The University Of Sheffield.

Magnetic Resonance Imaging to Enhance the Diagnosis of Fetal Brain Abnormalities *in utero*

Deborah Ann Jarvis

A Thesis Submitted in Fulfilment of the Requirements for the Degree of Doctor of Philosophy

July 2017

Faculty of Medicine Dentistry and Health

Department of Infection, Immunity and Cardiovascular Science

Acknowledgements

I would like to express my sincere gratitude to my supervisors Professor Paul Griffiths and Dr Paul Armitage for their exceptional guidance, support and for being so accessible throughout my Ph.D. study. I want to thank Professor Griffiths for the many opportunities he has given me during his supervision of this work. His patience, motivation, and the generous amount of time he has invested to share his vast knowledge and answer my endless questions is very much appreciated. I want to thank Dr Paul Armitage who has managed to teach me enough of his immense knowledge of software and image processing to make this research possible and whose calm, patient and reassuring approach has given me clarity and motivation at significant points when I have needed it.

I am also thankful to all those in Academic Radiology for their help and words of support and encouragement throughout. Special thanks go to my fellow Radiographers whose camaraderie, encouraging banter and essential coffee making services have been vital for the completion of this work. To Julia Bigley and Pam Greenwood for the time they have given to read this manuscript, for their helpful comments and correction of grammatical errors I am also very thankful. I would also like to thank Leanne Armstrong for her excellent administration and organisation of study data which has made several aspects of this research so much easier. I also wish to thank the staff at ScHARR for their guidance regarding the systematic review, Mike Bradburn for statistical input, and in particular Cara Mooney for her efficient management of the MERIDIAN study, her help collating study data and the time invested being second reviewer for the systematic review for which I am incredibly grateful.

Finally, I would like to thank my family for their support, encouragement and their understanding when I have been busy working instead of spending time with them. Most of all I thank my amazingly patient and understanding husband Neil whose constant encouragement and unwavering belief in me throughout this PhD has given me the determination to finish. Thank you.

Abstract

Purpose

This thesis aims to determine the diagnostic performance of in utero MR (iuMR) imaging to diagnose fetal brain abnormalities and describes the development, application and processing of a 3D volume MR acquisition.

Methods

A systematic review and meta-analysis of existing evidence was conducted. A prospective multicentre study of pregnant women, with a fetal brain abnormality on ultrasound (USS), was undertaken – The MERIDIAN study. In addition, an investigation of fetuses with no brain abnormality on USS was undertaken. Diagnostic accuracy and confidence, as well as positive and negative predictive values, were calculated. A 3D image acquisition technique was introduced, its ability to aid diagnosis measured and computational post-processing applied. Fetal brain volumes were extracted from the 3D data using image segmentation and these were assessed for reproducibility and validity. Resultant data allowed 3D models of fetal brains to be printed. Normally developing fetal brain volumes were plotted graphically thereby allowing comparison with abnormal fetuses.

Results

A total of 570 complete datasets were available from 903 eligible participants. Diagnostic accuracy was 68% for USS and 93% for iuMR. 95% of diagnoses made by iuMR were reported with high confidence compared to 82% on USS. Changes in pregnancy management occurred in 33% of cases. Positive and negative predictive values of iuMR were 93% and 99.5% respectively. 3D image quality was diagnostic in 89.6%, of which 91.4% gave an accurate diagnosis. Intra- and inter-observer agreement of brain volume measurements was high. Agreement between computer based and brain model volume measurements was also high.

Conclusions

iuMR imaging improves diagnostic accuracy and confidence for fetal brain abnormalities, influencing pregnancy management in a high proportion of cases. 3D imaging enables versatile visualisation of fetal brain anatomy and reliable extraction of volumes. This additional quantitative information could improve diagnosis in relevant cases.

Contents

Abbreviations

2D	Two dimensional
3D	Three dimensional
ADC	Apparent diffusion coefficient
ACC	Agenesis of the corpus callosum
AUR	Academic unit of radiology
BPD	Biparietal diameter
CC	Corpus callosum
CNS	Central nervous system
CMV	Cytomegalovirus
CNR	Contrast to noise ratio
CSF	Cerebrospinal fluid
CT	Computed tomography
DAMR	Diagnostic accuracy MR
DAUS	Diagnostic accuracy USS
DWM	Dandy walker malformation
DWI	Diffusion weighted imaging
FIESTA	Fast imaging employing Steady sTate acquisition
FLAIR	Fluid attenuated inversion recovery
HPE	Holoprosencephaly
HTA	Health technology assessment
ICC	Intraclass correlation coefficient
IuMR	*In utero* magnetic resonance
MR	Magnetic resonance
NICE	National institute of health and care excellence
NIHR	National institute of health and research
NPV	Negative predictive value
OFD	Occipital frontal diameter
ORD	Outcome reference diagnosis
PF	Posterior fossa
PPV	Positive predictive value
PRISMA	Preferred reporting items for systematic reviews and meta-analyses
PROM	Premature rupture of the membranes
PROSPERO	International prospective register of systematic reviews

PVL	Periventicular leukomalacia
QALY	Quality adjusted life years
QUADAS	Quality assessment of diagnostic accuracy studies
RF	Radiofrequency
SAR	Specific absorption rate
ScHARR	School of Health and Related Research, University of Sheffield
SNR	Signal to noise ratio
ssFSE	Single shot fast spin echo
SWA	Score based weighted analysis
T1W	T1 weighted images
T2W	T2 weighted images
TBV	Total brain volume
TE	Time to echo
TI	Time interval
TICV	Total intracranial volume
TR	Recovery time
TTTS	Twin to twin transfusion syndrome
USS	Ultrasound scan(ing)
VM	Ventriculomegaly
VV	Ventricular system volumes
ZIP	Zero filling of k-space

List of Figures

List of Tables

Thesis Aims and Overview

The use of magnetic resonance for imaging the fetal brain *in utero* (iuMR) has grown significantly over the last 15 years and has become an integral part of the prenatal assessment when abnormalities are suspected following prenatal ultrasound scanning (USS). In spite of this increase the evidence to support its additional value remains unclear. IuMR imaging technology has also advanced enabling the possibility of ultrafast acquisitions beyond 2D imaging, potentially increasing information regarding fetal brain development and improving diagnosis. The aim of this research is to determine the diagnostic performance of iuMR as an adjunct to USS, and consists of two separate, but related parts:

1. To measure the ability of iuMR to improve the diagnostic accuracy and diagnostic confidence over ante-natal USS for the detection of fetal brain abnormalities.
2. To report the development, application and clinical evaluation of a 3D volume iuMR acquisition for fetal brain imaging.

At the start of this research there had been no formal, unbiased assessment to determine the additional value of using iuMR imaging as an adjunct to USS for the diagnosis of fetal brain abnormalities, despite a significant increase of its use over the last 10-15 years.
The first part of this work evaluated the multiple studies already carried out in this field by undertaking a systematic review and meta-analysis (Chapter 2). Although this was undertaken concurrently with our study to investigate the additional benefit of iuMR (the MERIDIAN study, reported in Chapter 3), it was able to provide a baseline with which the results of MERIDIAN could be compared. The review protocol followed established guidelines to ensure a thorough and complete assessment of all the relevant literature. Our aim was to ascertain the improvement in diagnostic accuracy due to iuMR imaging in the diagnostic pathway and to identify the strengths and weaknesses of iuMR in terms of

abnormalities diagnosed more or less consistently than USS. Although multiple studies had been published only 34 met our inclusion criteria and due to small study numbers and methodological weaknesses there was still a need to clarify the additional benefit of iuMR. The Academic Unit of Radiology, University of Sheffield was one of the first sites in the UK to develop and implement MR imaging of the fetus *in utero*. As one of the leading centres, we were given the opportunity to undertake MERIDIAN, a large UK multi-centre study to evaluate the diagnostic impact of iuMR imaging, following prenatal USS, in order to direct future clinical practice. The study was funded by the NIHR as part of their Health Technology Assessment program. MERIDIAN was a large multi-centre prospective study that was appropriately powered, provided a comprehensive assessment of iuMR imaging and addressed the methodological weaknesses of previous studies.

Although determining the diagnostic accuracy of iuMR in comparison to USS was the primary aim of MERIDIAN, an evaluation of the confidence with which the diagnoses were made by both iuMR and USS, and its ultimate effect, was a unique and highly relevant part of the study. This, along with an assessment of the changes in management of pregnancies as a result of iuMR gives a more complete view of the benefit of iuMR. The project took a further development when it became apparent that, in order to fully compare the diagnostic capabilities of both USS and iuMR, the positive and negative predictive values of both modalities needed to be established. Neither MERIDIAN nor any of the studies included in the systematic review recruited women whose fetus were considered normal by USS. The MERIDIAN Add-on study (Chapter 4) was therefore undertaken in order to recruit a cohort of normally developing fetuses to establish the true negative capability of both USS and iuMR imaging. For this part of the research we recruited a cohort of 200 pregnant women in whom the fetus had no abnormalities identified on routine USS and who subsequently underwent fetal brain iuMR imaging.

Improvements in MR imaging technology have allowed the possibility of the long acquisition times normally required for advanced MR sequences to be reduced making them a realistic

option for fetal brain imaging. Alongside, but not as a requirement for MERIDIAN, this enabled us to develop and test a 3D MR volume sequence *in utero*. The resultant higher resolution and the option for reformatting post acquisition, allowed a more versatile way of examining fetal brain anatomy and resolving suspected abnormalities. A limitation of the 3D volume sequence is that fetal motion, however small, has a direct impact on the resultant image quality of the whole acquisition. As we initially only had anecdotal evidence of its 'success' we undertook a study to establish its reliability and ability to clearly depict the anatomy to facilitate accurate diagnosis (Chapter 5). As a result of incorporating the 3D acquisition into our routine fetal imaging protocol we have been able to reduce the number of 2D sequences.

The resultant MR data from the 3D volume acquisitions also initiated work to explore additional advanced post processing methods. Using open source software, we manually segmented the fetal brain from the surrounding anatomy, which allowed us initially to visualise the external surfaces of the developing brain as electronic 3D models. The same data was subsequently used to have 3D printed models produced by the department of Advanced Manufacturing within the University. The 3D printed models included a range of normal brains at different gestations and a range of brains affected by different abnormalities which we used to create a teaching file that could potentially be used to train future fetal neuroradiologists.

