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The current state of MR imaging of the fetal brain in utero

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Abstract

In this article, we provide an overview of fetal brain development, describe the range of more common fetal neuropathology and discuss the relevance of *in utero* MR (iuMR). Although USS remains the mainstay of fetal brain imaging, iuMR imaging is both feasible and safe but presents several challenges. We discuss those challenges, the techniques employed to overcome them and new approaches that may extend the clinical applicability of fetal iuMR.

Introduction

Magnetic resonance (MR) imaging of the unborn baby is probably one of the most difficult targets for clinical imaging for several reasons including the non-predictable and extreme movement, small anatomical structures and, for the fetal brain in particular, expected low tissue contrast. Before the introduction of hardware that allowed ultrafast MR imaging the

only possibility of imaging the fetus with MR was to try to limit its movement. This was done initially by injecting muscle blocking agents into the umbilical vessels (the blood supply and drainage mechanism for the fetus), a procedure with a relatively high complication rate. It was usually performed only because the vessels were being cannulated for other diagnostic purposes and it was never going to be a widely adopted technique. Maternal sedation was also used (and still is in some centres) with a view to keeping the fetus still by way of the drug crossing from the maternal to fetal circulation via the placenta. By and large, the uptake of that method was low because of the requirement for monitoring in the MR scanner. It was also generally accepted amongst obstetricians and fetal maternal clinicians that there was no diagnostic advantage for in utero MR imaging (iuMR) over the established method of visualising the fetus – ante-natal ultrasonography (USS).

Things change. There is no doubt that a major step forward was the ability to perform single shot fast spin echo (ssFSE) sequences on scanners in the mid to late 1990s and those sequences remain the backbone of most iuMR protocols because the heavily T2-weighted images are ideal for imaging the fetal brain for reasons explained below. In this article we provide a background for the rationale of ante-natal detection of brain abnormalities with iuMR imaging, we will describe the range of more common fetal neuropathology and discuss new approaches that may extend the clinical applicability of iuMR.

Stages of pregnancy and the use of diagnostic imaging

It is usually not possible to know with certainty when fertilisation of the egg by a sperm occurs in humans so timing the fertilisation to delivery interval directly is impossible. Hormonal changes in a woman after fertilisation inhibit further egg release and menstruation

so in clinical practice pregnancies are timed from the first day of the woman's last menstrual period (LMP). This is approximately two weeks before fertilisation. By this method a typical pregnancy lasts 39-40 weeks and is divided into three 13-week epochs called trimesters (first, second and third) which provide reference points for key developmental milestones (figure 1). Fetal development is monitored at various stages of pregnancy through screening programs in many countries although there is considerable variation in approach. The purpose of those studies is to detect structural problems that may lead to changes in management of the pregnancy. There are few structural abnormalities that can be rectified *in utero* (especially brain abnormalities) so in many situations this leads to discussions about termination of pregnancy (TOP) in countries where there is a legal basis for that intervention.

It is vital, therefore, that the information obtained from ante-natal imaging is reliable. USS is an integral part of ante-natal screening programmes, being cost efficient, easily accessible and safe so it is the undisputed primary imaging method for assessment during pregnancy. USS is routinely offered in Britain at the end of the first trimester (11-13 gestational weeks – gw) in order to exclude major developmental abnormalities and to look for anatomical evidence for being at increased risk for Down's syndrome (increased thickness of the soft tissues at the back of the neck). A further detailed screening USS is offered in the second trimester (19-20gw) and involves taking a series of fetal measurements, evaluation of fetal anatomy and wellbeing, and an assessment of the environment e.g. placenta and amniotic fluid by a trained sonographer. If an abnormality is detected, the woman is referred to a fetal maternal expert for specialist investigations including a further detailed USS anomaly scan. It is possible that other abnormalities may be recognised later in pregnancy when USS studies are done for specific reasons in fetuses such as poor growth or reduced movements.

The use of iuMR, therefore, is always as a supplementary examination that is usually targeted to the anatomical region(s) of the fetal body that were highlighted as abnormal or possibly abnormal on the USS performed by the fetal maternal specialist. There is now good quality data from prospective studies and systematic reviews that iuMR imaging improves the diagnostic accuracy for fetal brain abnormalities[1,2,3] and leads to changes in clinical management in a significant proportion of cases.[4]

Normal fetal brain development

An overview of normal brain development is given here as it provides a useful template to classify and define structural abnormalities discussed later.

Primary Neurulation

Brain and spine development is a highly complex process that begins with the formation of the neural tube by a process called primary neurulation. The outer part of the embryo (ectoderm) develops specialist cells that are destined to become the brain and spine (neuroectoderm).

Ventral Induction

Between 3 and 4 weeks after fertilisation in humans (five to six weeks after LMP) the neural plate begins to fold, separate from the non-neuro ectoderm and form the neural tube.[5] The head end of the neural tube then undergoes a period of considerable expansion particularly the future cerebral hemispheres, along with division of the future brain in the midline. This process of 'ventral induction' is usually complete by 7 weeks post fertilisation (9gw calculated from LMP).[6]

Commissuration

As soon as the future cerebral hemispheres are separated axonal fibres from the cerebral hemispheres begin to grow across the midline in order to connect homologous parts of the

hemispheres. This process is called 'commissuration' and continues until approximately 18-19gw.[7] The largest commissural tract in the human brain is the corpus callosum.

Cortical Formation

The development of the cortex of the cerebral hemispheres starts as early as 8-10gw with neurons and glia proliferating at the ventricular surface of the brain in the germinal matrices.[8] Those cells migrate through the fetal cerebral hemisphere and subsequently organise on the surface of the hemispheres to become the cerebral cortex.[9] The proliferation and migration of the neurons and glia is a prominent feature of the second trimester and account for the transient layers described on histology but are also visible on iuMR imaging (figure 2). Neuronal migration is completed by the end of the second trimester after which the transient layers become less prominent and subsequently disappear. Any of these processes (proliferation, migration and cortical organisation) can be abnormal and lead to particular types of 'developmental' brain pathology and signature examples are described below and illustrated in the figures.

Structural brain abnormalities in the fetus demonstrated by iuMR

Abnormalities of the fetal central nervous system occur in 2-3/1000 pregnancies and the brain is involved much more frequently than the spine.[10,11] A high proportion of the brain abnormalities encountered are developmental in origin, implying a fundamental anomaly of how the brain was destined to form.

Primary Neurulation Anomalies

Abnormal primary neurulation, for example, results in structural anomalies of the neural tube. When the head end of the neural tube fails to form completely a severe developmental abnormality called anencephaly results.[5] In this abnormality most of the brain and cranium does not form and there is no chance of extended post-natal survival. Failure of the head end

of the neural tube to close results in a group of abnormalities called cephaloceles in which some of the cranial contents protrude through a defect in the skull (figure 3). Prognosis depends on which intracranial structures are involved; if a large volume of brain tissue is involved prognosis is poor whereas a defect only involving the covering of the brain (meninges) can often be corrected surgically with good long-term prospects.

Ventral Induction Anomalies

Abnormal ventral induction produces a group of brain abnormalities called holoprosencephaly, all of which have some degree of incomplete separation of the cerebral hemispheres and underdevelopment of the frontal lobes.[12] Severe forms (alobar) are not compatible with long term ex-utero survival whereas the lesser forms (lobar) can be associated with relatively mild clinical sequelae. Most of the cases referred for iuMR imaging fall into the intermediate category (semilobar holoprosencephaly – figure 4) in which survival is expected but often with pronounced neurodevelopmental problems.

Failure of commissuration

Failure of commissuration leads to varying degrees of underdevelopment of the corpus callosum, most of which involve complete absence (agenesis) of the corpus callosum – figure 5. The accurate detection of abnormalities of the corpus callosum is one of the most important roles of iuMR because USS seems to have a particular problem in diagnosing this abnormality.[13] There is a high association between developmental abnormalities of the corpus callosum and other brain abnormalities, occurring in over two thirds of cases.

Cortical Formation Abnormalities

Abnormalities of cortical formation is the term used to describe the result of abnormal neuronal/glia proliferation, migration and/or organisation. Abnormal proliferation can involve reduced proliferation (one cause of primary microcephaly) or increased proliferation.[8] Abnormal migration can result in a wide range of abnormalities such as lissencephaly or

heterotopia (figure 6) whilst abnormal cortical formation can lead to cortical abnormalities such as polymicrogyria (figure 7).

