

MR Imaging of the Fetal Brain and Spine: A Maturing Technology

P D Griffiths,*^{FRCR, PhD}, M N J Paley,**^{PhD}, E H Whitby,***^{FFRCSI}

Abstract

Introduction: We describe the background and refinements to a 3-year research study designed to evaluate the role of magnetic resonance (MR) imaging in detecting and defining abnormalities of the fetal central nervous system in utero. **Methods:** We describe our experience of using ultra-fast MR imaging methods (specifically single-shot fast spin echo) in 250 fetuses at various gestational ages. All fetuses had known or suspected brain or spine abnormalities based on antenatal ultrasound imaging. We describe the ethical issues raised by this type of work and the differences in diagnostic accuracy between ultrasound and MR imaging. **Results:** We show that MR imaging can be performed in a clinical environment with a high degree of success: only 2 women out of 250 could not be examined (1 was claustrophobic and the other was too large for our scanner). In the 100 cases of singleton pregnancies, where detailed follow-up is available, there is a >40% improvement in diagnostic accuracy when MR imaging is included in the fetal assessment compared to ultrasound alone. **Conclusion:** We conclude that in utero MR imaging is a powerful tool in the assessment of fetal brain and spine abnormalities, and suggest that further work be undertaken to provide a widely available clinical service.

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Introduction

The introduction of a new diagnostic test into a clinical arena goes through a number of stages. The first stage is technical development. With magnetic resonance (MR) imaging, this is often not a carefully charted path and the ultimate clinical goal is not always firmly borne in mind from the outset, but rather a development in one area that is found to be useful in other areas at a later date. As described in this article, the ability to perform *in utero* MR imaging in the second trimester of pregnancy relies on ultra-fast imaging methods, such as echo planar or single-shot fast spin echo (SSFSE) imaging. Both methods were originally devised for reasons other than *in utero* MR imaging. The second stage requires a group of researchers who can recognise the potential of new applications and have the enthusiasm and influence to drive through the "technology overdrive" stage.¹ At this point, it is not unusual for a new method to be heralded in an over-enthusiastic manner, with the outrageous claims being made for the potential of the new technology. This frequently

coincides with the time that research grants are being sought by the first groups in the field.

In utero MR imaging has experienced this overly optimistic stage and, not surprisingly, has encountered a backlash from the doyens of the established ultrasonographic methods. The claim that new methods offer real improvements in clinical care is rebuffed on the grounds that the claims of improved diagnostic accuracy are false, and that there is no overall change in clinical management by using the new (and inevitably expensive) technique. This is often an uncomfortable and confrontational stage for proponents of new technology. Proponents of *in utero* MR imaging may find their claims disputed by obstetric ultrasonographers at scientific meetings and in clinical conferences within hospitals. A counterclaim disputing the improved diagnostic accuracy of MR imaging over ultrasound, which is being reported in the literature, insists that the ultrasonographic technique/interpretation performed in the comparative wing of those studies, is in some ways, substandard. Any group getting involved in

* Professor

** Professor of MR Physics

*** Senior Lecturer

Academic Unit of Radiology

University of Sheffield, United Kingdom

Address for Reprints: Professor Paul D Griffiths, Schering Professor of Radiology, Academic Unit of Radiology, Floor C, Royal Hallamshire Hospital, Glossop Road, Sheffield S10 2JF, United Kingdom.

Email: P.Griffiths@Sheffield.ac.uk

this type of work must guard themselves against such criticism and must be prepared for such questions to be posed to them at interdisciplinary meetings.

Often, the implementers of the new technology become weary or bored at this stage and move onto the next project, which may secure research funds. This is a pity because the real goals of clinical research must be to judge the effects on the higher of the 6 criteria put forward by Fryback and Thornbury.² These are patient outcomes and societal efficacy. Over time, the new method becomes accepted and is used with existing methods. The overwhelming optimism held by proponents of new technology is often tempered by a few serious errors, while users of older methods are impressed by the significant contribution made by the new method in a few difficult cases.

In this paper, we describe the evolution of our *in utero* MR imaging programme over the first 3 years since its implementation. During this time, we performed approximately 250 examinations for known/expected central nervous system (CNS) abnormalities of the fetus.