A further aim of post-processing the MR 3D volume acquisition was to analyse the fetal brain quantitatively. This had the potential to provide additional relevant information for diagnosing abnormalities. With this prospect in mind it was necessary to define reference values of 'normal' brain volume at each gestational age, which would utilise data from the MERIDIAN Add-on study which recruited a normal control cohort and included the necessary 3D volume iuMR acquisitions. We have subsequently processed and analysed 132 datasets, from which

the data was used to produce a reference chart of normal fetal brain growth, a unique aspect of this work (Chapter 6)

The final part of this work (Chapter 7) shows how the resultant electronic surface representations, 3D printed models and quantitative data has been used to review the most common brain abnormalities and to evaluate and analyse several clinical cases. This shows how the 3D acquisition and post processing techniques we have developed could be used in future clinical practice to improve diagnosis and highlights the potential for quantitative analysis of the fetal brain in future studies.

Peer Reviewed Publications Arising From the Thesis

1. 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.

2. Jarvis D, Armitage P, Dean A, Griffiths PD. Surface reconstructions of foetal brain abnormalities using ultrafast steady state 3D acquisitions. Clinical radiology. 2014;69(10):1084-91.

3. Griffiths PD, Jarvis D. In Utero MR Imaging of Fetal Holoprosencephaly: A Structured Approach to Diagnosis and Classification. AJNR American journal of neuroradiology. 2016;37(3):536-43.

4. 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.

5. Jarvis D, Griffiths P, Majewski C. Demonstration of Normal and Abnormal Fetal Brains Using 3D Printing from In Utero MR Imaging Data. American Journal of Neuroradiology. 2016;37(9):1757-61.

6. 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 fetal brain abnormalities In Utero. European radiology. 2017;27(6):2367-80.

7. Griffiths PD, Bradburn M, Campbell M, Connolly D, Cooper C, Jarvis D, *et al*. Change in diagnostic confidence brought about by using in utero MRI for fetal structural brain pathology: analysis of the MERIDIAN cohort. Clinical Radiology. 2017;72(6):451-7.

8. 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.

9. Paddock M, Akram R, Jarvis D, Griffiths PD *et al.* The assessment of fetal brain growth in diabetic pregnancy using in utero magnetic resonance imaging (iuMRI): A pilot study. Clinical Radiology. 2016;71:S30.

10. Jarvis D, Griffiths PD. Clinical applications of 3D volume MR imaging of the fetal brain in utero. Prenatal Diagnosis. 2017, 37, 556–565

Chapter 1

Introduction and Background

1.1 Summary

This chapter provides an overview of the range of neuropathology that occurs most frequently in the developing fetus, allowing an appreciation of the range of abnormalities that prenatal imaging aims to diagnose. This information is derived from existing literature, including textbooks, and is appropriately referenced. An overview of *in utero* imaging techniques, primarily iuMR, and the concept of diagnostic performance are also introduced. Again, this information is gleaned from the literature and from the author's own experience of MR imaging.

It is important to review the range of fetal brain abnormalities to become familiar with the common patterns of imaging findings, in order to make accurate diagnoses. The approach taken in this work has been to categorise abnormalities into 'developmental' and 'acquired' pathology of the fetal brain. Ventriculomegaly (VM) is discussed as a separate entity as it is the single most common cause for referral for iuMR imaging of the brain and it may result from several processes, both developmental and acquired.

1.2 Normal and Abnormal Development of the Brain

The development of the human brain involves many interrelated and overlapping processes, evolving to become the most complex organ in the body. Deviation from the normal pathway of development results in brain malformations that can have deleterious consequences for the fetus and, ultimately, the child/adult. Abnormalities of the fetal central nervous system occur in approximately 24 per 10,000 births in the UK (1, 2) and can be the result of genetic and chromosomal defects, exposure to potentially toxic substances (e.g. alcohol) and infections (e.g. Cytomegalovirus). An understanding of the normal and abnormal development of the brain is required to appreciate why both USS and iuMR are needed for antenatal imaging. Normal brain development of the cerebral hemispheres is often described as four processes: primary neurulation, ventral induction, commissuration and cortical

formation. There are many resultant abnormalities with various associations and combinations of anomalies that can occur. To discuss all these is beyond the scope of this work, therefore only the most common brain abnormalities are reviewed. A summary table (Table 1.1) of the images showing the abnormalities discussed in this chapter is given below.

Page	Table 1.1 Summary of the images showing pathology and the gestational age at which iuMR imaging was performed		
31	1.1 a	Axial T2W ssFSE image of a fetus with a defect in the skull affecting the pariato-occipital bones with resultant encephalocele.	19 weeks
31	1.1 b	Sagittal T2W ssFSE image of a fetus with a defect in the midline of the skull affecting the occipital bone with resultant encephalocele.	32 weeks
32	1.2 a	Coronal T2W image showing Alobar holoprosencephaly	19 weeks
32	1.2 b	Coronal T2W image showing semi-lobar holoprosencephaly	20 weeks
32	1.2 c	Axial T2W image showing lobar holoprosencephaly	19 weeks
32	1.2 d	Coronal T2W image of a normal fetus	20 weeks
34	1.3 a	Coronal T2W ssFSE showing a fetus with agenesis of the corpus callosum.	33 weeks
34	1.3 b	Coronal T2W ssFSE of a normal corpus callosum for comparison.	33 weeks
34	1.4 a	T2W coronal image of a fetus at 22 weeks gestation showing the dark signal band of the cortical plate and germinal matrix.	22 weeks
34	1.4 b	Pathology slide of a fetal brain showing the dark signal band of the cortical plate and germinal matrix.	22 weeks
35	1.5	Coronal T2W ssFSE image of a fetus with Hemimegalencephaly.	23 weeks
37	1.6	Axial T2W ssFSE showing a fetus with subpendymal heterotopia lining the ventricles.	32 weeks
38	1.7	Axial T2W image of a fetus with thick cortex and agyria as seen in Lissencephaly.	31 weeks
38	1.8	Coronal T2W image of a fetus with multiple abnormal small folds (arrow) typical of Polymicrogyria	28 weeks
39	1.9	Axial T2W ssFSE demonstrating clefts in the cortex (arrows) typical of open lipped Schizencephaly	33 weeks
40	1.1	Sagittal T2W image of a fetus with a Dandy Walker Malformation	21 weeks
42	1.11	Axial and sagittal T2 FIESTA images of a fetus with a myolmeningecole and Chiari II malformation.	32 weeks
44	1.12	Axial T2W image showing abnormal cerebellum and absent vermis typical of rhombencephalosynapsis	30 weeks
47	1.13	Axial and coronal T2 weighted ssFSE images of a with abnormalities as a result of CMV infection	30 weeks
48	1.14	Images of a fetus with Right temporal lobe subacute stroke as a result of alloimmune thrombocytopenia.	35 weeks
49	1.15	Sagittal and axial views showing an example of thrombus within the sagittal sinus	20 weeks
50	1.16	Sagittal, axial and coronal views showing polymicrogyria and infarction in a surviving twin of twin to twin transfusion syndrome.	25 weeks
53	1.17	Axial T2W demonstrating unilateral VM, with enlarged left ventricle.	26 weeks

1.2.1 Primary Neurulation

Primary neurulation occurs between 3 and 4 weeks gestation in humans and involves the formation and enclosure of the neural tube. Developmental problems result from failure of the neural tube to form or to close at the head end of the fetus (3). Anencephaly occurs when the neural tube fails to form at the cranial end, so the cranial vault and most of the brain is absent. This is usually diagnosed on USS (4).

Failure of the neural tube to close at the cranial end results in a group of abnormalities called cephaloceles. A Cephalocele is a defect in the skull which allows the intracranial contents (meninges, brain tissue or both) through but are encompassed in a membrane sac (figure 1.1). This occurs in 1 in 5000 live births (5). The sac contents, the effects on the remaining brain within the skull and any other associated abnormalities all have a bearing on the clinical outcome (3). A cephalocele is usually seen on USS but if the skull defect is small it can be misdiagnosed as a subcutaneous cyst or a cranial haemangioma (6). iuMR imaging can more accurately define the contents of a cephalocele and the appearance of the remaining brain, which has been found to be particularly helpful in parent counselling (7).

The failure of the neural tube to close at the caudal end causes the condition of myelomeningocele, resulting in a spinal defect, and often has a significant impact on brain development due to its association with Chiari 2 malformations (8) (discussed further in section 1.2.5).

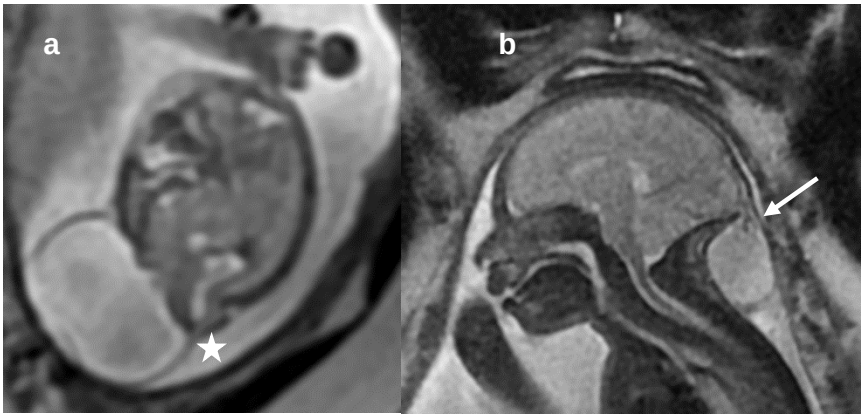


Figure 1.1 T2 weighted ssFSE images showing two examples of encephaloceles with associated cysts. (a) axial image of a fetus of 19 weeks gestation with a defect in the skull affecting the parieto-occipital bones with protrusion of the parietal/occipital lobes and the posterior lateral ventricles through the defect (star). (b) sagittal image of a fetus at 32 weeks gestation with a smaller defect in the midline of the occipital bone. Only a small portion of the occipital lobes protrude at the defect (arrow).

1.2.2 Ventral Induction

Ventral induction occurs between 5 and 7 weeks gestation and involves the differential growth of the forebrain structures (future cerebral hemispheres) and the sagittal cleavage of the brain. Failure of this process results in a range of abnormalities grouped as holoprosencephaly (HPE) (9). Alobar holoprosencephaly is the severest form, consists of no inter-hemispheric fissure or falx, and a single ventricle and forebrain with no attempt at sagittal cleavage (10). The olfactory bulbs and tracts do not develop and severe facial malformations are common (11). Semi-lobar HPE (Figure 1.2) is less severe and there may be an element of separation of the posterior hemispheres. The frontal horns of the lateral ventricles are absent, the interhemispheric fissure is incompletely formed, although there is some development of the mesial temporal structures. Lobar HPE is the mildest form of the disease. Separation of the cerebral hemispheres is almost normal. All other structures are present but may not be fully formed. HPE occurs in 1 in 1300 fetuses at 11- 13 weeks gestation and it may be related to increasing maternal age and chromosomal abnormalities.