Acquired Brain Pathology

The second group of fetal brain abnormalities that may be diagnosed on iuMR imaging occur when the development of the brain is progressing normally but is damaged by an external process or event. These 'acquired' pathologies may arise from conditions such as intracranial haemorrhage or cerebral infarction (fetal stroke – figure 8), infections or trauma. Acquired fetal neuropathology is relatively rare and accounted for approximately 7% of cases in a large recent prospective study,[14] whereas approximately 40% of the abnormalities were developmental in origin. By far the largest group, however, were fetuses with ventriculomegaly (enlarged cerebral ventricles) which accounted for over 50% of the total. Fetuses with ventriculomegaly have iuMR imaging because they have an increased chance of further brain abnormalities, either developmental or acquired, that may affect counselling. However, in most situations the enlargement of the ventricles is the only intracranial abnormality.[15]

Routine iuMR imaging: theory

The use of iuMR has grown significantly since its inception in the 1990's and is now considered a valuable modality for depicting both normal brain development and as an adjunct to USS when abnormalities are suspected.[4] USS is sometimes limited by technical and patient related factors such as high maternal body mass index, reverberation artefacts and oligohydramnios and these can prevent adequate visualisation of the fetal brain.[16] This is particularly the case in the third trimester. MR imaging is not limited by the same technical restrictions as USS and can provide excellent visualization of the fetal anatomy due to its superior tissue contrast resolution. MR imaging of the fetus is considered safe when standard

procedures for safety in the MR environment are adhered to. Initial concerns regarding damage to fetal hearing due to the inherent loud noise and the potential heating due to radio frequency (RF) exposure during imaging have not been substantiated.[17-19] Regulatory Bodies[20,21] state that iuMR can be performed when the benefit is considered to outweigh risk and the information obtained from iuMR cannot be obtained by other non-ionising means. It is recommended that MR exposure should be kept to a minimum by restricting SAR exposure to 2 W/Kg.

Prenatal imaging of the fetus presents several challenges requiring MR sequences that can minimise the effects of movement by the fetus and from maternal respiration. Image quality and resolution must adequately depict the inherently small anatomical detail and maximise the low contrast differences to define the brain parenchyma adequately. The mature brain can be subdivided into areas that are cell dense (grey matter structures) and those that are cell sparse (white matter structures). These regions are well demarcated in most brain areas and differences in the chemical composition between grey and white matter regions account for the available tissue contrast on MR imaging. The major chemical differences leading to the excellent contrast resolution in the mature brain arise from differences in water content and lipid concentration. Table 1 shows there are substantial differences in water content between mature grey and white matter but the predominant factor for MR contrast resolution is the lipid in myelin, which is found in high concentration in white matter regions of the mature brain.

The situation in the immature, non-myelinated, brain is very different (Table 1). The third trimester brain (and that of the premature baby) is effectively myelin free and the differences in water content and lipid concentration of grey and white matter regions are minimal. In addition, the water content is much higher in the pre-myelinated brain when compared with

the mature brain and there is virtually no sphingomyelin. As such, MR contrast between the cell dense and cell sparse areas is poor and any differences probably arise from inherent differences in protein content (cell dense areas have higher T1 and lower T2 signal compared with the cell sparse regions – see figures 2 and 10). Good T1 contrast, in particular, can be exceptionally difficult to bring out on iuMR imaging of the immature brain.

The same physical principles concerning pre-myelination apply when imaging the second trimester fetus but there is an extra level of complexity in these fetuses. The formation of the normal cerebral cortex is a centrifugal migration of neurons and glia formed in the germinal matrix, which produce transient layers in the second trimester cerebral hemispheres. Those layers have alternating cell dense (germinal matrix, intermediate zone and cortical plate) and cell sparse (subventricular zone and subplate) regions (figure 2 and 10). It is important that iuMR sequences bring out the differences in contrast between those structures adequately because they may provide the only hint of cortical formation abnormalities before sulcation/gyration of the cerebral hemispheres is advanced. By and large this is best achieved with T2 weighted images.

iuMR imaging: practice

Imaging a fetus that is unrestrained and likely to move requires both a different approach by the radiographer performing the scan and the sequences employed. MR Imaging of the fetus is a dynamic process that starts with an initial localiser followed by the other sequences, each acting as a localiser for the next, the aim being to acquire images in all three anatomical planes. When severe fetal motion is persistent it is often necessary to prioritise and focus on the imaging planes that best demonstrate the anatomy to answer the clinical question. For this reason, it is beneficial for the radiologist responsible for reporting the study to be on hand

during the examination. Example sequence parameters for iuMR of the fetal brain are shown in Table 2.

T2 weighted imaging of the fetal brain.

T2 weighted (T2W) imaging is the most informative contrast when imaging the fetus as it allows visualisation of the changing characteristics of the fetal brain at any stage of development. T2W Fast Spin Echo (FSE) sequences can be performed in fetuses that are not moving a great deal and provide the clearest definition of the transient layers and of early myelination. The acquisition times are usually over one minute and is, therefore, highly sensitive to motion and as such is not the first line method of obtaining T2-weighted images in the fetus.

Single shot fast spin echo ssFSE is a T2W ultrasfast (≈30-40 seconds) scan technique that can provide imaging in any chosen plane making it the primary method used for iuMR. Each image is sampled after a single RF excitation, then reconstructed and displayed before the process is repeated for the next image. Any movement by the fetus is in essence 'frozen' as each image is acquired in 1-2 seconds.The advantage to this 'single shot' method is that if the fetus moves during acquisition, only the imaging slice(s) where this movement has occurred are affected.[22] Long echo trains and half Fourier techniques make the fast imaging times possible but at the expense of some loss of image quality. The long echo trains cause blurring in the phase direction because the weaker signals due to T2 decay from the later echoes are placed at the edges of k-space and determine the high resolution details in the image. Shorter echo spacing, achieved by increasing bandwidth, may reduce blurring, which also reduces scan time, but this is at the expense of signal to noise ratio (SNR). Half Fourier methods also result in loss of SNR, although spatial resolution is preserved. The resultant heavily T2 weighting of the ssFSE MR images provides good contrast between CSF and brain structures

and can demonstrate the different layers of the developing brain and the formation of sulci as the brain matures[23]

Gradient echo sequences are a faster alternative (≈20-25 seconds) to ssFSE sequences as scan times are reduced by smaller variable flip angles that allow shorter repetition times (TR). Steady State balanced gradient echo sequences (Fast Imaging Employing Steady-state Imaging - FIESTA, GE Healthcare, Milwaukee) produces images with high SNR that are less sensitive to motion than the ssFSE but require a larger field of view as they are susceptible to band artefacts, particularly at air/tissue interfaces. Because of the ultrashort TR used, resultant contrast is not based on the T1 and T2 relaxation times of tissues but rather on the ratio of T1 to T2. As a result signal from muscle and other tissues appear dark but the high signal of both liquids and fat appear very bright.[24] This means that the FIESTA provides limited contrast between the different components within the brain, particularly as there is little resultant contrast between grey and white matter or the transient layers within the cortex.[25] For this reason we no longer routinely acquire 2D FIESTA images of the fetal brain but keep the sequence in reserve for cases where there is persistent fetal movement. We do, however, use 3D volume FIESTA sequences as they can be acquired in similar scan times to the 2D FIESTA but have the advantage of being able to be used post acquisition for reformatting into orthogonal and non-orthogonal anatomical planes. Additionally, whilst the resultant contrast of the FIESTA has limited value for assessing the brain parenchyma, it is excellent at demonstrating CSF and tissue boundaries a feature that aids our method for quantitative analysis of brain growth[26] (described later).

T1W Imaging

T1 weighted imaging remains a challenge for fetal MR, although some manufacturers have made better progress than others. The high water content in all parts of the developing brain provide little T1 contrast between brain parenchyma and CSF and the transient layers within the cortex (figure 9). Maximising those differences is difficult when scan times need to be as short as possible. T1W images are possible using ultrafast gradient echo sequences but due to longer acquisition times they are more prone to movement artefact than ssFSE. Image resolution is also limited in order to keep scan time as short as possible. Because of this, T1W images are used to make gross assessment rather than delineate smaller anatomical structures. For example, T1W sequences are mainly used to detect haemorrhage, fat and microcalcification.[27] T1W imaging in the third trimester is used to demonstrate signal changes from the myelination process, particularly when it is abnormal, as it manifests on T1W images before T2W images.[28] 3D SPGR (spoiled gradient echo) T1 sequences, designed for postnatal abdominal and liver studies, have also been adapted and applied to demonstrate the T1 contrast in fetal imaging studies. This high resolution sequence is achieved in ultrashort scan times due to short TR/TE times, parallel imaging and partial k-space filling methods. T1 contrast is maximised by an inversion pulse and fat suppression, the optimal flip angle being automatically selected so that when the centre of k-space is filled the signal from fat is null.[29] 3DSPGR sequences are even more prone to movement artefact than 2D T1 imaging as the data to fill the whole of k-space is acquired in one acquisition.

Fast Fluid Attenuated Inversion Recovery (FLAIR)

FLAIR sequences can be useful in clarifying areas of signal change and sometimes provide T1 information, but like T1 imaging it has a long acquisition time and therefore tends to be affected more by movement[30]

Diffusion weighted imaging (DWI)

DWI measures the random thermal Brownian motion of water molecules within tissues by applying strong gradients either side of the 180° pulse in the three orthogonal axes during an EPI spin echo sequence.[30] The apparent diffusion coefficient (ADC) provides a measure of the magnitude of this diffusion process (i.e. the mean displacement of a molecule during the application of the diffusion gradients) and differs for different body fluids and tissues.[31] It is possible to alter the diffusion weighting by changing the b-value, which adjusts the strength, duration, and spacing of the diffusion gradients. b-values are reduced for *in utero* DWI with values of b0 and b700 ms/mm^2 compared to b values of b0 and b1000 ms/mm^2 used in adult neuroimaging. DWI has become invaluable postnatally for the evaluation of pathological processes such as tumours and ischaemia, as normal diffusion is altered enabling visualisation of changes that are not always clearly identified on routine structural MR imaging.[32,33] Diagnostic *in utero* DWI is frequently inhibited by fetal and maternal motion but normal ADC values for the developing fetal brain have been successfully measured and reported.[34] DWI is able to provide useful information about the brain as it is able to demonstrate the developing layers within the cortex (figure 10) and changes in diffusion demonstrated by signal change on DWI MR images can highlight developmental pathology[35] (figure 11).