The First Studies

In utero MR imaging has been performed for a number of years before we started our programme, but the major limiting factor was motion artifact resulting from factors such as fetal movement, maternal arterial pulsation and maternal respiration. Earlier groups overcame these problems in 1 of 2 ways: muscular blockade of the fetus³ or deep maternal sedation using benzodiazepines.⁴ Both methods introduce a small but finite risk to the procedure, a risk many groups thought was unacceptable for widespread clinical application. It was the introduction of ultrafast MR imaging, towards the end of the 1990s, which opened up the field, namely echo planar and SSFSE imaging methods, the latter being the most widely practised. An overview of SSFSE MR imaging is given in Appendix I. These methods produce an image per second or less, and effectively freeze physiological movement without recourse to pharmacology.

The Procedure

After the attending radiologist explained and obtained the woman's full consent, she was advised to empty her bladder prior to getting on the MR imaging scanner. A flexible phased array coil was placed around the lower abdomen and a series of 3 plane scout views were made. Brain imaging was obtained in the 3 natural orthogonal planes in all patients and the coil was moved if the fetal brain was not in the high signal region of the coil on the scout views. The spine was imaged (sagittal and axial) only if there had been some concern over the ultrasound (Figs. 1a to 1c). This often required repositioning of the coil.

Appendix I: Single-Short Fast Spin Echo (SSFSE)

The SSFSE sequences was introduced for clinical magnetic resonance (MR) imaging examinations in 1988 by Jurgen Hennig.⁵ Initially, it was called rapid acquisition recalled echo. As the initial implementation of the sequence was very much T2-weighted, it was used to produce MR imaging "myelograms" of the cerebrospinal fluid in the spinal column. SSFSE is essentially the spin echo analogue of the gradient called echo planar imaging (EPI) sequence. It was devised by Sir Peter Mansfield and co-workers in Nottingham in 1977.⁶

Following an initial excitation pulse, a train of radiofrequency (RF) pulses with close spacing (typically 64 to 128 pulses spaced to 4 to 10 milliseconds) are applied in rapid succession. This high RF duty cycle leads to very high specific absorption rates (SARs) for the SSFSE sequence, potentially giving rise to heating effects in the patient. However, as all the data for the sequence are acquired within a single shot, the effective repeat time may be very long and the average duty cycle can be reduced by leaving time between repeated image acquisitions. Also, it is possible to reduce the flip angle of the refocusing pulse to, say 140°, which can reduce the SARs by almost 50% while only reducing the signal to noise ratio (SNR) by approximately 10%. The long (effectively infinite) repeat time is used to allow normal interleaved, multislice operation and to ensure full longitudinal magnetisation is available for each shot, resulting in very good SNR for SSFSE.

Once the anatomical target had been located, the SSFSE sequences were run (TR:TE ms 20000:75) using an echo train length of 80. This used a 250-mm field of view and a matrix size of 256 x 144 (in plane resolution 1 x 1.7 mm). Twenty 5-mm thick slices were obtained in 20 s using this method. This sequence gives heavily T2-weighted images that have good contrast resolution in the fetal CNS due to the absence of myelin. Although the individual acquisitions were only 20 s in duration, the table occupancy was often quite long because of fetal movement and the "chasing" that was required to obtain the orthogonal planes. Radiographic experience is vital to reduce the overall examination time; the first case (a brain-only examination at 28 weeks of gestation) took 87 minutes of table time! We can now perform most brain-only examinations in 10 to 15 minutes irrespective of the gestational age and without the need to use a breath-hold technique, unless the fetus is in a breech position. Other research groups routinely use a breath-hold technique.⁷