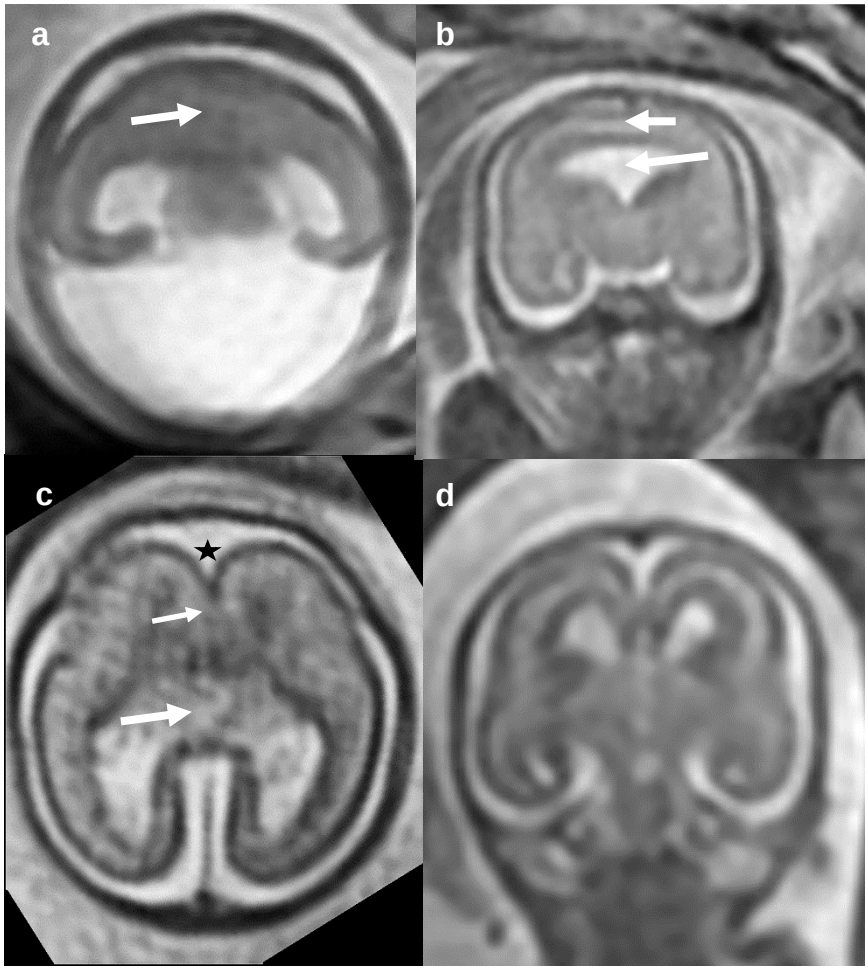


Figure 1.2 T2 weighted ssFSE images (a, b, coronal orientation and c axial) showing the different categories of HPE in fetuses of similar gestational ages. (a) Alobar- ontinuation of the cerebral cortex across the midline, arrow (b) semilobar, continuation of the cortex (small arrow) and a single ventricle (large arrow) across the midline (c) lobar holoprosencephaly- a degree of separation of the two hemispheres (star) with some continuation of the cortex and ventricle in the midline (arrows) and (d) shows a normally developing fetus for comparison.

The septum pellucidum is absent in all forms of HPE (12). Hypoplasia of the optic nerves is frequently found in cases of lobar HPE (11). Prenatal USS is able to detect the more severe forms of HPE but often has low sensitivity to lobar HPE, which is frequently misdiagnosed as isolated VM (13). iuMR has been shown to be more accurate in identifying all the different forms of HPE (14). It is essential that the iuMR imaging includes good quality coronal views as these are particularly useful to identify the different structures involved, a key sign being fusion of the hypothalamus.

1.2.3 Commissuration

Commissuration refers to the growth of axons that reconnect the cerebral hemispheres once they have been separated by ventral induction. There are several commissural pathways, but the corpus callosum (CC) is by far the largest and most important in terms of detecting brain malformations *in utero* (15). The CC is a wide, flat, bundle of axons that connect the homologous regions of the two hemispheres of the brain (16). Comissuration starts around 8 weeks and the CC is fully formed around 20 weeks gestation. There can be a complete failure of the CC to form (agenesis of the CC, Figure 1.3) or there may be a partial formation (hypogenesis of the CC (17).

Prognosis is variable, which makes prenatal counselling difficult. If, however, agenesis or hypogenesis of the CC occurs alongside other brain abnormalities then outcome, in terms of neurodevelopment, is worse (15, 16, 18, 19).The main associated brain abnormalities include cortical malformations and Dandy Walker malformations (20, 21),
The corpus callosum itself is difficult to visualise directly on USS unless using transvaginal probes, and instead relies on indirect signs to give an indication of its absence (15). The USS literature lists these signs as absent cavum septum pellucidum, widely displaced lateral ventricles, colpocephaly and upward displacement of the third ventricle (22). Hypogenesis is particularly difficult to detect on USS as the indirect signs are not always obvious (7). In contrast, the CC can be detected on iuMR imaging by direct visualisation in coronal and sagittal anatomical planes. The structure is seen as a band of low signal intensity in the midline. Several studies have shown that iuMR is superior to USS in detecting or excluding agenesis of the CC and in demonstrating other associated abnormalities (16, 17, 23-25).

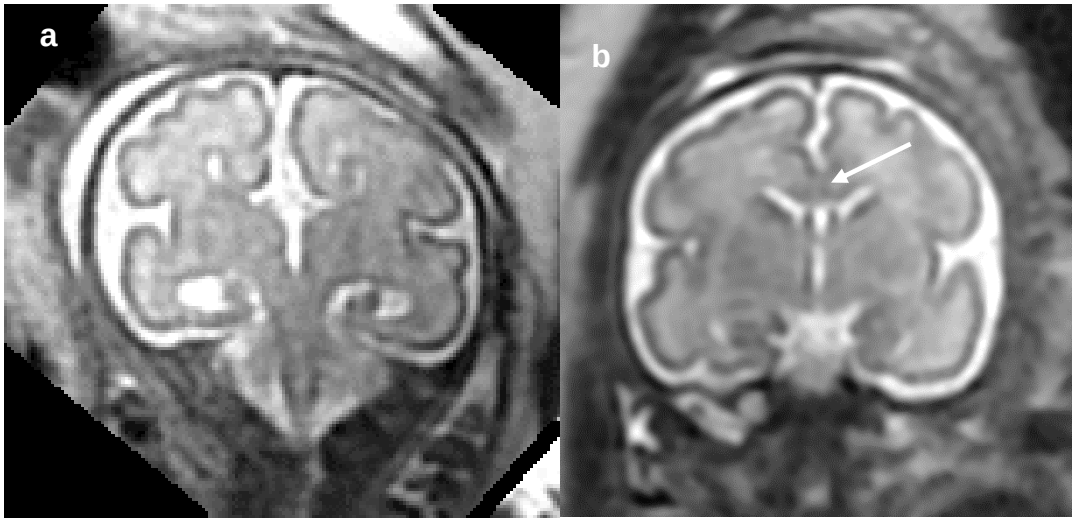


Figure 1.3 Coronal T2W ssFSE showing agenesis of the corpus callosum (a) and normal corpus callosum (b) (arrow)

1.2.4 Cortical Formation Abnormalities

Normal cortical development is by way of three overlapping stages: neuro-glial proliferation, migration and organisation (26). Each process is described below. Failure of any of these processes will produce a different type of cortical malformation (27). The normal fetal brain has several different layers of developing and migrating neurons and glia which can be identified on iuMR imaging. The outermost layer (the cortical plate), and the innermost layer (the germinal matrix), can both be seen as dark, low signal bands on T2-weighted (T2W) images (Figure 1.4) and bright high signal bands on T1-weighted (T2W) images (28). The adjacent white matter is seen as high signal on T2W and low signal on T1W images. These layers gradually disappear as the brain develops but the ability of iuMR to identify the cortical structure facilitates a greater sensitivity to developmental cortical abnormalities than ultrasound. (29).

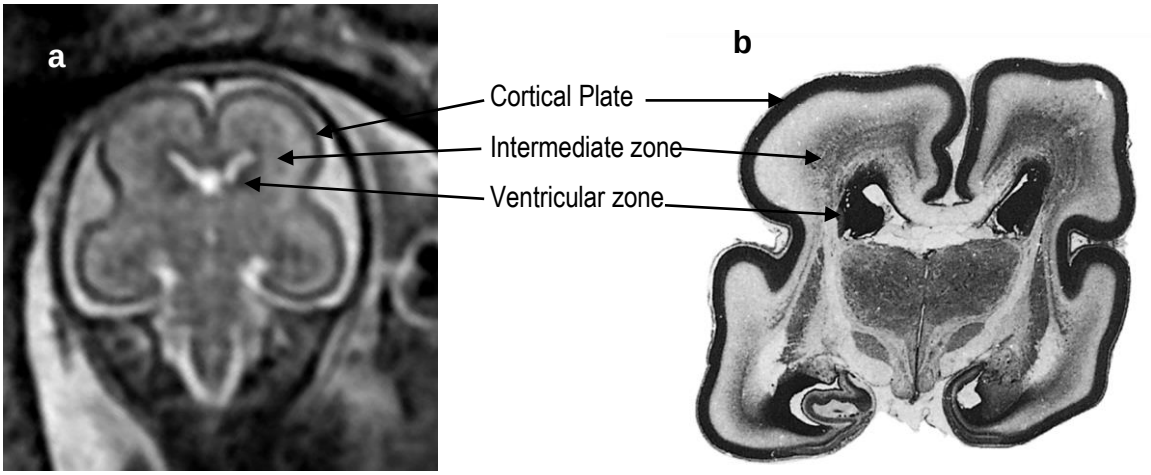


Figure 1.4 (a) Coronal T2 weighted ssFSE image of a fetus at 22 weeks gestational age showing the cortical layers and a pathology slide from a fetus at equivalent gestational age (b). Pathology slide reproduced with permission by Griffiths, P.et al (30) Atlas of Fetal and Postnatal Brain MR, MOSBY, Elsevier

Neuroglial proliferation starts at around 8 weeks gestation in the area of the brain closest to the ventricular system (ventricular layer or germinal matrix). Abnormal proliferation can involve either an over proliferation in neurons and glia, producing megalencephaly or an overall reduction resulting in microcephaly (3) .

The most common variety of megalencephaly involves only one hemisphere (hemimegalencephaly, Figure 1.5). As well as overgrowth, the neurons are structurally abnormal (large 'balloon' cells) and are usually associated with other brain abnormalities (31).