Advanced MR Imaging Techniques

Many of the advanced MR methods that are used in adult/pediatric clinical practice and research studies have been modified for use in iuMR of the fetal brain as described below.

MR Spectroscopy

Biochemical changes in the brain can be measured using MR spectroscopy (MRS) by interrogating tissue for the presence and concentration of different metabolites.[36] The ability to measure the metabolite concentrations in the fetal brain is hindered by the long acquisition

time (≈3-5 minutes) increasing the likelihood of fetal movement. Any fetal movement during MR acquisition will cause the spatial location of the voxel to change, possibly to one outside of the fetal brain. This causes contamination to the different resonate frequencies of each metabolite, resulting in loss of differentiation between the representative peaks in the resultant spectra.

MRS of the fetal brain is usually achieved using a single voxel and either a PRESS sequence using a long TE (figures 12 and 13) or with a STEAM sequence which can measure metabolites with a short T2* using a short echo time.[37]

In utero metabolite concentrations measured in normal fetuses have been found to be the same as those measured in preterm infants[38,39]and that as the brain matures N-acetylaspartate and creatine increase but levels of myo-inositol and choline decrease[40]. Studies involving fetuses with congenital heart disease found that this increase in N-acetylaspartate is slower than in healthy fetuses and often accompanied by evidence of cerebral lactate, a marker for hypoxia[41] The number of fetuses examined by these studies is very limited and further work is required to establish the concentrations of each metabolite at each gestational age and to determine the clinical relevance of changes to metabolite levels.

Diffusion tensor imaging

Diffusion tensor imaging (DTI) and tractography is a novel method of magnetic resonance imaging capable of investigating the neural networks and connections within the brain.[42] DTI is a form of DWI that harnesses the anisotropic direction of water along axons. Initially it was thought this inherent anisotropy was due to Myelin but is now thought to be due to the membrane integrity around axons.[43] The amplitudes and directions of diffusion along different axons or fibres are depicted using different colours. By using the diffusion

information sophisticated post processing has also made it possible to create 3D fibre tracts (tractography) that are projected onto brain images. The theoretical value of DTI is the ability to demonstrate failed or dysmorphic neural connections that could be the cause of conditions such as schizophrenia.[44] DTI in the fetus remains challenging. A study by Mitter et al[45] was only able to achieve successful mapping of fibre tracts in 20% of fetuses examined using DTI. In a reproducibility study by Jakab *et al* [46] fibre tracking using DTI data was possible in a higher percentage of the 30 cases studied, with a higher success rate for demonstrating the fibre tracks of the corpus callosum genu (76%) than than the fibre tracks of the brain stem (40%). This success rate may improve even further with emerging motion corrected methods such as those proposed by Marami *et al*[47] and Fogtmann *et al*[48] but the challenge of successful DTI studies means that it remains a research tool for the foreseeable future.

Motion correction of Fetal Imaging

The spatial mis-registration that can occur as a result of fetal movement between each individual imaging slice acquired using the ssFSE sequence has led to the development of motion correction methods that are retrospectively applied to the MR data. Using image registration software, developed specifically for this purpose, the boundaries of the anatomy on each image slice from one acquisition are aligned to create a complete motion free dataset.[49-51] An improvement on this method uses a two-step process which, in addition to the matching of slices from a single orientation, images from multiple acquisitions of different orientations are combined. The alignment of each slice is also aided by matching the signal intensities of different anatomical areas within the fetal brain. As a result of this slice to volume reconstruction method high resolution 3D datasets are created.[52-54] The ability to successfully correct for fetal motion in ssFSE sequences has led to its increasing application

to other iuMR sequences such as DWI[55], DTI[48] and fMRI[56] providing new insights into the developing fetal brain.

Measurement of Fetal Brain Volume

Quantitative analysis of fetal brain growth has been shown to be possible using two different methods. One method uses predefined, 3D atlases of the fetal brain created using the motion correction technique described previously. The 3D atlases act as template to guide automatic segmentation of anatomical areas using advanced software and to calculate the volumes of each.[57-64] Although this technique has been shown to be effective, it is limited. Automatic segmentation methods are based on templates created from imaging data of healthy fetuses and have yet to be applied reliably in cases where fetal development is not following normal trajectory of growth or has abnormal development. Additionally, the software and expertise to develop the sophisticated computer software is rarely available in clinical situations.

Another method used for quantitative analysis involves acquiring an MR data set of the fetal brain using a 3D FIESTA volume acquisition.[65,66] It is possible to use the resultant 3D data to identify and manually segment anatomical areas of the fetal brain and intracranial compartments using open source software (3D Slicer http://www.slicer.org[67]). This creates label maps of each anatomical area from which the information is used to create electronic 3D surface models of the fetal brain. The software is also able to determine the size of each brain segmented by multiplying the number of voxels by the voxel size in each region of interest. The primary advantage of this method is that it is not reliant on predefined templates therefore can be used to quantify brain size in both normally developing fetuses and those affected by structural abnormalities. Our group has been able to build up a database of normative volume data from 200 fetuses using this method (figure 14)[68] and this information has been vital to demonstrate how brain size is altered when abnormalities are present.[69]

The Requirement for Normative MR Data Sets

Many of those methods move away from making specific neuropathological structural diagnoses in individual fetuses and towards acquiring data that will be used in population studies. For example, it is possible to hypothesise that brain volumes in fetuses with non-neurological abnormalities (such as congenital cardiac disease) may be smaller than expected. In this situation, it is an absolute requirement to have large volumes of data from a population of normal fetuses for comparison on a group basis. Some data is now available for some of the advanced methods but such studies are expensive, time intensive and often difficult to recruit into. Another issue that is raised by this approach is quality control. It is usually possible to judge if structural fetal MR images are of sufficient quality for diagnostic purposes (although it is difficult to apply non-subjective criteria) but this may be exceptionally difficult for studies such as DTI and BOLD-based fMR studies that have been attempted *in utero*.

In spite of those reservations, advanced imaging methods allow the possibility to improve our understanding of brain development and potentially improve the diagnosis of brain abnormalities *in utero*. However, most still remain within the realms of research and will continue to do so until the software and/or hardware are widely available and the techniques can be applied in routine clinical practice. Additionally, further work is required to acquire data from low risk fetuses to establish normal appearances or, in the case of quantitative imaging, establish reference values. A key limitation of fetal imaging is that normative data is either lacking, is drawn from limited numbers or restricted to a narrow range of gestational ages. Frequently, normal reference data has also been acquired from fetuses who were referred for MR imaging due to a suspected abnormality such as mild VM, following USS, that was subsequently excluded. Alternatively, reference data has been taken from fetuses

who have a known abnormality that is not thought to effect brain development e.g. abdominal abnormalities. [61,62] It is questionable that data from these groups can be considered 'normal' as there is a risk that the brain is affected to some unknown extent.

Summary

The use of MR to image the fetal brain during pregnancy has become an established part of ante-natal care. A range of ultrafast imaging methods have been developed on all manufacturers' platforms that reliably show brain abnormalities in the fetus and there is good evidence that this improves diagnostic accuracy and confidence when attempting to diagnose structural fetal neuropathology. The development and evaluation of advanced MR methods, such as volumetric analysis, diffusion tensor imaging, proton spectroscopy, is under way with the aim of enabling the detection of neuropathology before it has overt structural sequelae. These methods are difficult to implement in the fetus and will need to be matched with large-scale studies of normal fetuses and strict quality control methods in order to evaluate their clinical value.

References

1. Rossi AC, and Prefumo F. Additional value of fetal magnetic resonance imaging in the prenatal diagnosis of central nervous system anomalies: a systematic review of the literature. Ultrasound Obstet Gynecol 2014; 44(4):388–93

2. Van Doorn M, Oude Rengerink K, Newsum EA, Reneman L, Majoie CB, Pajkrt E.Added value of fetal MRI in foetuses with suspected brain abnormalities on neurosonography: a systematic review and meta-analysis. J Matern Fetal Neonatal Med 2015; 29(18):2949-61

3. Jarvis D, Mooney C, Cohen J, Papaioannou D, Bradburn M, Sutton A, et al. A systematic review and meta-analysis to determine the contribution of MR imaging to

the diagnosis of foetal brain abnormalities In Utero. European Radiology 2017: 27(6): 2367–2380.

4. Griffiths PD, Bradburn M, Campbell MJ, Cooper CL, Graham R, Jarvis D, et al. Use of MRI in the diagnosis of fetal brain abnormalities in utero (MERIDIAN): a multicentre, prospective cohort study. The Lancet 2017;389(10068):538-46.

5. Radulescu M, Ulmeanu EC, Nedelea M, Oncescu A. Prenatal ultrasound diagnosis of neural tube defects. Pictorial essay. Medical ultrasonography. 2012;14(2):147-53.