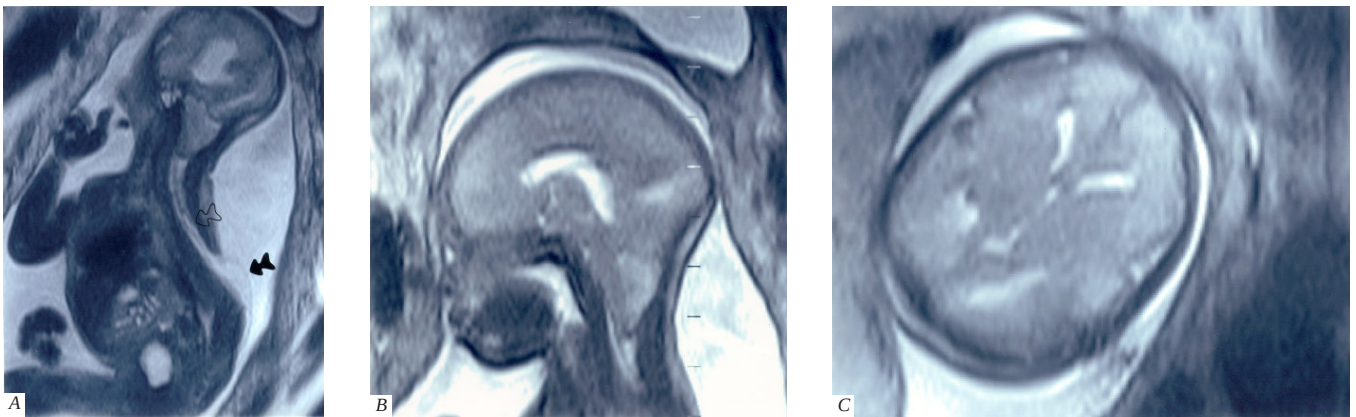


Fig. 1A. This fetus has a myelomeningocele and Chiari 2 deformity at 26 weeks' gestation. The sagittal SSFSE T2-W MR image shows a defect in the musculature in the lower thoracic region (closed arrow) with a sca and visible placode. There is a small syrinx in the central canal of the cord (open arrow).

Fig. 1B. Sagittal MR image of the brain shows low-lying cerebellar tonsils.

Fig. 1C. Axial image shows ventriculomegaly and a paucity of cerebrospinal fluid on the surface of the brain. These findings were in agreement with the antenatal ultrasound and post-natal findings.

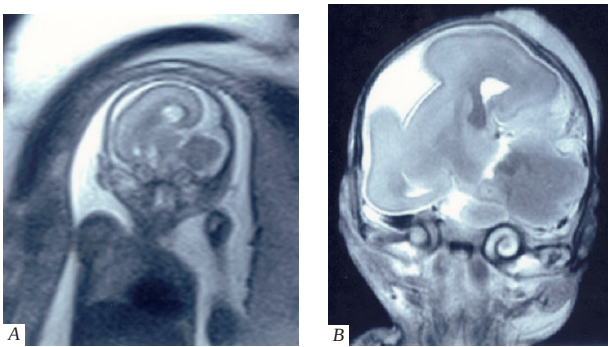


Fig. 2. Twenty-two weeks' gestation fetus.

Fig. 2A. There is a grossly disorganised hemisphere thought to be the single ventricle that was seen on antenatal ultrasound. In utero MR image shows a right cerebral hemisphere occupying most of the cranial space while there is a rudimentary left cerebral hemisphere. There was also a sphenoidal encephalocele.

Fig. 2B. These findings were confirmed on the post-mortem MR image.

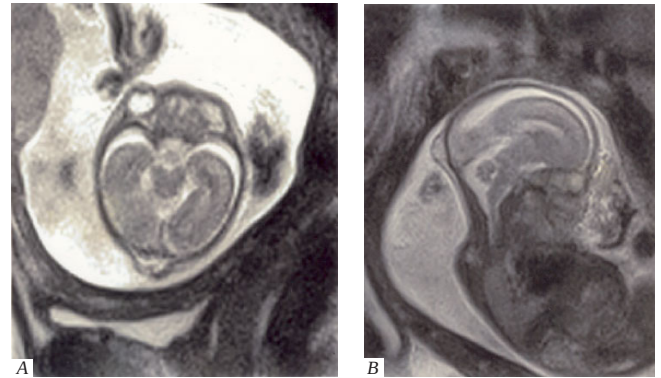


Fig. 3. The ultrasound diagnosis in this case was parietal encephalocele. In utero MR images at 20 weeks' gestation show a swelling in the superficial tissues overlying the calvarium, but no brain or skull abnormality could be seen. The swelling was less pronounced at 24 weeks. A provisional diagnosis of atretic meningocele was made. At birth, the skin overlying the lesion was hairless and histological studies, after resection at 12 months, defined a dermoid. Fig. 3A. Axial image. Fig. 3B. Sagittal section.