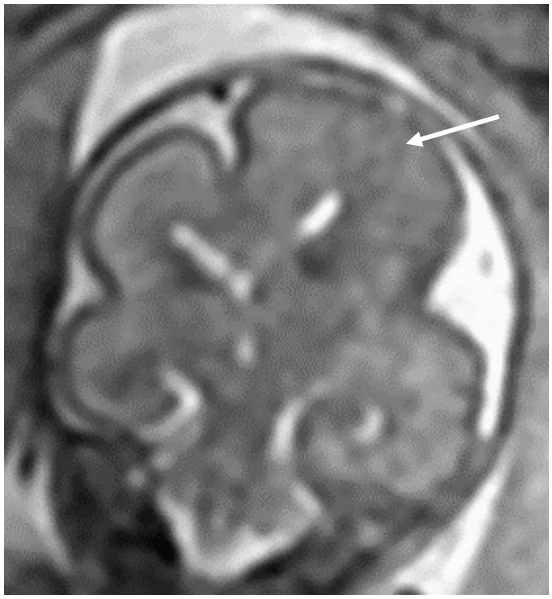


Figure 1.5 Coronal T2W ssFSE image of a 23 week old fetus with Hemimegalencephaly with the left hemisphere affected it being significantly larger than the right (arrow)

Megalencephaly is an increase in the size and weight of the whole brain (3). Hemimegalencephaly is less easy to diagnose on USS as it is characterised by a region of enlarged echogenic cortex that can easily be mistaken for tumour (32). Nakahashi *et al* (33) examined the ability of MR imaging to identify megalencephaly, hemimegalencephaly and the differential diagnosis of cortical dysplasia in 43 patients. They described imaging features suggestive of T1 and T2 shortening, abnormal large shallow gyri and poor cortical white matter differentiation in the hemimegalencephaly group. Diffusion weighted imaging has also been shown to demonstrate restricted diffusion due to the abnormal cell structures (34).

Microcephaly due to under proliferation is visualised as a small brain where the head circumference is 2 standard deviations below average for any given gestation. The reduction in head size is thought to be due to destructive processes, such as infections, or associated with developmental abnormalities. USS can accurately measure head size but iuMR is more

able to distinguish between the different destructive processes and provide additional information (35).

After proliferation the neurons must migrate from their periventricular position out towards the cortical plate (future cerebral cortex). They are guided by radial glial fibres and detach when they reach their correct place in the cerebral cortex (31). Failure of this process results in heterotopia or lissencephaly. Heterotopia occurs when neurons fail to migrate to their correct locations within the cortex. Subependymal heterotopia can be single or multiple clusters of neurons and appear as nodules lining the ventricular wall. Subcortical heterotopia are found within the cortex at any location, usually with an abnormal sulcal pattern, and are often the cause of epilepsy. Distinctive banding is another form of subcortical heterotopia that gives the appearance of a double cortex (36). Heterotopia are easier to diagnose on iuMR imaging than with USS, particularly when they are subependymal. They are hyperintense on T1W and hypointense on T2W MR imaging (37). They also appear isointense to the cortex. Periventricular heterotopia are seen as nodules along the edges of the ventricle (Figure 1.6). They have the same signal as grey matter on both T1 and T2W MR imaging, are associated with other pathology, and are more easily detected on MR than USS (38). IuMR is more accurate at detecting heterotopia if seen on two imaging planes and if the fetus is older than 24 weeks gestation (39). Associated features of subcortical heterotopias seen on MR imaging include: reduced size of the affected hemisphere in unilateral heterotopia, decreased white matter, and thinned overlying cortex with abnormal sulci (40).

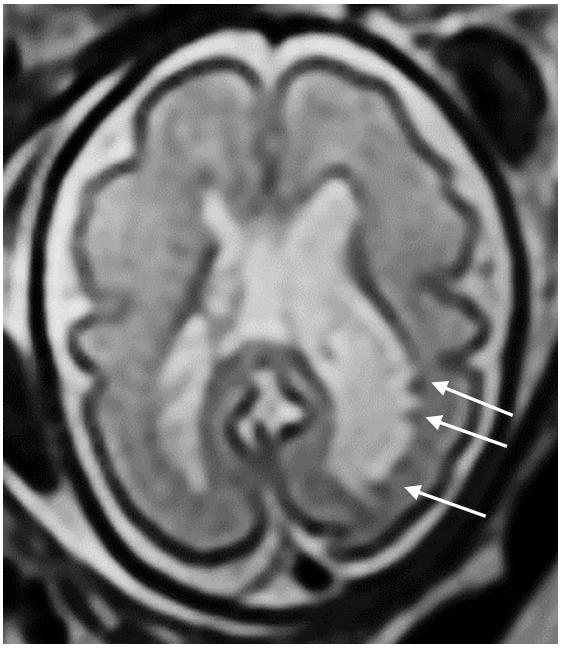


Figure 1.6 Axial T2W ssFSE showing subependymal heterotopia lining the ventricle (arrows)

Lissencephaly is characterised by (Figure 1.7) a thick cortex due to laminar heterotopia. It is accompanied an absence (agyria) or reduction (pachygyria) of the cerebral folds giving the brain a smooth appearance (36). Lissencephaly is often associated with syndromes (Miller–Dieker or Norman- Roberts), but can also occur in isolation. It has a poor outcome, so early detection is necessary to facilitate management of the pregnancy (41).

Cortical development has been demonstrated by iuMR imaging in the normal fetal brain as early as 14 weeks gestation when the interhemispheric fissure can be visualised (42). Gyration is very immature before 22 weeks, so diagnosis is difficult before this time. It has been found that cortical sulci are detected more easily and at earlier gestation with iuMR than with USS (43). Lissencephaly is usually diagnosed in the third trimester when lack of sulcation and a thickened cortex is more apparent (44). T2W images provide good tissue

contrast between the brain and the cerebrospinal fluid (CSF) adjacent to it, enhancing the outline of the sulci and gyri.

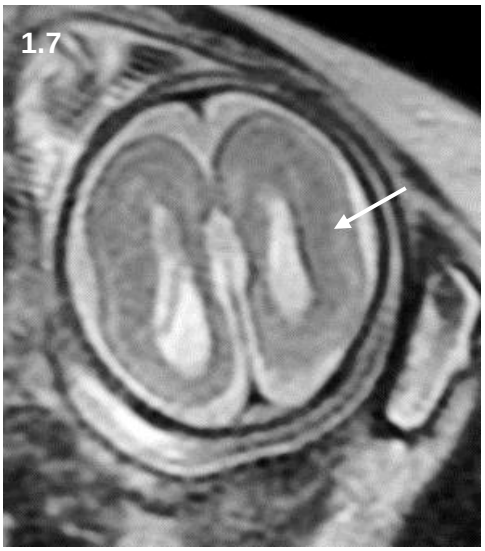


Figure 1.7 Axial T2 ssFSE image of a 31 weeks gestation fetus with thickened cortex (arrow) and agyria as seen in Lissencephaly

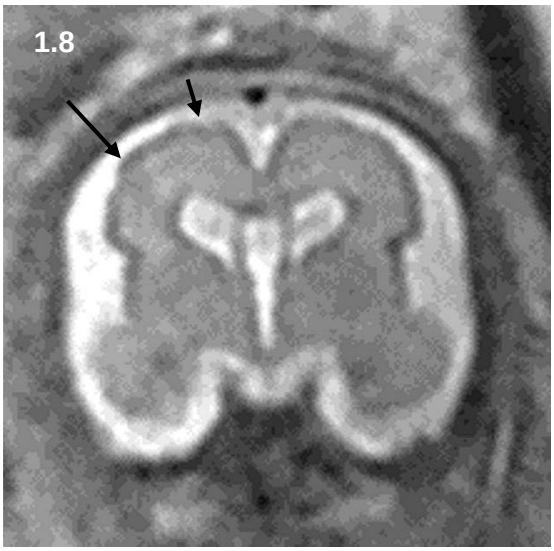


Figure 1.8 Coronal T2W image of 28 week old fetus with abnormal small folds (arrows) typical of Polymicrogyria

The neurons which reach the cortical plate in the third stage of development, organise into the normal 6 layer structure of the neocortex. Failure of this organisation within the cortex results in conditions such as polymicrogyria or focal cortical dysplasia. Both can be difficult to detect on imaging, even in children and adults (36). Polymicrogyria (Figure 1.8) is demonstrated as excessive number of small folds of the cerebral cortex and can be focal or generalised. It is associated with epilepsy and poor speech, motor and neurodevelopment (45). Polymicrogyria is visualised on T2W iuMR images as numerous small packed gyri with an irregular junction between the white matter and cortex. Gliosis and atrophy also feature, seen as abnormal signal on T1W and DWI images (Girard et al. 2009).

Schizencephaly, another example of cortical malformation, results in rare developmental or destructive clefts which can be unilateral or bilateral. The cleft extends from the ventricle to

the surface of the cortex and can be open or closed (fused). Schizencephaly nearly always occurs with polymicrogyria (31) and can be caused by both acquired and genetic factors (46). The contrast between CSF and the brain on T2W MR images allows the cleft in open lipped schizencephaly to be seen (Figure 1.9). iuMR allows better visualisation of the cleft compared to USS, as it can distinguish between schizencephaly and cysts (47). Schizencephaly is not usually identified before mid-pregnancy, and closed lipped schizencephaly, due to the absence of CSF within the cleft, is rarely found prenatally (48).

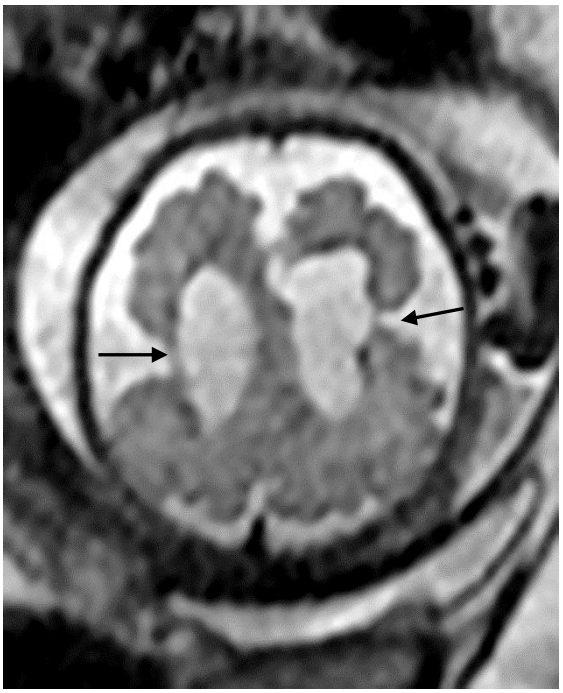


Figure 1.9 Axial T2W ssFSE demonstrating clefts in the cortex (arrows) typical of open lipped Schizencephaly

1.2.5 Developmental Abnormalities of the Infratentorial Brain.

The major difference between the supratentorial and the infratentorial brain is the degree of sagittal cleavage created at ventral induction. In the supratentorial brain division into two separate hemispheres is virtually complete, whereas, in the brain stem and cerebellum,

sagittal cleavage is relatively minor. As a result, commissuration does not occur infratentorially and a different approach is required for classifying brain stem and cerebellar abnormalities (49). One pragmatic approach (described here) uses the size of the bony posterior fossa (PF) which encloses the infratentorial brain (50).