6. Volpe P, Campobasso G, De Robertis V, Rembouskos G. Disorders of prosencephalic development. Prenatal Diagnosis. 2009;29(4):340-54.

7. Volpe P, Paladini D, Resta M, Stanziano A, Salvatore M, Quarantelli M, et al. Characteristics, associations and outcome of partial agenesis of the corpus callosum in the fetus. Ultrasound in Obstetrics & Gynecology. 2006;27(5):509-16.

8. Barkovich AJ, Kuzniecky RI, Jackson GD, Guerrini R, Dobyns WB. Classification system for malformations of cortical development - Update 2001. Neurology. 2001;57(12):2168-78.

9. Barkovich AJ, Kuzniecky RI, Jackson GD, Guerrini R, Dobyns WB. A developmental and genetic classification for malformations of cortical development. Neurology. 2005;65(12):1873-87.

10. European Surveillance of Congenital Anomalies EUROCAT. Prevelance Tables for Nervous system anomalies (per 10,000 births): EUROCAT; 2012 http://www.eurocatnetwork.eu/accessprevalencedata/prevalencetables.Accessed 02/07/2018

11. Boyd PA, Tonks AM, Rankin J, Rounding C, Wellesley D, Draper ES, et al. Monitoring the prenatal detection of structural fetal congenital anomalies in England and Wales: register-based study. Journal of Medical Screening. 2011;18(1):2-7.

12. Kagan KO, Staboulidou I, Syngelaki A, Cruz J, Nicolaides KH. The 11-13-week scan: diagnosis and outcome of holoprosencephaly, exomphalos and megacystis. Ultrasound in Obstetrics & Gynecology. 2010;36(1):10-4.

13. Levine D. MR imaging of fetal central nervous system abnormalities. Brain and Cognition. 2002;50(3):432-48.

14. Connolly DJA, Batty R, Mooney C, Jarvis D, Griffiths PD. A review of fetal brain pathology 'acquired' in utero and estimates of prevalence from the MERIDIAN cohort. Under review Neurographics

15. Griffiths PD, Brackley K, Bradburn M, Connolly DJA, Gawne-Cain ML, Griffiths DI, et al. Anatomical subgroup analysis of the MERIDIAN cohort: ventriculomegaly. Ultrasound in Obstetrics and Gynecology. 2017;50(6):736-44.

16. Levine D, Barnes PD, Madsen JR, Li W, Edelman RR. Fetal central nervous system anomalies: MR imaging augments sonographic diagnosis. Radiology. 1997;204(3):635-42

17. Clements H, Duncan KR, Fielding K, Gowland PA, Johnson IR, Baker PN. Infants exposed to MRI in utero have a normal paediatric assessment at 9 months of age. The British Journal of Radiology. 2000;73(866):190-4.

18. Reeves MJ, Brandreth M, Whitby EH, Hart AR, Paley MN, Griffiths PD, et al. Neonatal cochlear function: measurement after exposure to acoustic noise during in utero MR imaging. Radiology. 2010;257(3):802-9.

19. Bouyssi-Kobar, M., Du Plessis, A.J., Robertson, R.L. and Limperopoulos, C. Fetal magnetic resonance imaging: exposure times and functional outcomes at preschool age. Pediatric Radiology. 2015: 45(12):1823-1830.

20. MHRA. Safety Guidelines for Magnetic Resonance Imaging Equipment in ClinicalUse.https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/476931/MRI_guidance_2015-_4-02d1.pdf, Agency MaHPR; 2015. Report No.: v4.2

21. Kanal E, Barkovich AJ, Bell C, Borgstede JP, Bradley WG, Jr., Froelich JW, et al. ACR guidance document on MR safe practices: 2013. Journal of Magnetic Resonance Imaging. 2013;37(3):501-30.

22. Prayer D, Brugger PC, Prayer L. Fetal MRI: techniques and protocols. Pediatric Radiology. 2004;34(9):685-93

23. Glenn OA, Barkovich J. Magnetic resonance imaging of the fetal brain and spine: an increasingly important tool in prenatal diagnosis: part 2. AJNR American Journal of Neuroradiology. 2006;27(9):1807-14.

24. Chavhan GB, Babyn PS, Jankharia BG, Cheng HL, Shroff MM. Steady-state MR imaging sequences: physics, classification, and clinical applications. Radiographics 2008;28(4):1147-60.

25. Scheffler K, Lehnhardt S. Principles and applications of balanced SSFP techniques. European Radiology. 2003;13(11):2409-18.

26. Griffiths PD, Jarvis D, McQuillan H, Williams F, Paley M, Armitage P. MRI of the foetal brain using a rapid 3D steady-state sequence. The British Journal of Radiology. 2013;86(1030):20130168.

27. Girard N, Gire C, Sigaudy S, Porcu G, d'Ercole C, Figarella-Branger D, et al. MR imaging of acquired fetal brain disorders. Childs Nerv Syst. 2003;19(7-8):490-500.

28. Gholipour A, Estroff J A. Barnewolt C E. Robertson R L.Grant P. E. Gagoski Borjanet al. Fetal MRI: A technical update with educational aspirations. Concepts in Magnetic Resonance Part A. 2014;43(6):237-66.

29. Li, X. H., Zhu, J. , Zhang, X. M., Ji, Y. F., Chen, T. W., Huang, X. H., Yang, L. and Zeng, N. L. Abdominal MRI at 3.0 T: LAVA-flex compared with conventional fat suppression T1-weighted images. J. Magn. Reson. Imaging, 2014;40: 58-66.

30. Bushong S. Magnetic Resonance Imaging Physical and Biological Principles. Third Edition ed. St. Louis, Missouri: Mosby; 2003.pp 1-511

31. Bammer R. Basic principles of diffusion-weighted imaging. European Journal of Radiology. 2003;45(3):169-84

32. Desprechins B, Stadnik T, Koerts G, Shabana W, Breucq C, Osteaux M. Use of Diffusion-Weighted MR Imaging in Differential Diagnosis Between Intracerebral

Necrotic Tumors and Cerebral Abscesses. American Journal of Neuroradiology. 1999;20(7):1252-7.

33. Lövblad KO, Laubach HJ, Baird AE, Curtin F, Schlaug G, Edelman RR, et al. Clinical experience with diffusion-weighted MR in patients with acute stroke. American Journal of Neuroradiology.1998;19(6):1061-6.

34. Cannie M, De Keyzer F, Meersschaert J, Jani J, Lewi L, Deprest J, et al. A diffusion-weighted template for gestational age-related apparent diffusion coefficient values in the developing fetal brain. Ultrasound in Obstetrics & Gynecology 2007;30(3):318-24

35. Guimiot F, Garel C, Fallet-Bianco C, Menez F, Khung-Savatovsky S, Oury J-F, et al. Contribution of Diffusion-Weighted Imaging in the Evaluation of Diffuse White Matter Ischemic Lesions in Fetuses: Correlations with Fetopathologic Findings. American Journal of Neuroradiology. 2008;29(1):110-5.

36. Maheshwari SR, Fatterpekar GM, Castillo M, Mukherji SK. Proton MR spectroscopy of the brain. Seminars in Ultrasound, CT and MRI. 2000;21(6):434-51.

37. V. Berger-Kulemann, P.C. Brugger, D. Pugash, M. Krssak, M. Weber, A. Wielandner, and D. Prayer MR Spectroscopy of the Fetal Brain:Is It Possible without Sedation? Am J Neuroradiol. 2013;34:424 –31

38. Kok R D. van den Berg P. van den Bergh A. Nijland R. Heerschap A. Maturation of the human fetal brain as observed by 1H MR spectroscopy. Magnetic Resonance in Medicine. 2002;48(4):611-6.

39. Heerschap, A., Kok, R.D. & van den Berg, P.P. Antenatal proton MR spectroscopy of the human brain in vivo. Childs Nerv Syst. 2003; 19(7-8): 418-421.

40. Girard, N. , Gouny, S. C., Viola, A. , Le Fur, Y. , Viout, P. , Chaumoitre, K. , D'Ercole, C. , Gire, C. , Figarella-Branger, D. and Cozzone, P. J. Assessment of normal fetal brain maturation in utero by proton magnetic resonance spectroscopy. Magn. Reson. Med.,2006; 56(4): 768-775.

41. Limperopoulos C, Tworetzky W, McElhinney DB, Newburger JW, Brown DW, Robertson RL, et al. Brain Volume and Metabolism in Fetuses With Congenital Heart Disease. Evaluation With Quantitative Magnetic Resonance Imaging and Spectroscopy. Circulation 2010;121(1):26-33.

42. Mori S, Zhang J. Principles of Diffusion Tensor Imaging and Its Applications to Basic Neuroscience Research. Neuron. 2006;51(5):527-39.

43. Beaulieu C, Allen PS. Determinants of anisotropic water diffusion in nerves. Magn Reson Med. 1994; 31(4):394–400. PMID: 8208115

44. Kubicki, M. , Westin, C. , McCarley, R. W. and Shenton, M. E. The Application of DTI to Investigate White Matter Abnormalities in Schizophrenia. Annals of the New York Academy of Sciences.2005:1064: 134-148.

