Clinical review

Science, medicine, and the future

In utero magnetic resonance imaging for brain and spinal abnormalities in fetuses

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In the past eight years magnetic resonance imaging has been used to detect fetal abnormalities in utero at many centres around the world. An increasing number of published papers have shown improved diagnostic accuracy with in utero magnetic resonance imaging compared with obstetric ultrasonography, the current reference standard. This is particularly so in cases of brain and spine abnormalities in the fetus, and much of the published work has concentrated on those anatomical regions. When a new application for an existing technology is discovered, there is a delicate balance between assessing the method adequately in a research environment and the desire to introduce it into the clinical arena as soon as possible. Here we describe the current status of in utero magnetic resonance imaging and outline some of the ethical issues raised by working with a new application in this complicated clinical environment.

Methods

The fictional case we outline is a composite story of circumstances we found ourselves in soon after we started our research programme on in utero magnetic resonance imaging in 1999. Our situation was helped by foresight and by discussing it prospectively with the local research ethics committee. We have used this scenario to introduce the topic of in utero magnetic resonance imaging, to show its potential benefits, and to outline the practical and ethical issues that are raised by using the technique.

A hypothetical clinical case

The obstetrics and radiology departments of a teaching hospital decide to carry out clinical in utero magnetic resonance imaging in some pregnant women whose fetuses have developmental brain problems diagnosed by ultrasonography. The first case attempted is technically successful, but the agenesis of the corpus callosum and Dandy-Walker malformation detected by ultrasonography cannot be confirmed by in utero magnetic resonance imaging. The brain seems to be normal. The woman had decided to terminate the fetus on the basis of the ultrasonography findings and agreed to have in utero magnetic resonance imaging to help other women in the future. A normal corpus callosum or cerebellar vermis was still not shown on

Summary points

Magnetic resonance imaging can provide detailed information about fetal anatomy in utero

Magnetic resonance imaging can be used in fetuses at 18 weeks gestational age or later

Most research and clinical work to date has concentrated on the fetal brain and spine

Good evidence shows that in utero magnetic resonance imaging can make a major contribution to the management of pregnancies with possible fetal brain or spinal abnormalities

repeat ultrasonography. The obstetrician who reported on the ultrasonogram has 15 years' experience of ultrasonography, but this is the first examination the radiologist has carried out. Ultrasonography is the accepted reference standard for this type of work, whereas the recent published literature suggests that in utero magnetic resonance imaging is better at showing these abnormalities. What happens next?

Background considerations

Imaging of the fetus using ultrasonography has been the mainstay of screening programmes and scanning for anomalies for many years. Major improvements have been made in the instrumentation over that time and, coupled with the training of ultrasonographers, has led to a high quality service in many parts of the world. The technique is not perfect, however, and various technical factors may conspire to obscure the fetus and preclude the diagnosis of structural abnormalities antenatally. In parallel, advances in magnetic resonance technology have allowed imaging of the fetus to become a realistic clinical possibility. In utero magnetic resonance imaging for brain and spinal abnormalities in the fetus is a powerful adjunct to ultrasonography. The box outlines the relative advantages and disadvantages of in utero magnetic resonance imaging. Most work has been directed at fetuses with possible developmental abnormalities in the second trimester,

but the potential is great for investigating acquired brain abnormalities that may accompany the failing placento-uterine unit. The most pressing practical issue is making the service widely available to pregnant women in the light of limited access to magnetic resonance scanners and a scarcity of experts in fetal magnetic resonance imaging.

Using magnetic resonance imaging to assess the fetus in utero was probably one of the last applications the early proponents of the procedure would have envisaged. It is fraught with technical challenges, including the major problem of artefacts caused by movement of both the mother and the fetus. Until recently clinical magnetic resonance imaging consisted mainly of spin echo methods with long duration of imaging (4–10 minutes). Magnetic resonance is sensitive to motion and even minor movements may render the scans unusable. For this reason in utero magnetic resonance imaging of the fetus was impossible without other interventions. The first consistently successful attempts at fetal imaging using magnetic resonance were made by paralysing the fetus with muscular blocking agents given through the umbilical vessels.¹ This introduced an element of risk to the procedure but was often carried out in conjunction with other procedures that required cannulation of the umbilical vessel. Less invasive attempts involved maternal sedation, usually with intravenous benzodiazepines,² but these were not completely without risk, and the adequate monitoring of sedated women in the scanners was a problem.

The introduction of ultrafast imaging methods had the most important impact in the field of in utero magnetic resonance imaging. Echo planar imaging and single shot fast spin echo techniques allow the acquisition of single, high resolution images in less than one second, which effectively freezes physiological movement and allows imaging with no invasive interventions. The methods have been described elsewhere.^{3,4} The procedures require high gradient performance (available on most modern scanners),

Fig 1 Sagittal (above) and axial (right) in utero magnetic resonance images showing brain substance protruding through posterior bony defect of 20 week old fetus with large parietal encephalomeningocele

and comparatively large amounts of energy are deposited per unit time in the mother and fetus.