Enlargement of the PF, identified by a raised tentorium and insertion of the venous confluence, can be due to several anomalies. The main being Dandy Walker malformation (DWM) (51), which occurs in approximately 1:30000 births (52). There are three key signs that are used to diagnose DWM: an enlarged posterior fossa (which displaces the tentorium, transverse sinuses and torcula superiorly); a variable degree of hypogenesis of the cerebellar vermis, and an abnormally wide egress from the fourth ventricle which can be seen on sagittal MR imaging (Figure 1.10). Hydrocephalus can also be shown in utero or can occur postnatally (53). Developmental outcome in cases of DWM is variable, but is worse in all cases of identified DWM if there are other associated malformations (54, 55).

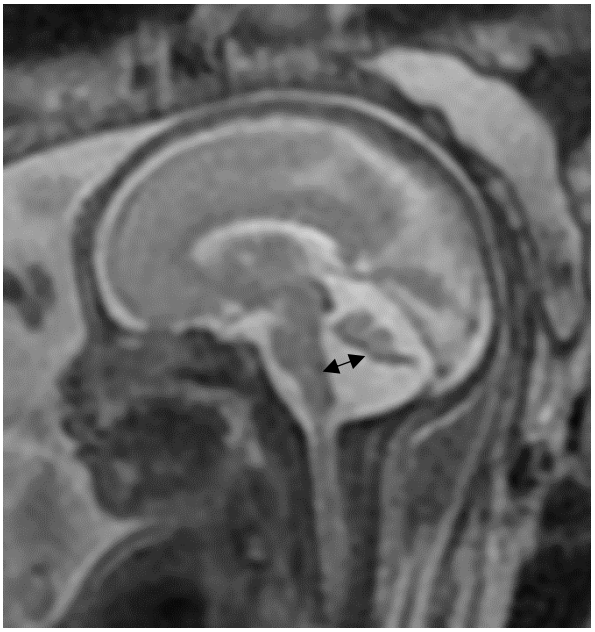


Figure 1.10 Sagittal T2W image of a fetus with a DWM. The abnormally wide egress from the fourth ventricle is clearly seen (arrow).

Imaging the PF and its contents by USS is difficult as angulation of the probe can give the false impression of an enlarged cisterna magna and vermian defects can be missed (56). Several authors claim iuMR is superior to USS in detecting PF abnormalities but when they investigated further found the accuracy of iuMR to detect or clarify posterior fossa abnormalities to be modest, with performance similar to ultrasound (24, 57). When iuMR and postnatal PF imaging findings were compared there was agreement in 59% of cases, with additional abnormalities identified in 26% that were missed by iuMR. Postnatal imaging also found false positive iuMR findings involving the vermis in 15% of cases (58). Problems correctly identifying anomalies of the vermis by iuMR are frequently reported (52, 59, 60) mainly due to limited anatomical resolution and partial voluming.

Chiari II malformation is associated with open spinal dysraphism, e.g. myelomeningocele (61) and is characterised by a relatively normal sized cerebellum trying to grow into a restricted posterior fossa (Figure 1.11). This produces inferior displacement of the cerebellar tonsils, vermis and brainstem, through an enlarged foramen magnum, into the spinal compartment. Hydrocephalus is common both pre- and post-natally (3). Chiari II abnormality is thought to be caused by the open neural tube at the caudal end disrupting the normal outward pressure from ventricular fluid held in the cranial compartment of the neural tube. This pressure usually determines the volume of the cranial cavities but, when atypical, normal skull growth is prevented, resulting in a small posterior fossa. As a result, the cerebellum, tonsils and vermis do not have enough space in which to grow and expand and therefore herniate into the spinal canal (8).

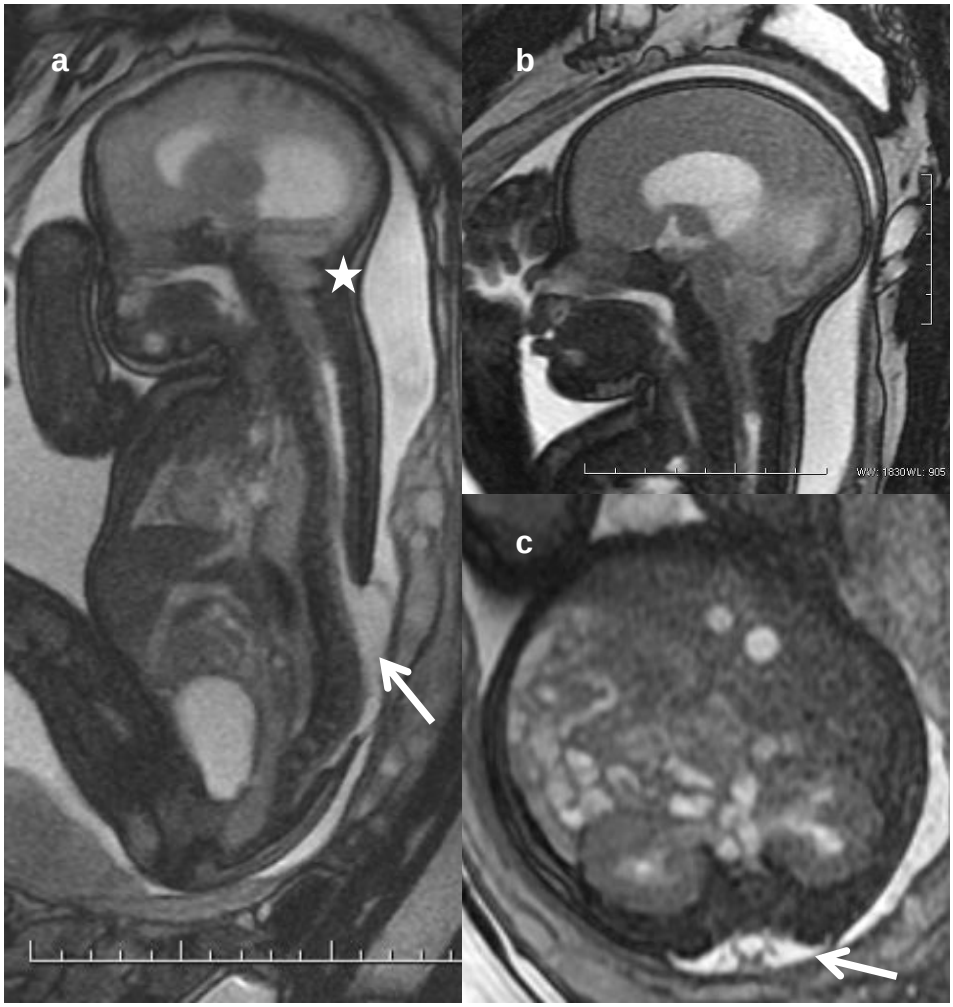


Figure 1.11 (a) Sagittal T2W image of a fetus with a myelomeningocele spinal defect (white arrow) and PF contents herniation (white star) typical of Chiari II malformation. (b) Sagittal T2W image showing the herniation of the PF contents and (c) Axial T2W image of the myelomeningocele (white arrow).

USS is able to detect Chiari II abnormality and associated spinal defects, but iuMR can better visualise the degree of displacement of the posterior fossa contents, examine the brain parenchyma and identify any associated abnormalities. In particular Sagittal T2W images can demonstrate displacement of the cerebellar tonsil and assess whether the spinal defect is covered or uncovered (62). A typical associated finding of Chiari II malformation is the ‘lemon’ shaped head and a ‘tight’ posterior fossa with reduced hindbrain CSF signal noted on iuMR (63).

Myelomeningocele is the consequence of the failure of the neural tube to close at the caudal end, resulting in a sac containing spinal canal contents protruding through a defect in the vertebrae, most frequently in the lumbar region (Figure 1.11) (13). IuMR imaging has been found to be helpful in cases of myelomeningocele when the spinal defect is particularly low (7). Axial and sagittal images of the spine using the T2W balanced steady state sequences are particularly helpful in depicting the fetal intervertebral discs and visualising the level of the defect (64) T1W images are useful to exclude lipomas (57). Griffiths *et al* (65) reported the results of a retrospective analysis of 50 fetuses with spinal abnormalities identified by USS that were subsequently referred for assessment by iuMR imaging. While USS and iuMR were in agreement in 80% of cases, iuMR was able to correct false positive US findings in 8 cases and change the diagnosis in 2 cases. These findings were similar to those by von Koch *et al* (66) and Blaicher *et al* (67).

Rhombencephalosynapsis is a rare disorder of the cerebellum, whereby the vermis is absent and the cerebellar hemispheres are fused across the midline, the dentate nuclei and cerebellar peduncles (Figure 1.12). Associated abnormalities include ventriculomegaly, absence of the septum pellucidum and fusion of the thalamus (68). Rhombencephalosynapsis can be detected on iuMR imaging. The cerebellar hemispheres appear flat on T2W axial images and there is fusion across the midline characterised by continuation of the folia and absence of the vermis (69). Clinical outcome is poor with symptoms such as ataxia and gait abnormalities, seizures and psychiatric abnormalities (69).

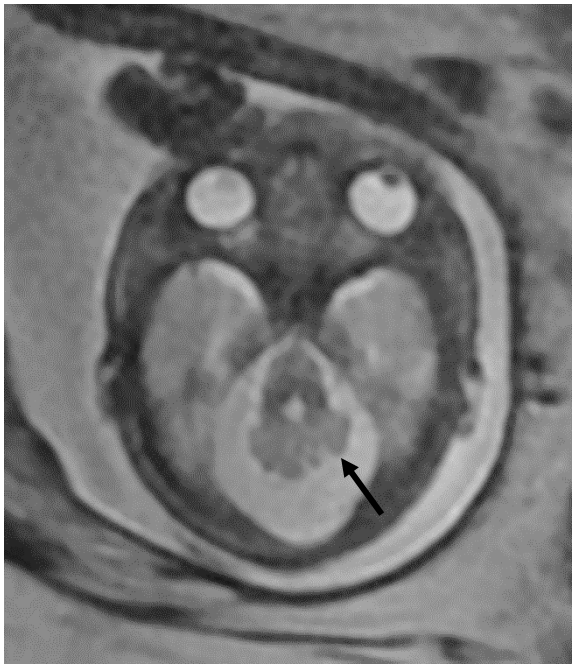


Figure 1.12 Axial T2W image showing abnormal cerebellum (arrow) and absent vermis typical of rhombencephalosynapsis

1.3 Acquired Abnormalities of the Fetal Brain

Acquired brain abnormalities result from external insults or injury acquired *in utero* to a brain that was otherwise destined to be normal. Causes include maternal trauma, intake of toxins such as recreational drug abuse and alcohol, infections, and haemodynamic insults. Other causes of acquired pathology can be due to twin to twin transfusion syndrome (TTTS), in utero death of a twin, or through premature rupture of the membranes (PROM). Whilst all have the potential to have a significant and deleterious impact on fetal brain development, infections and stroke are the most common and are described below.