45. Mitter C, Prayer D, Brugger PC, Weber M, Kasprian G In Vivo Tractography of Fetal Association Fibers. PLoS ONE:. 2015: 10(3): e0119536.

46. Jakab, A., Tuura, R., Kellenberger, C. and Scheer, I. In utero diffusion tensor imaging of the fetal brain: A reproducibility study. NeuroImage: Clinical: 2017: (15).601-612.

47. Marami, B., Salehi, S.S.M., Afacan, O., Scherrer, B., Rollins, C.K., Yang, E., Estroff, J.A., Warfield, S.K. and Gholipour, A.. Temporal slice registration and robust diffusion-tensor reconstruction for improved fetal brain structural connectivity analysis. NeuroImage, 2017: (156) 475-488.

48. Fogtmann, M., Seshamani, S., Kroenke, C., Cheng, X., Chapman, T., Wilm, J., Rousseau, F. and Studholme, C., A unified approach to diffusion direction sensitive slice registration and 3-D DTI reconstruction from moving fetal brain anatomy. IEEE Transactions on Medical Imaging, 2014:33(2),.272-289.

49. Kuklisova-Murgasova M, Quaghebeur G, Rutherford MA, Hajnal JV, Schnabel JA. Reconstruction of fetal brain MRI with intensity matching and complete outlier removal. Medical Image Analysis. 2012;16(8):1550-64.

50. Rousseau F, Glenn OA, Iordanova B, Rodriguez-Carranza C, Vigneron DB, Barkovich JA, et al. Registration-based approach for reconstruction of high-resolution in utero fetal MR brain images. Academic Radiology. 2006;13(9):1072-81.

51. Jiang SZ, Xue H, Glover A, Rutherford M, Hajnal JV. A novel approach to accurate 3D high resolution and high SNR fetal brain imaging. 3rd Ieee International Symposium on Biomedical Imaging: Macro to Nano, 2006; 1-3. 662-5.

52. Gholipour A, Estroff JA, Warfield SK. Robust super-resolution volume reconstruction from slice acquisitions: application to fetal brain MRI. IEEE Transactions on Medical Imaging. 2010;29(10):1739-58.

53. Kainz B, Steinberger M, Wein W, Kuklisova-Murgasova M, et al Fast Volume Reconstruction From Motion Corrupted Stacks of 2D Slices. IEEE Transactions on Medical Imaging. 2015:34(9):1901-1913

54. Gholipour, A., Rollins, C.K., Velasco-Annis, C., Ouaalam, A., Akhondi-Asl, A., Afacan, O., Ortinau, C.M., Clancy, S., Limperopoulos, C., Yang, E. and Estroff, J.A.. A normative spatiotemporal MRI atlas of the fetal brain for automatic segmentation and analysis of early brain growth. Scientific Reports,2017: 7(1):476

55. Hutter, J., Christiaens, D., Schneider, T., Cordero-Grande, L., Slator, P.J., Deprez, M., Price, A.N., Tournier, D., Rutherford, M. and Hajnal, J.V. Slice-level diffusion encoding for motion and distortion correction. Medical Image Analysis.2018:48:214-229

56. Ferrazzi, G., Murgasova, M.K., Arichi, T., Malamateniou, C., Fox, M.J., Makropoulos, A., Allsop, J., Rutherford, M., Malik, S., Aljabar, P. and Hajnal, J.V., 2014. Resting state fMRI in the moving fetus: a robust framework for motion, bias field and spin history correction. Neuroimage, 2014;101(1):555-568.

57. Habas PA, Kim K, Corbett-Detig JM, Rousseau F, Glenn OA, Barkovich AJ, et al. A spatiotemporal atlas of MR intensity, tissue probability and shape of the fetal brain with application to segmentation. NeuroImage. 2010;53(2):460-70.

58. Campadelli P., Casiraghi E., Lombardi G., Serrao G. 3D Volume Reconstruction and Biometric Analysis of Fetal Brain from MR Images. In: Masulli F., Tagliaferri R., Verkhivker G.M. (eds) Computational Intelligence Methods for Bioinformatics and Biostatistics. CIBB 2008. Lecture Notes in Computer Science, 2009:(5488). Springer, Berlin, Heidelberg

59. Habas PA, Kim K, Rousseau F, Glenn OA, Barkovich AJ, Studholme C. Atlas-based segmentation of developing tissues in the human brain with quantitative validation in young fetuses. Human Brain Mapping. 2010;31(9):1348-58

60. Wright R, Vatansever D, Kyriakopoulou V, Ledig C, Wolz R, Serag A, et al. Age dependent fetal MR segmentation using manual and automated approaches. MICCAI workshop on Perinatal and Paediatric Imaging. 2012:97-104.

61. Gholipour A, Estroff JA, Barnewolt CE, Connolly SA, Warfield SK. Fetal brain volumetry through MRI volumetric reconstruction and segmentation. International Journal of Computer Assisted Radiology and Surgery. 2011;6(3):329-39

62. Scott JA, Habas PA, Kim K, Rajagopalan V, Hamzelou KS, Corbett-Detig JM, et al. Growth trajectories of the human fetal brain tissues estimated from 3D reconstructed in utero MRI. International Society for Developmental Neuroscience. 2011;29(5):529-36.

63. Wright, R., Kyriakopoulou, V., Ledig, C., Rutherford, M.A., Hajnal, J.V., Rueckert, D. and Aljabar, P., 2014. Automatic quantification of normal cortical folding patterns from fetal brain MRI. NeuroImage. 2014;(91):21-32

64. Kyriakopoulou, V., Vatansever, D., Davidson, A., Patkee, P., Elkommos, S., Chew, A., Martinez-Biarge, M., Hagberg, B., Damodaram, M., Allsop, J. and Fox, M. Normative biometry of the fetal brain using magnetic resonance imaging. Brain Structure and Function. 2017; 222(5):2295-2307.

65. Link D, Braginsky M, B, Joskowicz L, Ben Sira L, Harel S, Many A, Tarrasch R, Malinger G, Artzi M, Kapoor C, Miller E, Ben Bashat D, Automatic Measurement of Fetal Brain Development from Magnetic Resonance Imaging: New Reference Data. Fetal Diagn Ther 2018;43:113-122

66. Griffiths PD, Jarvis D, McQuillan H, Williams F, Paley M, Armitage P. MRI of the foetal brain using a rapid 3D steady-state sequence. The British Journal of Radiology. 2013;86(1030):20130168.

67. Fedorov A, Beichel R, Kalpathy-Cramer J, Finet J, Fillion-Robin JC, Pujol S, et al. 3D Slicer as an image computing platform for the Quantitative Imaging Network. Magnetic Resonance Imaging. 2012;30(9):1323-41.

68. Jarvis D, Akram R, Mandefield L, Paddock M, Armitage P, Griffiths PD. Quantification of total fetal brain volume using 3D MR imaging data acquired in utero. Prenatal Diagnosis. 2016;36(13):1225-32.

69. Jarvis D, Griffiths PD. Clinical applications of 3D volume MR imaging of the fetal brain in utero. Prenatal Diagnosis. 2017;37(6):55

Table 1.

From: Johnson AC, McNabb AR, Rossiter RJ. Concentration of lipids in the brain of infants and adults. J Biochem 1949 44:494-499

	Mature brain: grey matter	**Mature brain: white matter**	**Pre-myelinated brain: grey matter**	**Pre-myelinated brain: white matter**
Water content	84%	71%	90%	91%
Sphingomyelin content	0.53%	2.00%	0.12%	0.13%

Table 2. Typical MR parameters used for fetal imaging (1.5T GE Healthcare, Milwaukee)

	T2 ssFSE	T2 FSE	3D FIESTA	DWI	FLAIR	T1	MOVIE
Repetition Time	Minimum (2000)	Minimum (4.2)	Minimum (4.4)	4000	Minimum (2700)	Minimum (6.2)	4.6
Time to Echo	120	Minimum (2.2)	Minimum (2.4)	Minimum	122	Minimum (3.3)	3
Flip Angle	-	70	60	-	-	45	45
Bandwidth(KHz)	37	100	125	250	41	31	166
Inversion Time	-	-	-	-	2000	-	-
PREP TIME	-	-	-	-	-	2000	-
NEX	1	1	0.75	4	0.5	1	1
Slice Thickness/ Slice Gap (mm)	4/0	3/0.3	2.0 - 2.6/0	4/0.5	4/0.4	4/0	18
Field of View (Adjusted to patient)	32x32	38x34	32x26	40x36	35x35	38x32	42x42

Freq/ Phase Matrix	256/256	384/256	320/256	128/128	256/192	192/128	192/256
B Value				600-800			-
Approx. Scan Time (Secs)	32	92	21	64	54	51	50

Figure 1. A schematic showing the important developmental events during pregnancy and the timings of routine imaging events in the United Kingdom.