Safety issues

Magnetic resonance imaging in adults has no known deleterious effects whereas the effects of exposure in the fetus cannot be known with certainty. Another concern is the potential effects on a child's hearing, as the scanners produce considerable noise (around 99 dB in our experience). Initial studies suggest that this is not a major problem,^{5,6} but further large, multicentre long term studies are required. These issues are particularly relevant to institutional ethics review boards because if the procedure is to be used there must be a good chance of important benefits to pregnant women.

Starting a programme for in utero magnetic resonance imaging

Most doctors who use in utero magnetic imaging are radiologists working in close conjunction with obstetricians and other radiologists with established antenatal ultrasonography practices. Although knowledge of normal fetal anatomy using ultrasonography is wide, a different knowledge base is required for interpreting images using in utero magnetic resonance. It could be argued that someone starting out in such imaging should begin with a large number of women with healthy pregnancies at different gestational ages to learn what is considered normal at each stage. This is how antenatal ultrasonography was introduced to clinical practice, and doing so is relevant because of the rapid change in normal fetal anatomy that accompanies development in the second half of pregnancy. This gives the operator the best chance of recognising and describing true abnormalities when present. The balance between the desire for a training curve and the non-quantifiable risk to the normal fetus presents another dilemma for researchers and ethics committees.

When we embarked on our in utero magnetic resonance imaging programme in 1999 we decided not to carry it out in women with apparently normal pregnancies, a decision made in conjunction with our local research ethics committee. Instead we recruited women with fetuses known to have abnormalities of the central nervous system on ultrasonography and who agreed to undergo in utero magnetic resonance imaging for research purposes. The initial part of that

Advantages and disadvantages of in utero magnetic resonance imaging

Advantages

Improved diagnostic accuracy—Better contrast between different tissues allows improved visualisation of anatomy

No adverse effects from physical factors—In utero magnetic resonance imaging is not affected by physical factors that can degrade ultrasonography, such as the lie of the fetus, the habitus of the mother, and reduced volume of liquor

Disadvantages

Cost and limited resources—In utero magnetic resonance imaging is more expensive than ultrasonography, is not as widely available, and at present lacks experienced staff for reporting on the scans

Limited research—Most research and clinical work has concentrated on fetal abnormalities in the second trimester, but controlled, large studies are required to evaluate the role of in utero magnetic resonance imaging in acquired problems later in pregnancy, such as the effects of in utero growth restriction on the fetus's brain

Potential effects on hearing—High auditory noise during the procedure may affect a child's hearing

Fig 2 Axial (left) and coronal (right) in utero magnetic resonance images of brain of 20 week old fetus with known congenital heart malformation. Defects are well defined in cortical mantle, indicative of multiple infarctions probably due to emboli

study was divided into two parts. The first women recruited were in the third trimester of pregnancy and had decided against, or not considered, termination of pregnancy. It seemed logical to start with them because, although the central nervous system of their fetuses was known to be abnormal, we could use our neuroanatomical experience of premature babies to provide some points of reference. As it was our intention to provide the imaging facility for pregnancies as early as 19 or 20 weeks, the second study included women at 20-24 weeks gestation who agreed to undergo imaging before termination of pregnancy. We were advised by our local research ethics committee that the information obtained in both studies should not be used to direct clinical management and that a formal report should not be produced.

The results of the first study have been reported elsewhere.³ We were encouraged by the perfect agreement between the results of in utero magnetic resonance imaging and the postnatal findings (clinical and radiological), which acted as the reference standard. Out of 20 cases, agreement between the antenatal ultrasonography and in utero magnetic resonance imaging was complete in eight and in utero magnetic resonance imaging provided extra (correct) anatomical information in four and changed the diagnosis appropriately in eight. Postnatal clinical and

radiological follow-up in this type of research is important. For the second study, it soon became obvious that it was going to be difficult to draw conclusions by involving fetuses that had been terminated because of issues on the reference standard. The number of parents who agree to autopsy on aborted fetuses has dramatically decreased and of the first 18 women in this study only 11 agreed to autopsy; we had, however, shown that good quality fetal images could be obtained with magnetic resonance imaging at this earlier gestational age. It was this problem that led us to explore the use of postmortem magnetic resonance imaging for fetuses in 2000.⁷ This is under further study.

