged by both assessors, in 7/9 the effects were considered major (Grade 3, 4a) by at least one assessor; both assessors agreed on this severity in 4/9 cases.

(a)

(b)

(c)

Figure 1. *In utero* MRI (iuMRI) images from a case in which the previous history, ultrasound findings and iuMRI findings were all congruent for Dandy-Walker spectrum (Case 61). iuMRI was performed at 23 weeks gestational age, and the (a) sagittal and (b) axial image through the cerebellum shows a hypoplastic cerebellar vermis (arrows) and an enlarged posterior fossa. (c) An axial image through the lateral ventricles shows dysmorphic ventricles but no ventriculomegaly on the basis of trigone size (8 mm).

Figure 2. *In utero* MRI (iuMRI) images from a case in which the foetal ultrasound and iuMRI findings were discrepant (Case 30). There was a history of lissencephaly in a previous pregnancy and ultrasound showed mild foetal ventriculomegaly. (a) Axial and (b) coronal single shot fast spin echo sequences at 28 weeks gestational age shows virtually no sulcation; compare with (c) axial and (d) coronal images from a typically developing 28–29 week fetus.

Discussion

Genetic counselling in the absence of a syndromic diagnosis can be problematic. Imaging findings merely describe the phenotype of an abnormality, such as VM, lissencephaly or Dandy–Walker syndrome, rather than confirming a genotype. It is, therefore, often difficult to assign a prior risk to a pregnancy without other phenotypic information on the previous affected foetus. VM may be an isolated incidental finding or may be the

first observed manifestation of a major neuro-developmental disorder. Some conclusions can be drawn based on the degree of VM: Gaglioti et al [8] collated studies of pregnancy outcome and observed that borderline VM (below 12 mm) in the absence of any other malformation has a 96% chance of a normal pregnancy outcome, while only 26% of pregnancies complicated by severe VM have a normal outcome [8]. This conclusion is true only if the VM really is isolated, an assertion that is no longer tenable with ultrasound analysis alone.

Figure 3. *In utero* MRI (iuMRI) images from a case in which the foetal ultrasound and iuMRI findings were discrepant (Case 43). There was a history of myelomeningocele in a previous pregnancy and ultrasound showed moderate foetal ventriculomegaly. (a) Axial single shot fast spin echo sequences at 18 weeks gestational age show ventriculomegaly with dysmorphic ventricles and a paucity of fluid on the surface of the brain; compare with (b) a typically developing 19–20 week foetus. These features are highly suggestive of a Chiari 2 malformation. (c) This was confirmed by a small posterior fossa and descent of the cerebellar tonsils on a parasagittal image (arrow); a defect in the musculature is shown in the sacral region with a placode (arrowheads), consistent with a myelocele.

Where a genetic diagnosis has been made and the recurrence risk is known to be significant, it is easier to interpret the ultrasound and MRI findings. For example, our Case 86 had a previous pregnancy affected by Kallmann syndrome, and cleft lip and palate are well-described associated features of the condition, so it is likely that the pregnancy we report was also affected. In contrast, Case 58 illustrates a limitation of our study. The previous pregnancy was affected by Zellweger syndrome, which is associated with agenesis of the corpus callosum, lissencephaly and heterotopia, but not VM, which was detected in the pregnancy we report. At

present, however, we only know that the baby was delivered at term and do not have access to the results of neonatal very long chain fatty acid levels to confirm or refute the diagnosis.

Our results show that there was a 22% detection rate of brain abnormalities in the group of 100 females with “high-risk” pregnancies. This is considerably higher than our estimates made prior to the start of the study, which were in the order of 5%. One plausible explanation for the high rate is a selection bias. We believe that a foeto-maternal expert would be more likely to refer a female for the study with an unfavourable history and an

abnormality on ultrasound when compared with a female with an unfavourable history and a normal foetal ultrasound examination. It should be noted that all but three of the fetuses with CNS abnormalities on iuMRI had some abnormality shown on ultrasound, although some of those findings were not confirmed on iuMRI. The bias could have been circumvented if females had been recruited into the study before any second trimester ultrasound screening was performed. We view this as a methodological flaw that will be corrected in any future study.

There was agreement between the ultrasound and iuMRI for the presence of abnormalities in 13% of cases and in the majority of cases the findings were coherent with the previously detected CNS abnormality in the earlier pregnancy. There was disagreement, however, between the ultrasound and iuMRI findings in 9/100 cases. Ultrasound described some abnormality in only three of those cases, but in each case iuMRI described abnormalities that were previously unrecognised or more severe, and were judged to have a major effect on clinical management in 7/9 cases by at least one assessor. In four of those seven cases both assessors agreed on the major effects on clinical management, and there was disagreement in three; the type of disagreement was consistent in all three cases: Grade 2 by Reviewer 1 and Grade 4a by Reviewer 2 (Cases 11, 13 and 98). We believe that this apparent significant disagreement is due to a methodological flaw in our rather superficial analysis of a highly complicated process. On further analysis, Reviewer 2 said that in Cases 11, 13 and 98 he would have judged *any* imaging abnormality to be an indicator of serious risk (the cases all had abnormalities on ultrasound) in the background of the family history. Both assessors agreed that termination of pregnancy would have been discussed with those females.