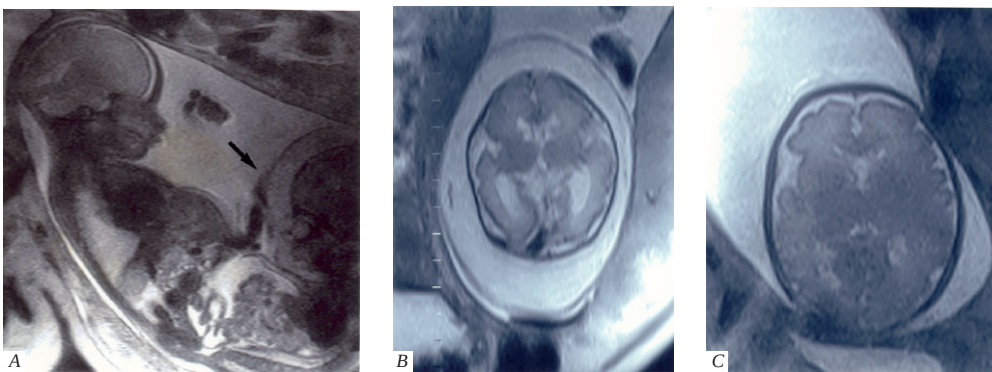


Fig. 4. MR images of conjoined twins at 30 weeks' gestation.

Fig. 4A. The twins are joined at the pelvis; the spinal canals are fused. Note the gross hydrops, ascites and pleural effusions in one twin (arrow).

Fig. 4B. Brain of the hydropic twin.

Fig. 4C. Normal twin. Note the difference in size of the brain compared to the hydropic twin (Fig. 4b).

Results and Criticisms of the First Studies

The results of the 21 subjects who continued their pregnancies were reported elsewhere,⁶ but are summarised here. In 8 cases, antenatal ultrasound, *in utero* MR imaging and post-natal imaging were in complete agreement. In 4 cases, *in utero* MR imaging provided more information compared to ultrasound, but this was judged by the authors as not being sufficient to alter any counselling that may have been given to the parents. However, in 8 cases (40%) the diagnosis made by ultrasound was changed, in a fundamental way, by *in utero* MR imaging and would probably have altered counselling. The MR imaging diagnoses were found to be correct by post-natal imaging in all cases.

An obvious criticism of that study was the lack of impartial experts to assess, retrospectively, the effects on management. Other criticisms made at clinical and scientific meetings were more cryptic. It was felt that staff at the fetal assessment units who referred the early cases were sceptical about the value of MR imaging and believed that obstetric ultrasound, in good hands, was probably all that was required. This probably led to the early referrals being difficult ultrasound cases, as the ultrasonographer was unsure of the diagnosis. Therefore, our sample was not representative of the total workload. The reverse scenario must be viewed in a more optimistic light; *in utero* MR imaging appeared to be able to unravel difficult CNS cases (Fig. 2a & 2b)!

The next 10 subjects who were studied terminated their pregnancies on the basis of the ultrasound findings showed the same degree of improvement in diagnostic accuracy using MR imaging, as described in the previous group, but raised a series of unexpected problems. The first problem may be specific to the UK and other centres around the world where there is public concern over the retention of tissues by hospitals.⁹ The number of parents who agreed to an autopsy of their deceased child or fetus has dropped considerably in the UK over the last few years and this hampers confirmation of any *in utero* diagnosis by imaging. This led us to explore the possibility of using post-mortem MR imaging to provide anatomical diagnoses, which has been reported elsewhere.¹⁰

The second problem revolved around a major discrepancy between an ultrasound and an MR imaging diagnosis. A woman was referred at 20 weeks' gestation with a diagnosis of a large parietal encephalocoele affecting her fetus. She had agreed to *in utero* MR imaging prior to terminating her pregnancy. MR imaging could not show any brain or skull abnormality, but there was a small swelling in the dermal tissues overlying the parietal bone (Figs. 3a & 3b). We suggested the possibility of an atretic meningocele, which generally has a good prognosis at this anatomical site. We

contacted the referring clinicians and raised our concerns with the ultrasound diagnosis, and suggested a repeat ultrasound examination. This was performed the following day and a complete calvarium was confirmed in that study. We performed a repeat MR imaging at 24 weeks and the superficial mass was shown to be somewhat smaller. The parents decided to continue with the pregnancy and a girl was delivered with a small hairless patch overlying a small fluctuant lump. At 12 months she was developmentally and neurologically normal, and the lump was resected. A histological diagnosis of dermoid was made.