1.3.1 Infections of the Fetal Brain

Infections acquired during pregnancy rarely cause serious problems for the pregnant woman in the western world but can potentially have significant consequences for the developing

fetus, and it is estimated that infections account for 2-3% of congenital abnormalities (70). Infections affect the fetus *in utero* by ascending or trans-placental routes. Ascending infections residing in the external genitalia of the pregnant women are usually bacterial and pass directly to the fetus via the cervix as a result of chorioamnionitis or after premature rupture of the membranes (PROM) (71). Infants after prolonged PROM are at risk of premature delivery and its complications such as intraventricular haemorrhage, cystic periventricular leukomalacia with high rates of poor long term outcomes, for example moderate to severe infant neurodevelopmental impairment (72)

Trans-placental infections occur when the microorganisms (usually viral) circulating in the maternal blood stream infect the placenta and eventually infect the fetus by hematogenous spread. Infections within the placenta also affect its normal function. The most common trans-placental infections affecting the fetus *in utero* are grouped under the acronym of TORCH and include Toxoplasmosis, Other (syphilis, varicella-zoster, parvovirus B19), Rubella, Cytomegalovirus (CMV) and Herpes simplex virus. Additional infections include HIV, acute maternal sepsis and, more recently, the Zika virus but these are rare in the UK. Infections by HIV, Hepatitis C, syphilis, varicella-zoster, parvovirus B19 and Herpes simplex virus in the fetus are very rare. Transmission of these is primarily at delivery, although in utero infection is possible (73). Primary rubella viral infection has almost been eradicated in developed countries due to widespread immunisation, although importation from less developed countries, or noncompliance to immunisation, does result in a small number of cases. The fetus is more at risk of congenital abnormalities if infection occurs in the first trimester (74). Toxoplasmosis, due to infection from toxoplasma gondii, is common in humans due to ingestion of infected meat or contamination from cat faeces. This rarely causes symptoms but infection during pregnancy causes focal lesions to develop in the placenta and, consequently, infection is transmitted to the fetus (75). Infection of the central nervous system can cause mild or severe abnormalities. Prenatally they cause hydrocephalus and/or intracerebral calcification. Postnatally, convulsions and problems with

vision are common (76). Prevention or limitation of perinatal infections can be achieved by vaccine, immunoglobulins, or antibiotics. However, when a pregnancy is affected, disruption of normal development in the fetus can occur resulting in a variety of anomalies. When infection is suspected, based on serologic testing and USS, further investigation is necessary to exclude any effects on the fetus. (77)

CMV is the most common trans-placental infection with occurrence in up to 1-1.5% of pregnant women in the UK (78, 79) with primary CMV infection and reactivation of previous maternal infection approximately occurring in equal proportions. Previous infection increases the likelihood of reoccurrence in subsequent pregnancies (80). CMV resides in humans, particularly in young children, and is spread by direct human to human contact. Screening for CMV during pregnancy is not routinely performed and it rarely causes any symptoms in the pregnant woman, therefore clinical diagnosis is difficult prenatally. Serology testing usually confirms the presence of the infection but initial suspicion is often raised by abnormal imaging findings (81). The virus invades the germinal matrix and interferes with the normal transformation of precursor neuronal cells into neurons. Infection during early gestation therefore interrupts, and reduces, neuron migration. This results in microcephaly and gyration disorders such as lissencephaly (82) (Figure 1.13). Heterotopia, intraventricular haemorrhage and ventriculomegaly are also common findings in infected fetuses but most prevalent, and usually the first indication of infection, are calcifications (74). As shown in previous studies USS is more accurate in identifying calcification but iuMR is often better at demonstrating abnormalities at earlier gestations as well as identifying cortical abnormalities (83, 84). Around 10-12% of infected fetuses have symptoms at birth with a high risk of neonatal death or more frequently poor neurodevelopmental outcome or sensorineural hearing loss (84, 85)

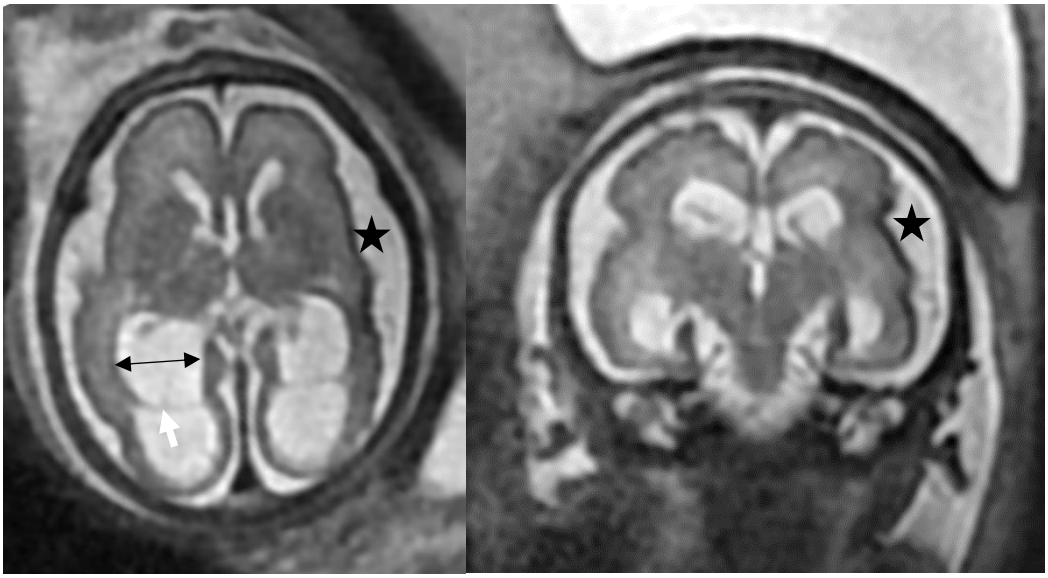


Figure 1.13 Axial (a) and coronal (b) T2 weighted ssFSE images of a fetus at 30 weeks gestation with VM (black arrow), intraventricular stranding (white arrow), Lissencephaly with poorly developed Sylvian fissures (stars) as a result of CMV infection

1.3.2 Fetal Stroke

A healthy uninterrupted blood supply to the fetus is necessary in order to maintain the health and brain development of the fetus. This is reliant on the health of the mother, the placenta and umbilical vessels and the vasculature of the fetus. Fetal stroke, a result of disruption of the blood supply can be due to an ischaemic or haemorrhagic event (37). Prognosis after fetal stroke is often poor with cerebral palsy, postnatal seizures and poor neurodevelopment being common in surviving fetuses, although some may be close to asymptomatic (86).

A haemorrhagic stroke as a result of trauma to a vessel wall is rare but a common site for this to occur with subsequent haemorrhage is the germinal matrix. This area of the brain has a rich blood supply but the vessels are very fragile (87). A hypoxic ischemic event elsewhere within the circulatory system can cause ischemia, and subsequent reperfusion within germinal matrix results in rupture of the fragile vessels with blood collecting within the

ventricles. Initial haemorrhage often causes obstruction within the venous outflow resulting in a combination of acute and chronic response due to repeated insults.

Hypoxic ischemic stroke occurs as a result of occlusion of a vessel most frequently due to thrombus carried to the cerebral vessels from a distal location. Ischemic stroke is often caused by placental aetiologies, maternal hypotension, hypoxia or drug use or fetal cardiac abnormalities (88). A maternal condition linked to haemorrhagic fetal stroke is alloimmune thrombocytopenia, which occurs when a woman becomes alloimmunised against fetal platelet antigens inherited from the fetus's father (89). Resultant haemorrhage is often not discovered until the neonatal period where the cause is often mistaken as the result of the trauma of birth (90). It is possible to identify haemorrhage due to alloimmune thrombocytopenia prenatally and a case is shown in Figure 1.14.

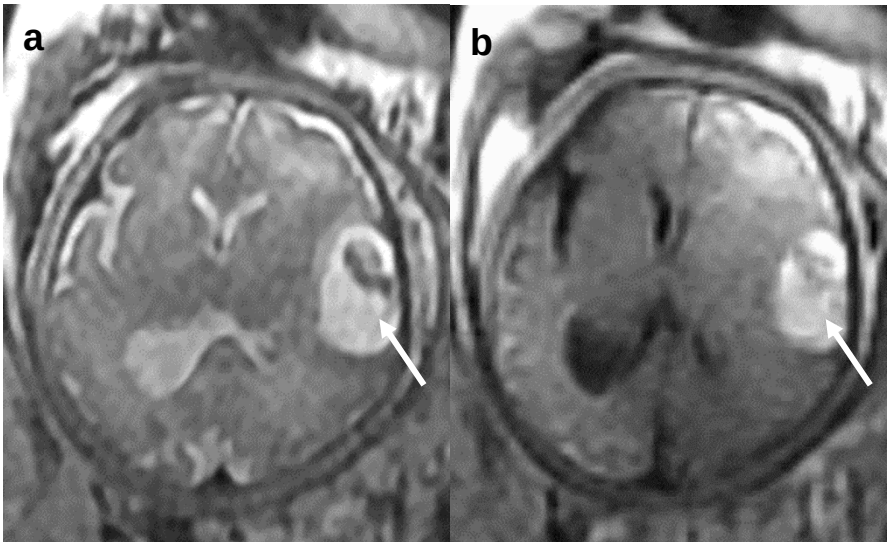


Figure 1.14 Images of a 35 weeks gestation fetus with right temporal lobe subacute haemorrhagic stroke (arrows) as a result of alloimmune thrombocytopenia (a) Axial T2 ssFSE and (b) Axial T1 weighted FLAIR images

Structural causes of stroke which have a predisposition for thrombus and consequent ischemic brain injury in the fetus include embryonic malformation of the Vein of Galen, dural sinus malformations, and hypo- or aplasia of the internal carotid arteries, all of which are

relatively rare (91-94). An example of thrombus within the sagittal sinus is shown in Figure 1.15.