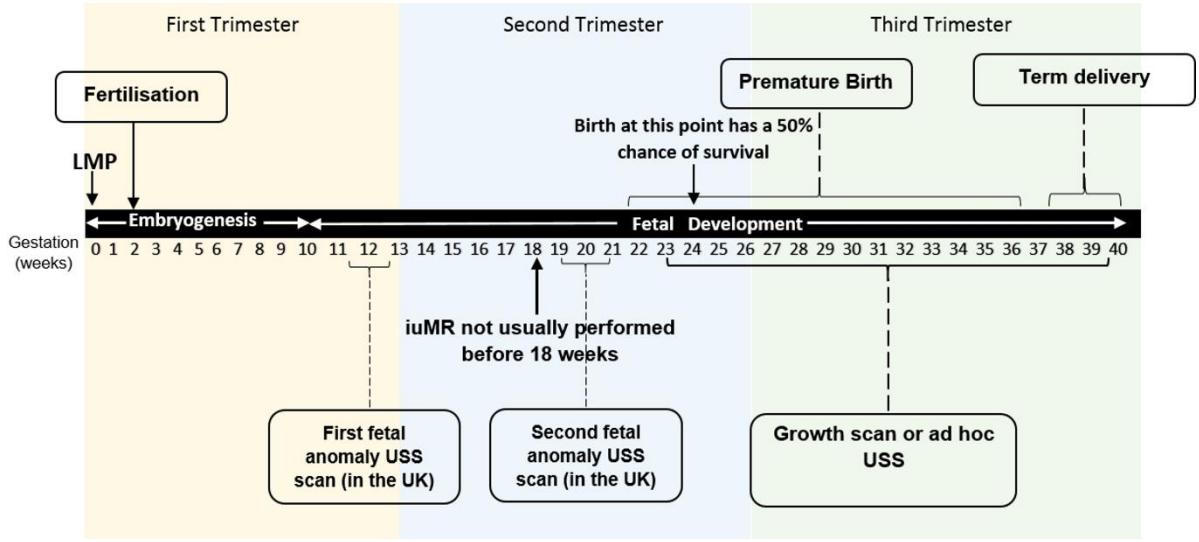


Figure 2. Coronal T2-weighted image (ssFSE) of a fetus at 22 gestational weeks (2a) showing the transient layers of the developing cerebral hemispheres alongside a brain section from a fetus at equivalent gestational age (2b). The transient layers are formed by the migration of neurons and glia from the ventricular zone (germinal matrix) to the cortical plate. Figure 2b is reproduced with permission by Griffiths, P et al. Atlas of Fetal and Postnatal Brain MR, MOSBY, Elsevier.

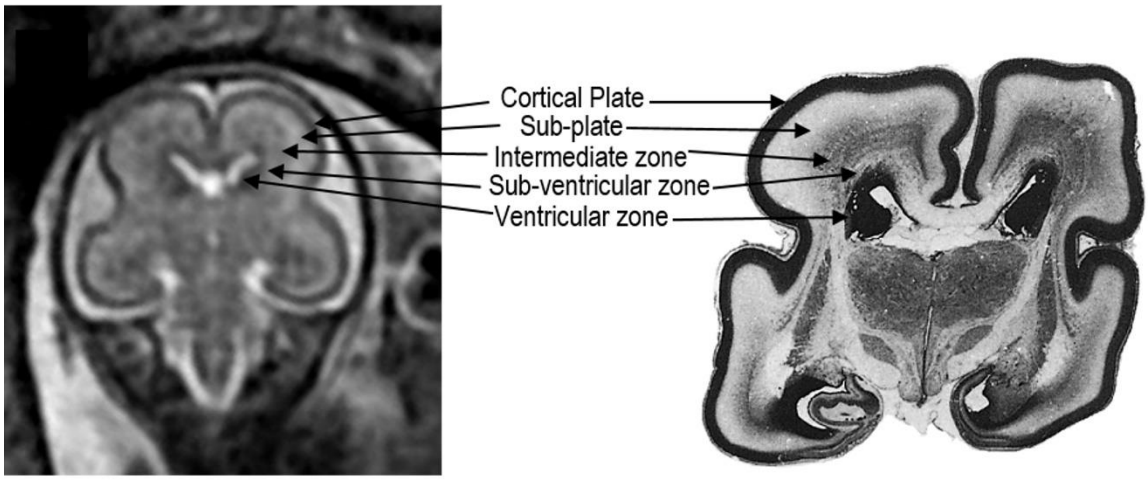


Figure 3. An example of failed primary neurulation in a fetus at 28 gestational weeks. Sagittal (3a and 3b) and axial (3c) T2-weighted images (ssFSE) show a midline cystic abnormality (arrowed on 3a and 3c) related to the occipital bone. There is a small bony defect in the skull (arrowed on 3b) and, although the brain does not protrude into the cyst, there are some soft tissue components (star on 3a) which are probably duro-venous structures. Diagnosis - meningocoele.

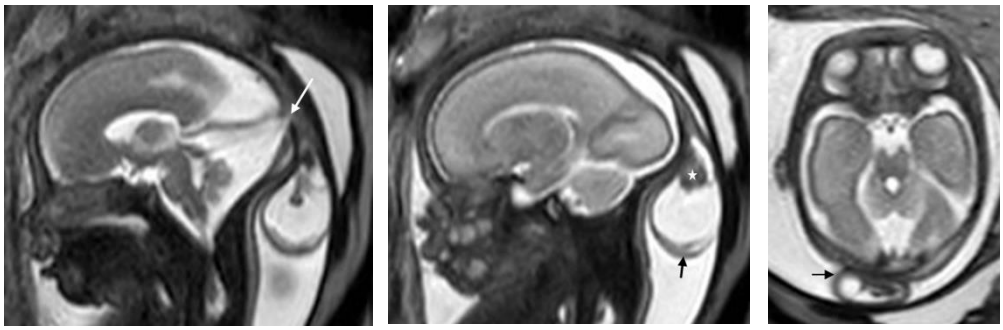


Figure 4. An example of failed ventral induction in a fetus at 21 gestational weeks. Coronal (4a), axial (4b) and sagittal (4c) T2-weighted images (ssFSE) show failure of separation of the cerebral hemispheres (arrowed on 4a and 4c) and underdeveloped frontal lobes (star on 4b).

4d-4f are frontal, superior and left lateral projections of the fetal brain surfaces obtained from a 3D FIESTA sequence. Diagnosis – semilobar holoprosencephaly.

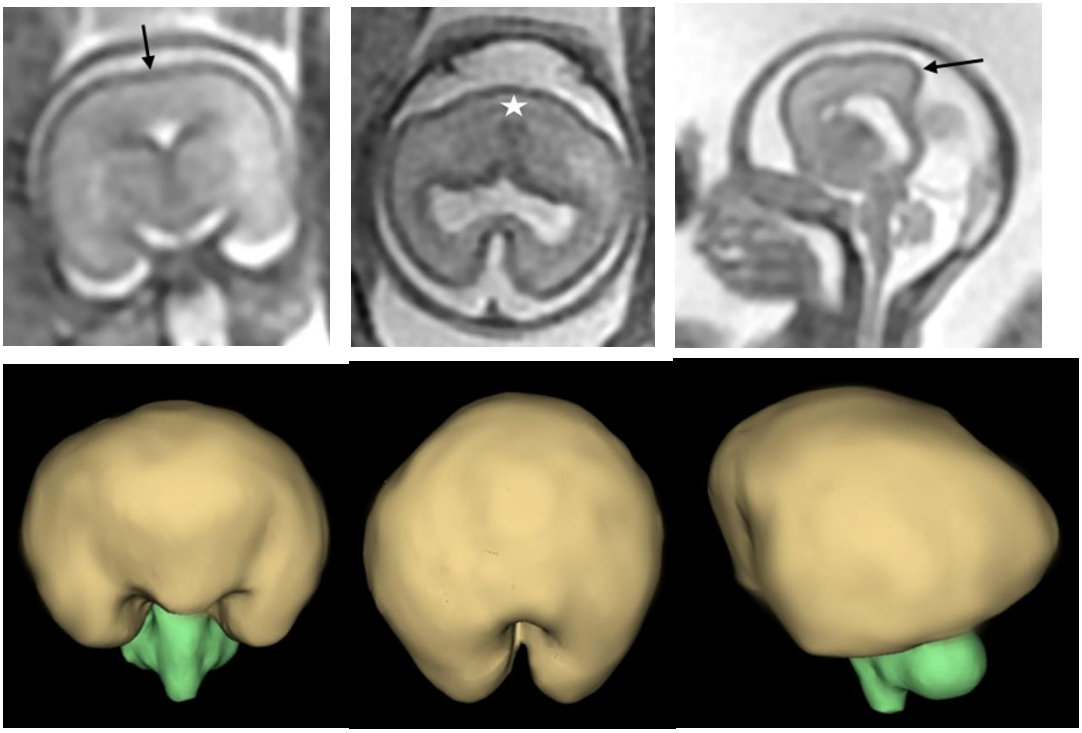


Figure 5. An example of failed commissuration in a fetus at 25 gestational weeks. Sagittal (5a), coronal (5b) and axial (5c) T2-weighted images (ssFSE) show absence of the corpus callosum associated with a midline interhemispheric cyst (compare with the equivalent images from a normal fetus (5d-5f). The left cerebral hemisphere is also abnormal see (figure 11). Diagnosis – agenesis of the corpus callosum and cortical formation abnormality.