The Later Studies

The first phase of the study showed that *in utero* MR imaging could be performed in a clinical environment at our institution and it showed great promise in improving diagnostic accuracy. The second phase of the study provided more exposure to the capabilities of *in utero* MR imaging of brain and spinal abnormalities, particularly before 24 weeks of gestation, and to confirm our initial impressions of improved diagnostic accuracy. Our referrals originated from 5 large fetal assessment units in North England (Hull, Leeds, Manchester, Nottingham and Sheffield) and the procedures were performed with 4 days of the referral. The major difference between the early and later patient groups was that decisions concerning termination of pregnancy had not been made at the time of the later MR imaging examinations. It was decided, in conjunction with the Ethics Committee, that information from the MR imaging examination would be made available to the referrer in the form of verbal and written reports, which clearly stated that the procedure had been performed as part of a research study. This would give the obstetrician/radiologist an opportunity to reproduce the MR imaging findings in cases where there is significant disagreement between the 2 modalities.

Significant technical improvements were made in the later studies. The software was upgraded to allow echo train lengths of 132 and the in-plane resolution was improved to 1 x 1 mm. Reduced partial volume errors were achieved performing 3-mm thick slices, which was particularly important for spine imaging. A robust, fast T1-weighted sequence was implemented using a gradient echo RF-FAST sequence (20-mm thick sections in 34 s). Though generally less useful than T2-weighted images of SSFSE sequences, T1-weighted imaging was used in cases of suspected haemorrhage or lipid deposition, such as abnormalities associated with agenesis of the corpus callosum.

Results of the Later Studies

At the time of writing, nearly 250 *in utero* MR imaging

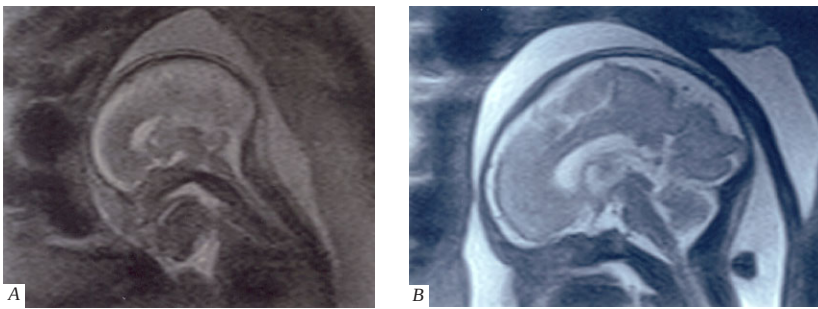


Fig. 5A. Sagittal MR image of fetus at 22 weeks' gestation shows mild ventriculomegaly, increased extra-axial cerebrospinal fluid space and increased nuchal thickness, suggesting a chromosomal or syndromic abnormality. It was later confirm as Down's syndrome.

Fig. 5B. In utero MR image of a normal fetus at the same gestational age.