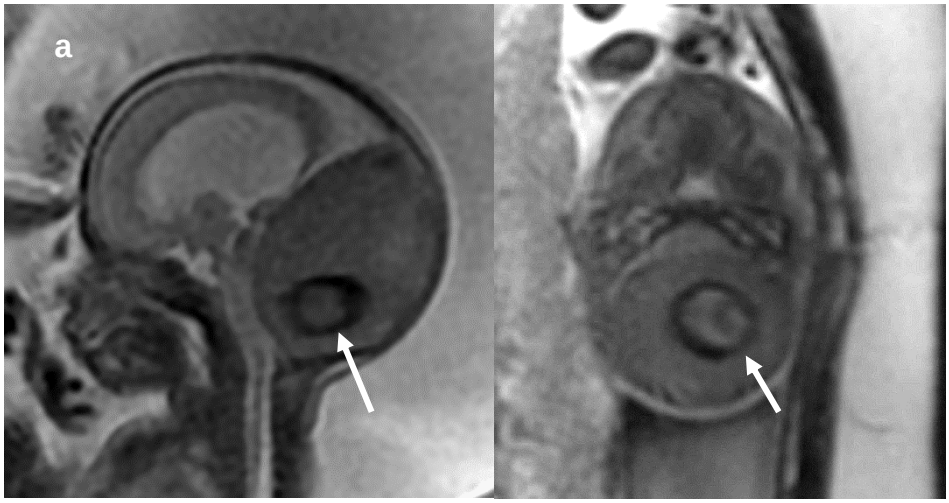


Figure 1.15 Sagittal T2W ssFSE (a) and axial T1 weighted FLAIR (b) images of a 20 weeks gestation fetus with a dural sinus thrombus

Twin to twin transfusion syndrome (TTTS) whereby an anastomosis between the monochronionic twins vascular supply within the placenta causes an uneven distribution of blood to each twin. This often results in the donor twin being much smaller, often with growth restriction, than the recipient. TTTS is detected using USS and identified by discordant fetal growth and amniotic sac size due to polyhydramnios syndrome (95). TTTS and its primary treatment, ablation therapy, carry a risk of morbidity and mortality both prenatally and postnatally with ischemic brain injury being common (96) with reports of brain abnormalities diagnosed in 24% of recipients and in 25% of donors on post-natal USS (97) (Figure 1.16). Fetal demise of the donor twin can cause hypoxic-ischemic damage in the surviving twin due to hypovolemia, hypotension and anaemia. Thrombus may also form in the placenta which detaches and travels through the vascular system in the surviving twin, occluding the blood supply causing injury (98, 99).

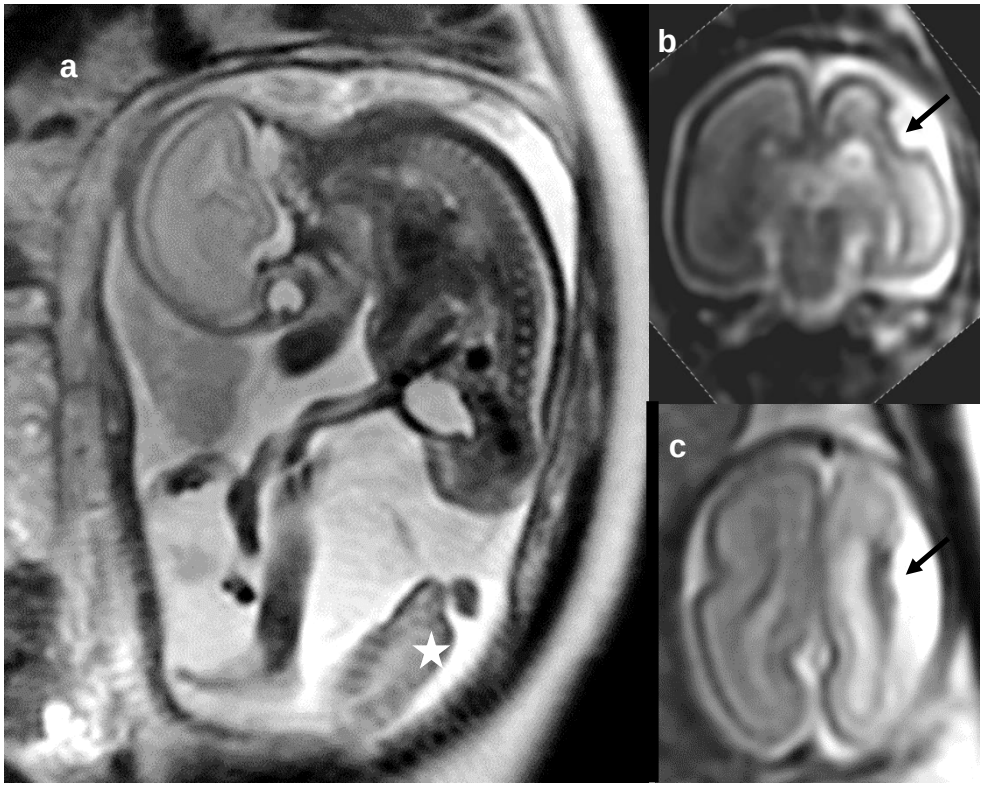


Figure 1.16 Twin to twin transfusion syndrome. (a) sagittal T2 ssFSE of a surviving twin at 25 weeks gestation after laser ablation at 18w resulting in co-twin (star) demise shortly after. (b) coronal and (c) axial T2 ssFSE images of resultant polymicrogyria and infarction (arrows) in the brain of the surviving twin.

Disruption of the blood supply in the fetal brain through haemorrhage or infarction results in death or malformations of brain tissue, the location and characteristics of which are dependent on the vessels involved and the gestational age at the time of insult (91). Although the mechanism of injury through stroke or infection may differ, their manifestation in the fetal brain can be similar and an insult during early gestation usually has a greater detrimental effect than at later gestations (74, 82). The consequent abnormalities such as schizencephaly or polymicrogyria, for example, have been described earlier, but there are several unique to infection or vascular insult that usually manifest as an acute or chronic response, or more commonly in the fetus, as a combination of the two (100).

T2W MR imaging is better at detecting cerebral parenchymal abnormalities as it can clearly delineate the ventricular walls and sulci compared to USS, particularly when lesions are

small. USS demonstrates more efficiently calcifications than IUMR, but it may be visible on T1W imaging gradient echo sequences. T1W imaging also highlights haemorrhage (bright signal) and T2* sequences can demonstrate by-products of blood breakdown. Diffusion weighted images are useful for showing areas of ischaemia and PVL in the acute stages and both appear bright on source images (44, 101)

Girard *et al* (44) collated and report the MR imaging findings from 215 fetuses with hypoxic brain damage, and found 178 fetuses with abnormalities as a consequence of infections. For both hypoxia and infections VM was the most prevalent finding (77 and 85% respectively). Destructive brain lesions were equally prevalent (35% and 34%) with cerebral abnormalities, haemorrhage and venous thrombus primarily due to hypoxia. Calcification and cerebral malformations were the most prevalent finding as a result of infections.
In the acute phase, oedema is a primary sign and is easily identifiable as high signal on T2w imaging. White matter oedema can lead to necrosis or be a transitionary finding. iuMR demonstrates signal changes in the white matter due to oedema, or changes in neuronal migration pattern (100). Acute ischemia is difficult to identify in the early stages, and is usually only visible on diffusion weighted imaging (101, 102).

VM, calcifications, leukomalacia and germinal matrix abnormalities are chronic responses to brain insult. VM is a consequence of haemorrhagic or ischaemic insult in a high proportion of cases, and is often the only anomaly detected by USS (37). Unilateral VM is more frequent in chronic response to injury, with bilateral VM more likely in malformations. Gliosis is also a common response but cannot be seen on standard iuMR but is often present at autopsy. Advanced MR techniques such as spectroscopy may demonstrate changes in the resultant spectra, but this type of imaging in utero is difficult due to long the long acquisition time and small anatomy which provides limited signal from which to derive the necessary information. Injury in the parenchyma also includes atrophy, malformations and cystic lesions such as hydranencephaly, multicystic encephalopathy and porencephaly, which are cavities that form

as a result of infarction. Cystic lesions can vary widely in size and location and are easily defined by both USS and MR imaging (91, 101)

Injury to the germinal matrix can also have both an acute and chronic response, with an early ischemic lesion within the vasculature often causing haemorrhage when re-vascularisation occurs. Injury is often between 24 and 32 weeks' gestation due to the presence of the rich blood supply for neuronal proliferation. This frequently leads to migration abnormalities, with microcephaly a common finding. Injury results in a thick and irregular appearance on MRI, although in the older fetus (after 30 weeks gestation) an irregular ventricular wall is seen (44). Intraventricular and germinal matrix abnormalities are more easily identifiable on iuMR imaging than USS (103). White matter near the germinal matrix can also be injured which results in leukomalacia. Cystic lesions seen as high signal on T2W imaging and low signal on T1W often appear adjacent to the ventricles (PVL) but can also affect the parieto-occipital white matter or, in severe cases throughout the white matter. Early manifestation of leukomalacia is often difficult to identify on iuMR as signal intensity is similar to that of the germinal zone and lesions may be indistinguishable from the ventricular wall (101).

1.4 Ventriculomegaly

VM, while not necessarily an abnormality of brain development, can be associated with, or be the main indicator of, brain abnormality, so is included at this point.
The ventricles are four interconnected chambers within the brain, the largest being the two lateral within the cerebral hemispheres. CSF produced by the choroid plexi circulates in a pulsatile manner from the lateral ventricles through the 3rd ventricle, cerebral aqueduct and 4th ventricle into the subarachnoid space, by way of the foramina of Magendie and Luschka (104).

The routine assessment of the ventricular system by USS involves measuring the size of the trigones of the lateral ventricles. It has been shown that they remain a constant size from 14 to 38 weeks gestation, measuring 7mm +/- 0.6mm (105). VM is arbitrarily defined as trigone measurements of 10mm or over at any stage of pregnancy. Trigone measurements of between 10 - 15 mm were originally considered mild, and over 15mm severe (106). It is, however, now more usual to subdivide the less severely enlarged ventricles into mild (10 -12 mm) and moderate (13 -15 mm) (107) (Figure 1.17).

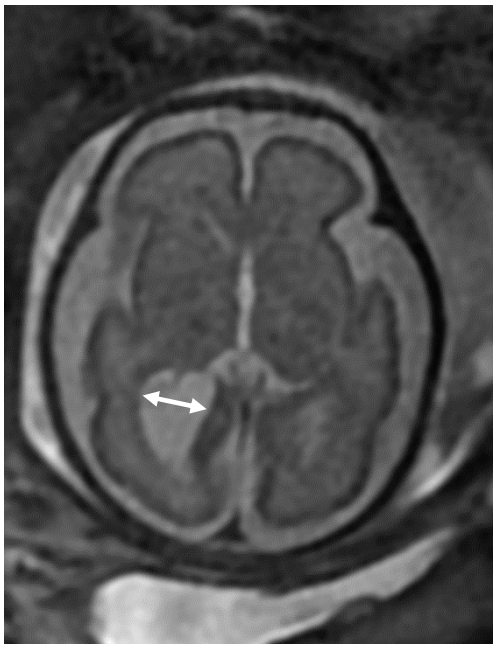


Figure 1.17 Axial T2W demonstrating unilateral VM, with enlarged right ventricle (arrow, trigone measurement 12mm).