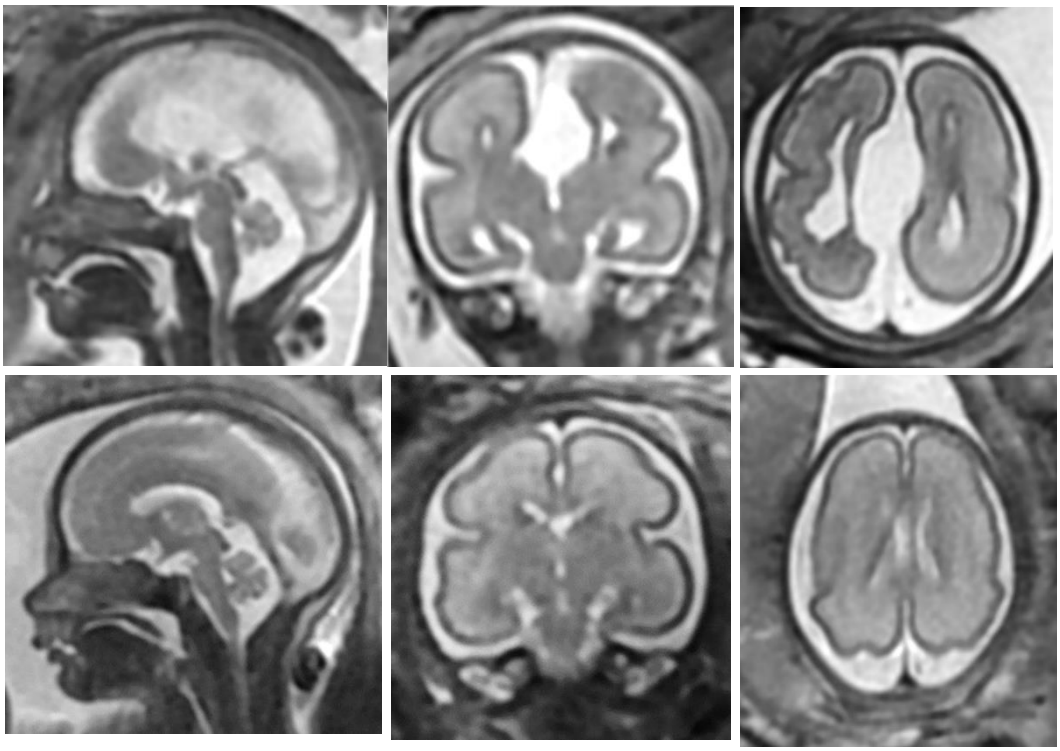


Figure 6. Three fetuses with abnormal migration of neurons/glia producing different varieties of heterotopia. Sub-ependymal heterotopia is shown in the left occipital horn (arrowed on 6a), nodular trans-mantle heterotopia (arrowed on 6b) and band heterotopia (arrows on 6c). All of these result from failure of normal passage of neurons from the ventricular zone to the cortical plate.

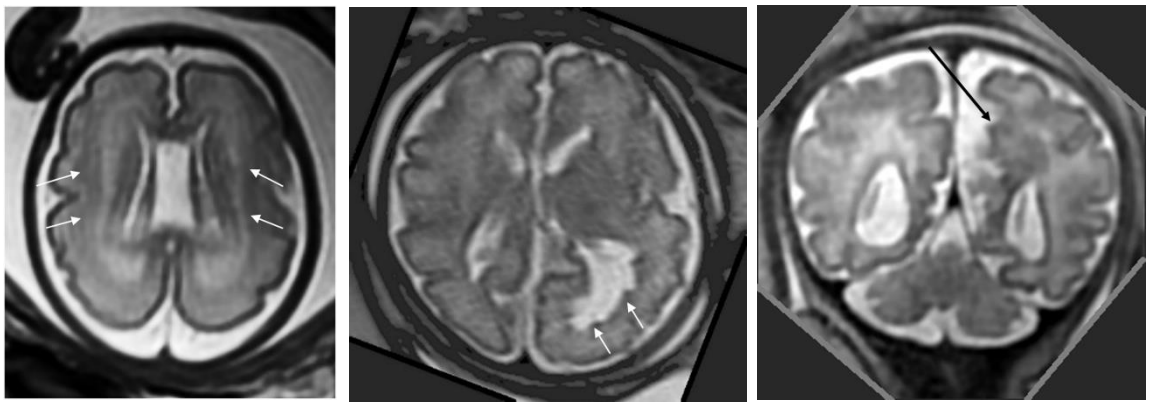


Figure 7. An example of failed cortical organisation in a fetus at 32 gestational weeks. Coronal (7a) and axial (7b and 7c) T2-weighted images (ssFSE) show abnormalities in both hemispheres but the right hemisphere shows more severe features. There is generally reduced sulcation in the right hemisphere with a irregular cortical plate (arrowed on 7a and 7c) and an abnormal superior extension of the sylvian fissure (arrowed on 7b). Diagnosis – bilateral asymmetric polymicrogyria.

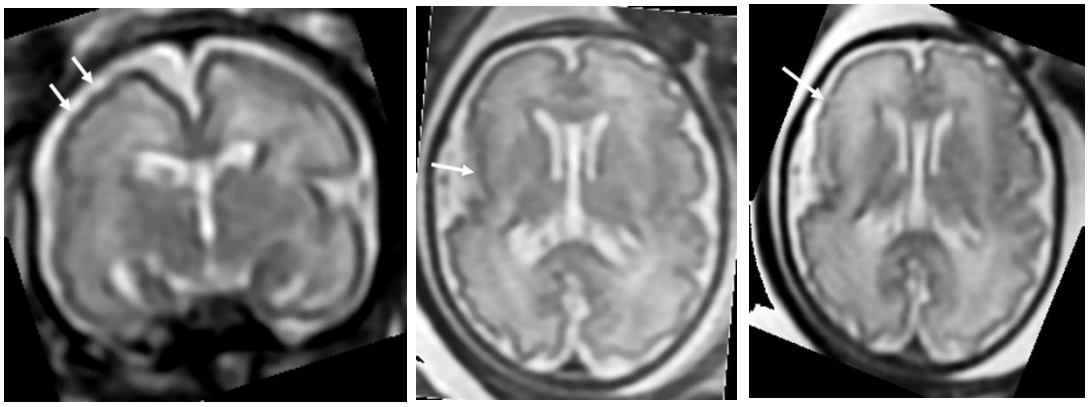


Figure 8. An example of acquired brain pathology in a fetus at 21 gestational weeks. Axial (8a and 8b) coronal (8c) and sagittal (8d) T2-weighted images (ssFSE) show two areas of low signal, one in the right cerebellar hemisphere (arrowed on 8a) and the other in the right peri-trigonal white matter (arrowed on 8b-8d). These areas are consistent with sub-acute haemorrhage although no specific cause was found.

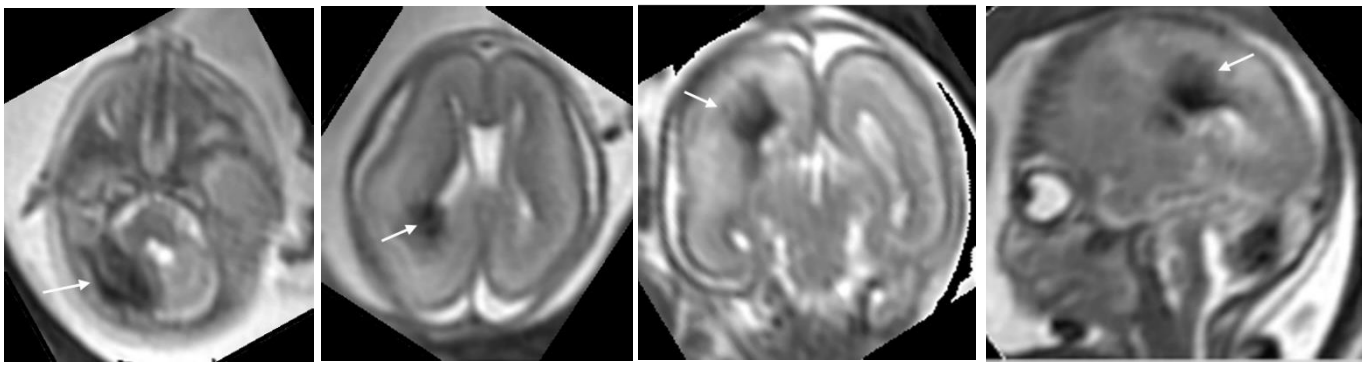


Figure 9. Axial T1-weighted images (9a-9c) in a fetus at 27 gestational weeks (courtesy of Dr C. Landes, Alder Hey Hospital Liverpool).