The current position and the future

Those early studies convinced us of the value of in utero magnetic resonance imaging. We therefore asked our local research ethics committee for advice on a larger study. The major practical change that was recommended was that the findings from the imaging should be made available to the referrer. This was to be in the form of a formal report (as for clinical cases), but with an introductory clause stating that the procedure had been carried out as a research study and should not be used to direct clinical management. If there was a major discrepancy between ultrasonography and in utero magnetic resonance imaging, the referring clinician was advised to repeat the ultrasound examination in the light of the findings on in utero magnetic resonance imaging. In cases of persisting disagreement, ultrasonography was to be believed over in utero magnetic resonance imaging as it was the accepted reference standard. Overall, 200 women were recruited and we have recently reported the results of the first 100 cases of singleton pregnancies in which only the brain of the fetuses was imaged.⁴ We have shown an increase in diagnostic accuracy of 48% for in utero magnetic resonance imaging over ultrasonography, and in 36% of all cases the imaging results were potentially of sufficient importance to change counselling. We are currently analysing the results of the cases where the reason for referral was a spinal problem in the fetus. Our initial impression of spinal cases is an improvement in diagnostic accuracy, but this is lower than when the brain is imaged (at about 20-25%). We are also reviewing the twin pregnancies we have imaged, a group that can present major practical difficulties for in utero magnetic resonance imaging.

Many centres worldwide are developing expertise in in utero magnetic resonance imaging, and most have concentrated on the fetus's central nervous system. A large proportion of the published early literature described the techniques required to carry out in utero magnetic resonance imaging along with anecdotal cases in which the imaging had been useful.⁸⁻¹³ This is supported by case reports and case series that indicate additional information may be obtained by using in utero magnetic resonance imaging as an adjunct to ultrasonography. Some papers describe relatively large numbers of cases of in utero magnetic resonance imaging, but many lack comparison with a reference standard, which is vital to confirm improved diagnostic accuracy. All groups have been criticised by specialists in fetomaternal sonography^{14 15} on the basis of artificially high detection rates for in utero magnetic

Fig 3 Two axial in utero magnetic resonance images from 35 week old fetus with features characteristic of established periventricular leucomalacia, probably indicating an active, damaging event from more than two weeks earlier

Additional educational resources

Garel C. *MRI fetal brain*. Secaucus, NJ: Springer-Verlag, 2004—highly pictorial atlas of fetal magnetic resonance images of the brain. Includes measurements of numerous parts of the brain at each gestational age, with range of normal values. The second half of the book provides examples of commonly encountered abnormalities of the fetal central nervous system

Avni FE, ed. *Perinatal imaging: from ultrasound to MR imaging*. Berlin: Springer-Verlag, 2002—textbook of all imaging modalities used in the perinatal period. Includes magnetic resonance images of the more common abnormalities, both fetal and neonatal

Nyberg DA, McGahan JP, Pretorius DH, Pilu G. *Diagnostic imaging of fetal abnormalities*. Philadelphia, PA: Lippincott, 2002—extensive textbook of fetal imaging with information on most abnormalities. The book is primarily ultrasound based but includes computed tomography and magnetic resonance imaging where appropriate

resonance imaging because of biased patient selection. In many cases, however, the patients selected were those in whom ultrasonography was practically difficult because of complex fetal anatomy, fetal lie, oligo-hydramnios, or unfavourable maternal habitus.

In the light of this debate we agreed with our hospital's trust board that we should start to offer a clinical service for in utero magnetic resonance imaging for central nervous system problems in the fetus. Referrals from within our centre and from other centres continue to rise steeply.

Although after four years of research studies we have introduced in utero magnetic resonance imaging as a clinical service, it does not mean that the research is complete. On the contrary, data showing effects on patient management and clinical outcomes are limited. Although most of our cases (and those in the published literature) have been investigated for developmental malformations (fig 1), in utero magnetic resonance imaging seems to be exceptionally good at also showing acquired brain abnormalities (figs 2 and 3). Great opportunities are available to study brain manifestations of in utero growth restriction and twin-twin transfusions, where the risk of brain damage is high. It is possible that some of the advanced magnetic resonance imaging methods could be converted for in utero use; early success has been shown with diffusion weighted imaging,¹⁶ magnetic resonance spectroscopy,¹⁷ and magnetic resonance angiography.¹⁸

Ongoing research studies

Whether in utero magnetic resonance imaging contributes to the management of women whose fetus has apparent isolated ventriculomegaly on ultrasonography

The use of in utero magnetic resonance imaging in women with increased risk of fetal abnormalities owing to an earlier, affected fetus or child

Can in utero magnetic resonance imaging redefine what constitutes in utero growth restriction

What is the clinical course of hydrocephalus and hindbrain deformity associated with myelomeningoceles

If the early promise of in utero magnetic resonance imaging is borne out by larger studies that tackle issues of improved clinical management rather than just diagnostic accuracy, the major concern is how to provide a good quality service to the entire population. We are increasingly aware of the pressures on many imaging departments from obstetricians in hospitals without access to in utero magnetic resonance imaging to start such a service. Few workers in the field of antenatal diagnosis deny the potential value of in utero magnetic resonance imaging and we believe that it is important to open up a national debate on how to make this technique available to the maximum number of women in the shortest possible time.

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