We cannot say, however, that iuMRI gave correct information in these cases as reference standard data is not available (e.g. autopsy or post-natal imaging). Our group has previously demonstrated a very close correlation between iuMRI findings and autopsy results, post-mortem MRI findings and post-natal imaging in such cases [2]. We would also add that some of the structural abnormalities diagnosed on iuMRI are "true by definition", such as Dandy-Walker syndrome and open dysraphic processes. We concede, however, that the sensitivity and specificity of iuMRI in diagnosing lissencephaly *in utero* is not known and is likely to be related to gestational age. If we assume that the iuMRI findings are correct, our results indicate that iuMRI has a role in the management of pregnancies at high risk of CNS malformations. This is supported by the retrospective and hypothetical assessments of what effect including iuMRI in the diagnostic pathway would have made as judged by foeto-maternal experts.

We also have to reconsider the role of iuMRI at the time of the previous pregnancy, where a foetal CNS malformation was originally diagnosed. It is obvious that the quality of the genetic counselling a female receives is directly related to the accuracy of diagnosis of the malformation. When this is achieved post-natally (either known pre-natally or not) the quality and confidence of the diagnosis made on post-natal MRI is likely to be high. If, however, the CNS malformation is diagnosed

pre-natally but the pregnancy is terminated, or if there is *in utero* demise, the best way to obtain the structural diagnosis is provided by autopsy. There are many situations, however, where that high level of confirmation by autopsy is not achieved. A leading example of this is when autopsy is not requested by clinicians or if the request is declined by the parents, a situation that is estimated to occur in approximately 70% of cases in the UK [9, 10]. In that case the only structural information available to estimate future risk is based on antenatal ultrasound, which has been shown to be incomplete or inaccurate in a high proportion of cases in comparison studies with iuMRI. The improvement in diagnosis accuracy provided by iuMRI, is highly dependent on the patient group studied; for example, we showed an improvement of 48% in 100 cases considered to be difficult cases for ultrasound based on difficult pathology or difficult ultrasonographic conditions [2]. At the other end of the spectrum, an improvement of 17% was found in cases of isolated VM diagnosed under good ultrasonographic conditions [1]. We must assume, therefore, that a significant proportion of females are counselled incorrectly if the structural diagnosis is made on antenatal ultrasound alone.

One approach to rectify this problem is to offer post-mortem MRI as an alternative if the family do not want autopsy. Several groups, including our own, have shown that this is an acceptable method of defining foetal CNS malformations (for a review, see [11]). Although this may be an acceptable alternative in some situations, it is not acceptable to all families, and in some centres post-mortem is not practicable. In this situation an iuMRI examination prior to a planned termination of pregnancy is likely to provide the best information possible in order to provide genetic counselling about future risk.

In summary, the primary purpose of the present study was to evaluate the use of iuMRI in subsequent pregnancies of females at increased risk of recurrence of foetal CNS malformation. We have shown that some variety of CNS abnormality was present in 22% of cases, including 13% detected by both ultrasound and iuMRI. The addition of iuMRI in the diagnostic pathway therefore increased the diagnostic information in 9% of all cases included in the study, and frequently has major effects on clinical management.

References

1. Griffiths PD, Reeves MJ, Morris JE, Mason G, Russell SA, Paley MNJ, et al. A prospective study of fetuses with isolated ventriculomegaly investigated by ante-natal ultrasound and in utero MR. *AJNR Am J Neuroradiol* 2010;31: 106–11.
2. Whitby EH, Paley MN, Sprigg A, Rutter S, Davies NP, Wilkinson ID, et al. Outcome of 100 singleton pregnancies with suspected brain abnormalities diagnosed on ultrasound and investigated by in utero MR imaging. *BJOG* 2004;111:784–92.
3. Levine D, Barnes PD, Madsen JR, Li W, Edelman RR. Fetal central nervous system anomalies: MR imaging augments sonographic diagnosis. *Radiology* 1997;204:635–42.
4. Simon EM, Goldstein RB, Coakley FV, Filly RA, Broderick KC, Musci TJ, et al. Fast MR imaging of fetal CNS anomalies in utero. *AJNR Am J Neuroradiol* 2000;21:1688–98.
5. Golja AM, Estroff JA, Robertson RL. Fetal imaging of CNS abnormalities. *Neuroimag Clin N Am* 2004;14:293–306.

6. Launay S, Robert Y, Valat AS, Thomas D, Devisme L, Rocourt N, et al. Cerebral fetal MRI and ventriculomegaly. [In French.] *J Radiol* 2002;83:723–30.
7. Simon Swartz E, Barkovich AJ. Congenital malformations of the brain and skull. In: Barkovich AJ, Raybaud C, eds. *Pediatric neuroimaging*. 5th edn. Philadelphia, PA: Lippincott, Williams and Wilkins; 2011. pp. 367–568.
8. Gaglioti P, Oberto M, Todros T. The significance of fetal ventriculomegaly: etiology, short and long term outcomes. *Prenat Diagn* 2009;29:381–8.
9. Snowdon C, Elbourne DR, Garcia J. Perinatal pathology in the context of a clinical trial: attitudes of bereaved parents. *Arch Dis Child Fetal Neonatal Ed* 2004;89:F208–11.
10. Snowdon C, Elbourne DR, Garcia J. Perinatal pathology in the context of a clinical trial: attitudes of neonatologists and pathologists. *Arch Dis Child Fetal Neonatal Ed* 2004;89: F204–7.
11. Griffiths PD, Paley MN, Whitby EH. Post mortem MRI as an adjunct to fetal or neonatal autopsy. *Lancet* 2005;365: 1271–3.