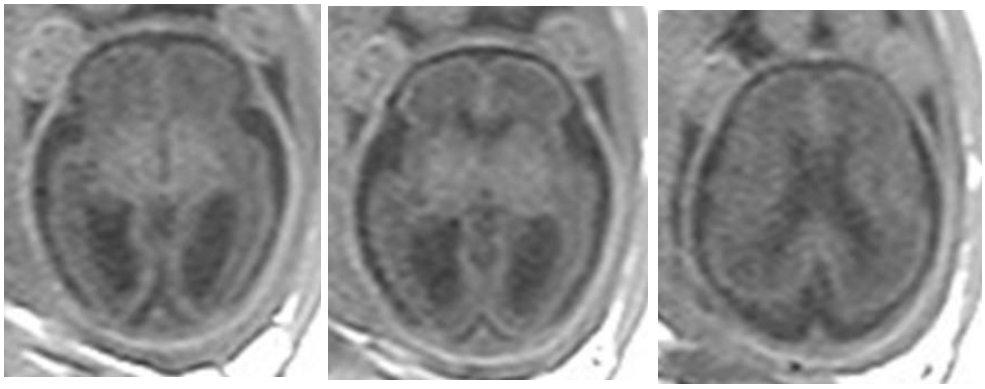


Figure 10. Axial brain sections (10a-10c) from a fetus with no structural brain abnormality at 22 gestational weeks showing the normal prominent transient layers. Those features can be difficult to show on ssFSE images (10d-10f) but are well shown on diffusion weighted imaging (10g-10i). The cell dense regions show restricted diffusion when compared to the cell sparse zones. Figures 10a-10c are reproduced with permission by Griffiths, P et al. Atlas of Fetal and Postnatal Brain MR, MOSBY, Elsevier (30).

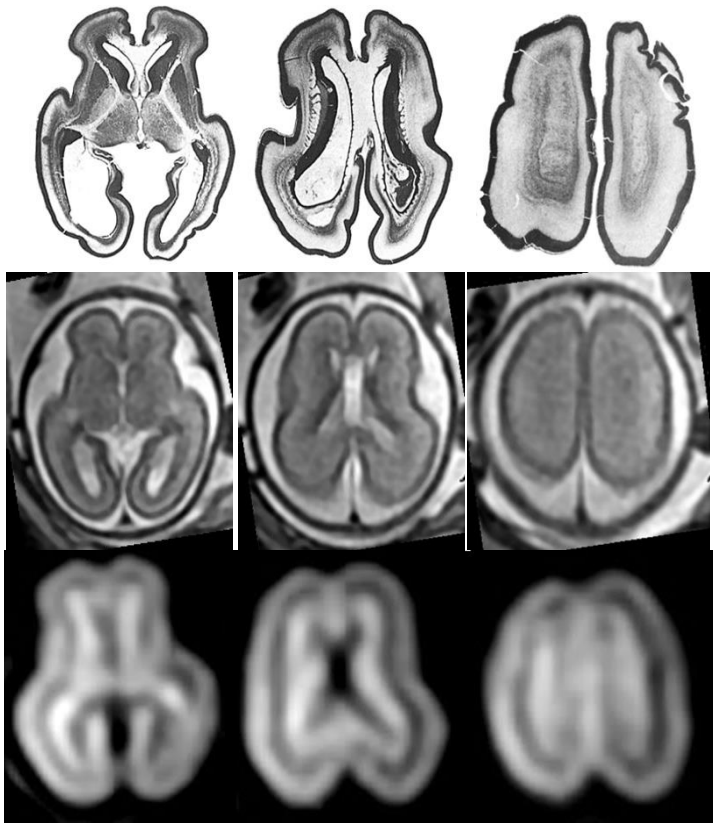


Figure 11. Same case as figure 5, a fetus with agenesis of the corpus callosum and a cortical formation abnormality in the left cerebral hemisphere. Axial T2-weighted image (11a) shows abnormal sulcation in the superior part of the left hemisphere whilst diffusion weighted images (11b) and ADC map (11c) shows extensive restricted diffusion in the abnormal hemisphere due to excess abnormally migrating neurons.

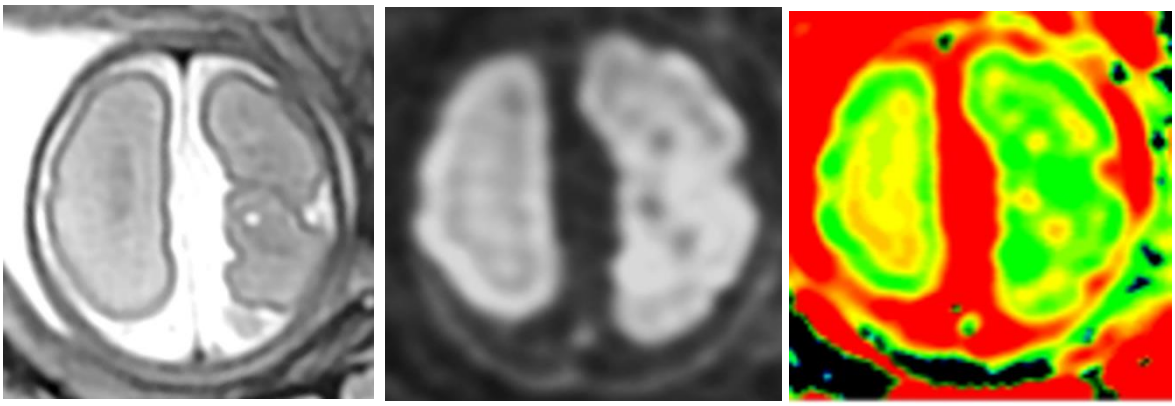
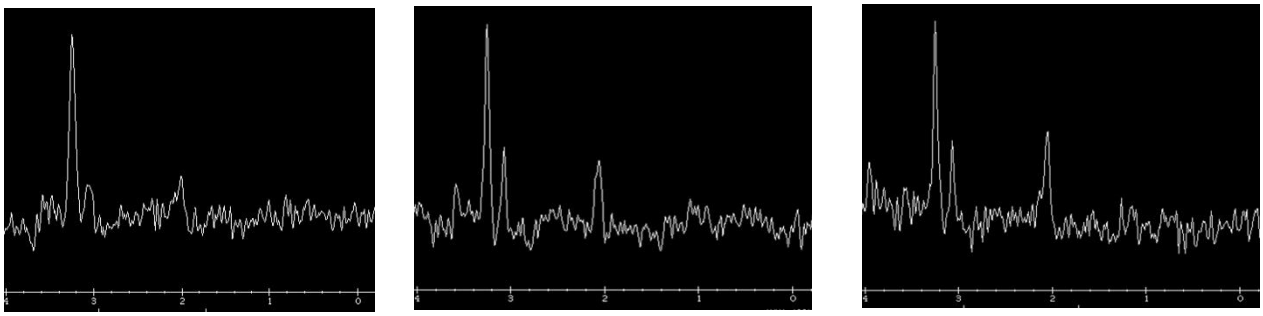


Figure 12. Single voxel proton spectroscopy (TE 144ms) from the basal ganglia and surrounding tissue in fetuses at 23 (12a), 29 (12b) and 35 (12c) gestational weeks. Note that there is a prominent choline peak at 23 weeks but the creatine and N-acetylaspartate peaks are barely discernible from the baseline. By 29 weeks the creatine and N-acetylaspartate peaks are much better resolved with the N-acetylaspartate peaks being slight smaller than the creatine although that is reversed at 35 weeks.



#Figure 13. In utero MR imaging in a recently demised fetus. This was twin pregnancy in which both fetuses were alive two days before the iuMR study was performed (25 gestational weeks). The axial T2-weighted image (13a - ssFSE) shows generalised swelling of the brain with poor contrast between the brain structures and an axial diffusion weighted image shows generalised restricted diffusion whilst single voxel proton spectroscopy (TE 144ms) shows a prominent inverted doublet due to lactate.

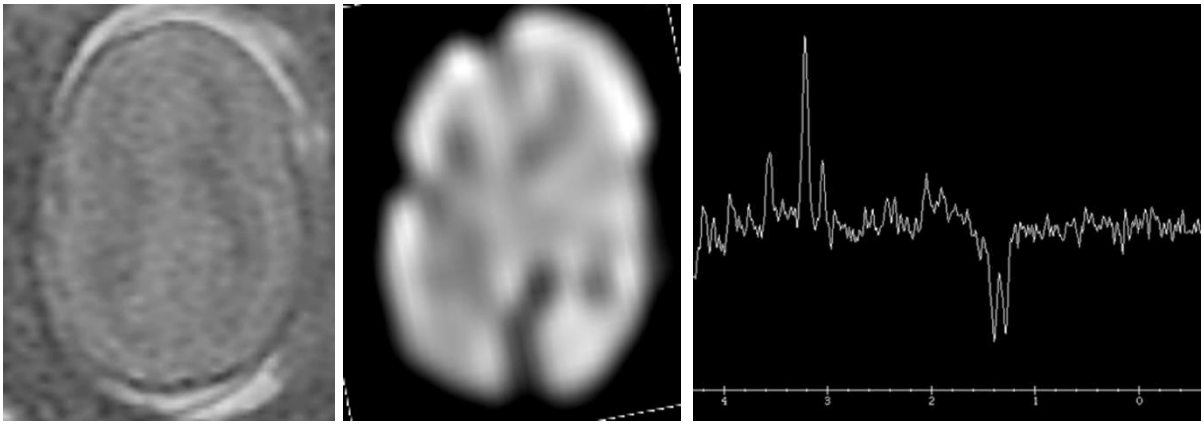


Figure 14. A graph showing the mean, 95% confidence intervals and 95% prediction intervals for brain volumes measured on 3D FIESTA sequences in normal fetuses ranging from 18-37 gestational weeks along with left lateral projections of the brain showing changes in sulcation during that period.