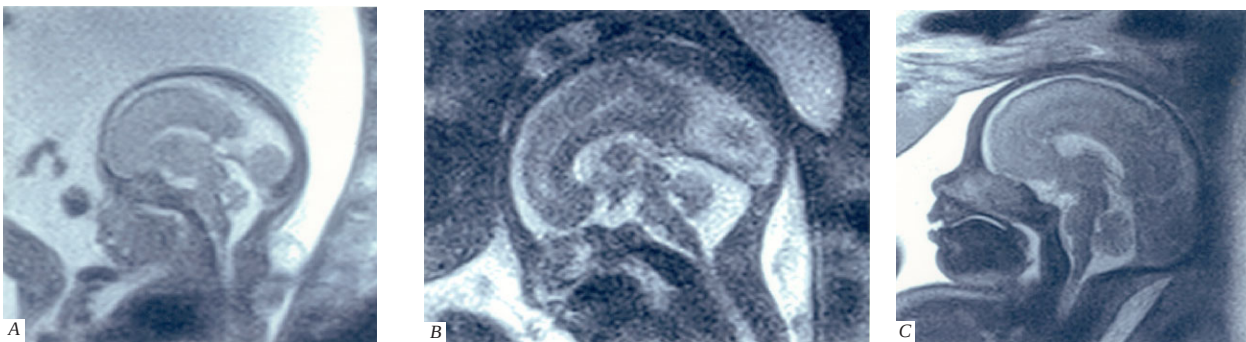


Fig. 6. In utero MR images at 3 gestational ages shows the degree of change in normal brain morphology over a period of 16 weeks. Note in particular the change in the degree of sulcation.

Fig. 6A. 20 weeks' gestation.

Fig. 6B. 28 weeks' gestation.

Fig. 6C. 36 weeks' gestation.

examinations for CNS abnormalities were performed. These included 2 women for whom no information was obtained on MR imaging: 1 woman was too claustrophobic to get on the scanner and the other was too large for the bore of our system (58 cm in diameter). Currently, we have the standard follow-up information on the first 100 singleton pregnancies (manuscript in preparation). It shows a 40% to 45% improvement in diagnostic accuracy when ultrasound is supplemented by MR imaging. We have extended our investigations to different clinical problems, most importantly multiple pregnancies (Figs. 4a to 4c) and screening of "high-risk" pregnancies. MR imaging of twin pregnancies can be challenging. The lack of real-time imaging capacity raises the issue of how to ensure that both fetuses have been imaged in twin pregnancies. This problem is further compounded in triplets. Valuable clinical information can be gained for conditions such as twin-twin transfusion pathology and developmental abnormalities.

When a woman has produced a fetus with an abnormal brain and/or spine in an earlier pregnancy, clinical genetic frequently becomes involved when she is considering another pregnancy. Empirical observation has shown that these women are, statistically, more likely to have abnormal

pregnancies in the future even if a true genetic cause cannot be found. In these women, future pregnancies are often monitored closely, and more frequently, by ultrasound examinations. It is possible MR imaging will play a leading role in monitoring this type of pregnancy. Fortunately, the majority of fetuses in such cases will have normal brains and spines as the recurrent risks are quite low. Providing that normality can be confirmed on post-natal follow-up, this can provide a database on normality that has been lacking in earlier studies.

Future Developments

Our group is concerned primarily with the detection of CNS abnormalities in the fetus. There is a growing body of literature on the value of *in utero* MR imaging for non-neuro applications, particularly thoracic, abdominal and pelvic developmental abnormalities.¹¹⁻¹³ As with the CNS applications, large prospective trials are still required to assess the true value of the new methods.

The scan and table occupancy times are generally modest for *in utero* cases. With experience, it is not unusual to perform singleton fetal brain examinations in 10 to 15 minutes, but examinations including the brain and spine in

multiple pregnancies can be lengthy. It is sometimes difficult for women in the second trimester to lie on the scanner for long periods of time. Therefore, research into faster methods of scanning is a justifiable goal. At present, the rate-limiting step is to find the appropriate planes for imaging. One method which holds promise in improving table occupancy time is “on-the-fly scouting”. It allows fast single-frame images to be acquired with good anatomical resolution, while rapidly varying the orientation in order to obtain the desired scan plane. At that point, the formal SSFSE sequence can be triggered off, giving the best chance of producing images in the natural orthogonal planes. Table occupancies of 5 minutes could be expected with the robust working of this technology.

There are many opportunities to develop other rapid imaging methods *in utero*. Early cases of time-of-flight MR imaging angiographic methods applied *in utero* have been published¹⁴ and presented at scientific meetings. Our group has had success in performing both MR imaging arteriography and venography in cases of vascular malformations using acquisition times of around 60 s to 100 s. Proton spectroscopy can also be performed *in utero*, but the clinical relevance of this method remains to be assessed. Lactate is present in sufficient quantity in the amniotic fluid of normal pregnancies to be detectable by MR imaging spectroscopy, and could be useful in the assessment of intra-uterine growth retardation and allied conditions.

Conclusions

There is no doubt that *in utero* MR imaging is a powerful method for detecting CNS abnormalities. However, the solutions to a number of issues or problems remain elusive. Fears over the safety of MR imaging on the fetus have not been allayed, although no adverse events have been reported to date. It would seem reasonable to expect that all the groups who have performed *in utero* MR imaging should pool their follow-up data together to resolve this concern as quickly as possible. *In utero* MR imaging does appear to improve diagnostic accuracy, as shown by those groups who have paid meticulous care to follow-up data, but there is still no strong evidence of improved patient outcome. This has been impossible to do so prospectively because our MR imaging data have not been used without knowing the results of the ultrasound. The best that we can do is to make retrospective “intention to treat” judgements based on the MR imaging and ultrasound examinations independently, and to compare those mock outcomes. That work is now in progress. Our initial impressions are that the group of fetuses referred with apparent isolated ventriculomegaly (Figs. 5a & 5b) on ultrasound benefit most, and that it is now our clinical practice to offer those

mothers *in utero* MR imaging before counselling.

At this stage we must think about how a clinical *in utero* MR imaging service would work in practice. Most modern MR imaging scanners can acquire SSFSE sequences. The greatest problem may be the lack of experienced radiologists to interpret the examinations. It is possible that this will make any future *in utero* MR imaging service a supra-regional referral.

We did not consider it appropriate to provide clinical *in utero* MR imaging from the beginning. Hence, we embarked on it as a research protocol. We approached the Ethics Committee to discuss a number of important problems, which are outlined in the next few sections.

Who Should Benefit from *in utero* MR Imaging?

This revolved mainly around the safety of MR imaging in pregnancy, a factor that was (and to a large extent, is still) unknown. Ideally, we would have examined control fetuses first in order to build up a database of normal findings, but we were advised against doing so. This was in marked contrast to the way that ultrasound was introduced into clinical practice in the 1970s, as it was considered to be entirely safe from the outset.

How Should the Results of *in utero* MR Imaging be Used?

It was decided that the results of MR imaging should not be used to direct clinical management. This is a reasonable approach when a new method is first introduced, and there is already a powerful benchmark in ultrasound. To guard against this, the woman recruited into the study had already made their decisions regarding termination of pregnancy on the basis of ultrasound data even before MR imaging was performed.

When Should the Examination be Performed?

The clinical driver for this work was to perform the examination before 24 weeks of gestation, after which not all centres in the United Kingdom (UK) would consider terminating the pregnancy. However, the authors were not familiar with neuroanatomy at this early gestational age as they were practitioners in paediatric neuroradiology and neonatal imaging, although they did have experience in MR imaging of the complications arising from prematurity. The first part of the study, therefore, was offered only to women between 28 and 32 weeks' gestation, with the plan to work towards 20 weeks after more experience had been gained with the later stages of fetal brain/spine development (Figs. 6a to 6c).

How Does One Show that the Antenatal Imaging is Correct or Incorrect?

This was a major problem that needed to be solved in

order to yield data on the relative diagnostic accuracies of antenatal imaging methods. Initially, we aimed to study two discrete groups: women who proceed to complete their pregnancies and those who terminate theirs. Our benchmark for the latter group was the results of the autopsy, while a combination of physical examination, post-natal imaging and clinical examination at 12 months' post-natal age was the yardstick for completed pregnancies.

What Should the Subjects be Told About the Safety of MR Imaging in Pregnancy?

As the examination was part of a research study, and not a clinical examination, informed consent was obtained from each subject, which included a discussion on safety issues. The subject and her spouse were told that the effects of MR imaging on the fetus were not known, although MR imaging was widely thought to be safe in children¹⁵ and in adults on the basis of millions of examinations that have been performed worldwide. The 2 theoretical concerns were possible heating from radio frequency deposition and acoustic damage. Heating could be an issue because of the high specific absorption rates of SSFSE sequences. All examinations conformed to the national guidelines (National Radiological Protection Board) and the fetuses were well protected from temperature changes, due to the surrounding volume of amniotic fluid with a massive blood supply. The concern over acoustic damage is real as the SSFSE sequences operate at around 98 dB. However, the amniotic fluid should help to dampen the noise. This question will only be addressed on detailed follow-up of surviving cases who have formal hearing tests in the first year of life.

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