VM is one of the CNS abnormalities most frequently detected at ultrasound, occurring as an isolated finding in 0.4 - 0.9 per 1000 births. When other pathology is present, it occurs in 0.5 - 2 per 1000 births (108). In most cases, a discrete cause of VM is not found. Possible causes, however, include destructive processes such as infections, haemorrhage, infarction, obstruction to the normal CSF flow (hydrocephalus) and developmental malformations of the

brain (such as agenesis of the CC and Dandy-Walker malformations). Chromosomal abnormalities are also known to be associated with VM (109).

It is known that ventricle size is a predictor of clinical outcome (110, 111), so measurement must be accurate. Previous studies comparing USS and iuMR (112-114) have all found good correlation between USS and iuMR measurements. Discrepancies mainly occurred when there was a significant delay in the time between USS and iuMR, an important factor when comparing accuracy of iuMR to USS. Measurement has also been found to be observer dependant. Levine *et al* (115) found that when inter-observer variability was assessed, the measurements between ultrasonographers agreed for 60% of the cases measured on USS, but only 47% of the measurements made by reporting radiologists on iuMR agreed. This is significant as the extent of VM is a predictor of the neurodevelopmental outcome of the fetus.

1.5 Fetal Imaging Techniques

This section introduces the two imaging techniques used to image the fetus in utero, with emphasis on MR imaging as it is the main focus of this study.

1.5.1 In Utero Ultrasound

USS is an integral part of antenatal care, being the primary screening tool which provides a valuable structural assessment of the whole of the fetus. It is widely available and has relatively low cost. USS also enables physiological assessments of the fetal heart, limb, body movements and 'breathing' (116). It is acknowledged that there are occasions when ultrasound may not be optimal, including: difficult fetal position; oligohydromnios; ossification of the fetal skull at later gestational ages; and maternal obesity; which all reduce visualisation of fetal anatomy (117). Transvaginal and 3D ultrasound have been shown to overcome these limitations to some extent (118), but there are still occasions when USS fails to recognise significant pathology (119, 120). Standard practice in the UK is for women to be

offered an ultrasound scan at around twelve weeks gestation to date the pregnancy and to screen for gross abnormalities such as anencephaly. A further anomaly scan is performed between 18 and 21 weeks gestation where detailed assessments of the fetus are made by a trained sonographer. If an abnormality is detected, the woman is referred to a fetomaternal expert for specialist investigations including a further detailed USS. The aim of these investigations is to either confirm or exclude suspected abnormalities or, if present, to provide a more accurate and confident diagnosis in order to assist prenatal counselling. Despite USS being the imaging modality of choice, in approximately 30% of cases pathology is missed or described incorrectly (121-123) . This has significant consequences for pregnancy outcome, therefore the exploration of other non-invasive tests in order to improve diagnostic accuracy is necessary.

1.5.2 *In Utero* MR Imaging

In utero MR imaging of the fetus was first attempted in the early 1980's with the first reported account by Smith (124). Scan times were long resulting in significant image degradation due to maternal and fetal movement. This, combined with lack of expertise and availability, meant that iuMR imaging was considered of little diagnostic value. The earliest reports of imaging the fetus in utero by MR concluded that while it had potential as an alternative imaging method, it was limited to gross anatomical measurements such as head circumference and should be used with caution as its safety profile remained unproven. Poor contrast and resolution of resultant images; and the inability to acquire the images in different anatomical planes, also limited the usefulness of iuMR (124-126). To overcome fetal motion, maternal sedation or muscular blockade of the fetus via the umbilical vein was sometimes used (127, 128).

By the mid-1990s, MR imaging sequences had been developed to the point where Levine *et al* (129) were able to demonstrate detailed fetal anatomy with both T1 and T2 weighted images. Advances in technology both of hardware (such as faster gradients), and

development of the fast imaging sequences still employed today, and described here, has enabled iuMR to be a useful addition to USS.

MR imaging of the fetus *in utero* remains challenging due to the unpredictable movement of the fetus, motion artefacts caused by maternal breathing and arterial pulsation. Fetal imaging primarily relies on T2 weighted imaging due to its excellent tissue contrast and fast imaging capabilities. The routine iuMR imaging protocol used for imaging the fetal brain at the Academic Unit of Radiology in Sheffield, and common to the studies reported in this thesis includes a range of sequences and typical scan parameters are presented in Table 1.2. The two primary T2 weighted sequences utilised are the Single Shot Fast Spin Echo (ssFSE) and Fast Imaging Employing Steady sTate Acquisition (FIESTA, GE Medical) and are described in detail below.

Table 1.2 Parameters for Fetal iuMR Brain Imaging

	T2 ssFSE	FIESTA	DWI	FLAIR	T1	MOVIE
Repetition Time (TR)	Minimum (2000)	Minimum (4.2)	4000	Minimum (2700)	Minimum (6.2)	4.6
Time to Echo (TE)	120	Minimum (2.2)	Minimum	122	Minimum (3.3)	3
Flip Angle	-	70	-	-	45	45
Bandwidth (KHz)	62.5	100	250	41	31	166
Inversion Time	-	-	-	2000	-	-
PREP TIME	-	-	-	-	2000	-
NEX	1	1	4	0.5	1	1
Slice Thickness/ Slice Gap (mm)	4/0	4/0	4/0.5	4/0.4	4/0	18
Field of View (cm) (Adjusted to patient)	32x32	38x34	40x36	35x35	38	41
Freq/ Phase Matrix	256/256	384/256	128/128	256/192	192/128	192/256
B Value			600-800			-
Scan Time (Secs)	32	25	64	54	51	30

ssFSE is a rapid scan technique that is widely used for fetal imaging as it can provide imaging in any desired oblique plane in an ultra-short scan time- approximately 1 image per second. Single shot refers to the fact that the entire image is sampled after a single RF excitation and is, reconstructed and displayed before the next. Therefore, if the fetus moves during acquisition, only the imaging slice(s) where this movement has occurred are affected (130). The fast scan times are achieved by utilising long echo trains and half Fourier techniques. The ssFSE sequence begins with a single 90 degree RF pulse followed by a long train of echoes created by 180 degree refocusing pulses in a single T2 decay, equal to the number of phase encoding steps for one image slice (Figure 1.18). The heavily T2 weighted images are the result of later echoes with long TEs contributing to overall signal. The T2 weighting can be adjusted by arranging for the centre of k-space to be refocused at a specific echo time. Further time reductions are achieved by half Fourier techniques which take advantage of the conjugate symmetry of the raw data in k-space. Data is only acquired for just over half the phase encoding steps, the rest being estimated from the acquired data, resulting in shorter scan times (131). However, to achieve suitable T2 weighting, long repetition times (TR ~ 10s) are used with ssFSE. This allows multiple slices to be interleaved and shorter echo train lengths allow more slices to be acquired per TR.

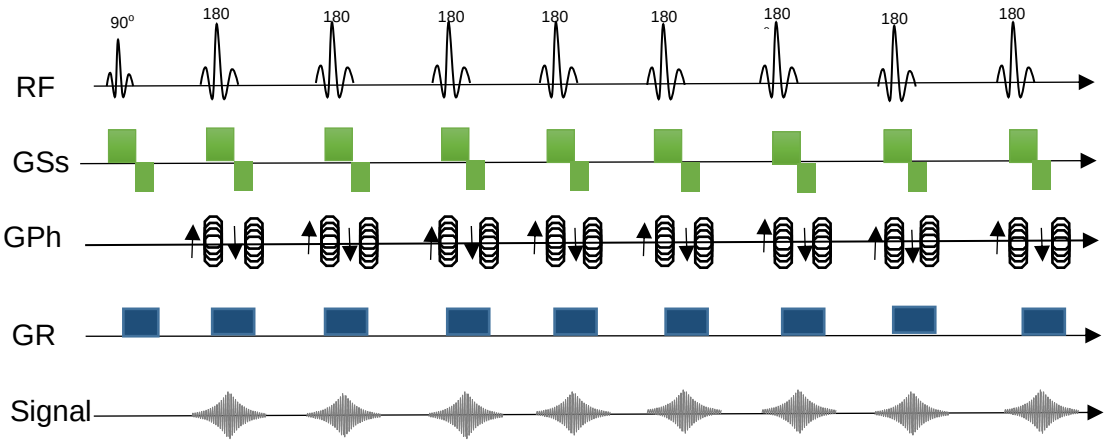


Figure 1.18 Pulse sequence diagram for the ssFSE. RF- radiofrequency excitation pulse, GSs- slice select gradient, GPh- phase select gradient, GR- readout gradient.

Faster imaging times are usually achieved at the expense of image quality. The long echo trains result in weaker signal from the later echoes due to T2 decay. These signals are placed at the edges of k-space and determine the high resolution details in the image. As the signal from the edges of k-space is weaker than that from the centre of k-space, this can appear as blurring in the phase direction (Figure 1.20). The disadvantage of the half Fourier method is the loss of signal to noise ratio (SNR), although spatial resolution is preserved. Increasing bandwidth may reduce blurring due to shorter echo spacing, which also reduces scan time, but this is at the expense of SNR. The resultant ssFSE MR images are heavily T2 weighted, providing good contrast between CSF and brain structures, and demonstrating the different layers of the developing brain and the formation of sulci as the brain matures (29).

Gradient echo sequences are an alternative to ssFSE sequences, and are faster due to smaller variable flip angles which allow shorter repetition times (TRs), thus reducing scan times. The FIESTA sequence (Figure 1.19) is a fully balanced steady-state coherent gradient echo sequence that produces images with high SNR in even shorter scan times than the ssFSE sequence. The echo for each k-space phase encoding value is collected individually rather than as a complete k-space echo train as used in the ssFSE sequence i.e. it is a multi-shot sequence. Steady state is achieved by the application of multiple RF pulses, at times less than the T2 relaxation times of tissues. As a result, the net magnetisation, determined by the flip angle and TR, reaches an equilibrium of both transverse and longitudinal magnetisations. Phase coherence is maintained, and due to the ultrashort TR the signal never completely decays, with residual magnetisation from the initial excitation pulse being refocused and contributing to the signal in the next cycle. This process is continually repeated and a steady state of non-zero magnetisation is established. The resultant equilibrium of magnetisation means that there is minimal T1 or T2 decay throughout the sequence, resulting in high SNR and less blurring than the ssFSE (Figure 1.20).

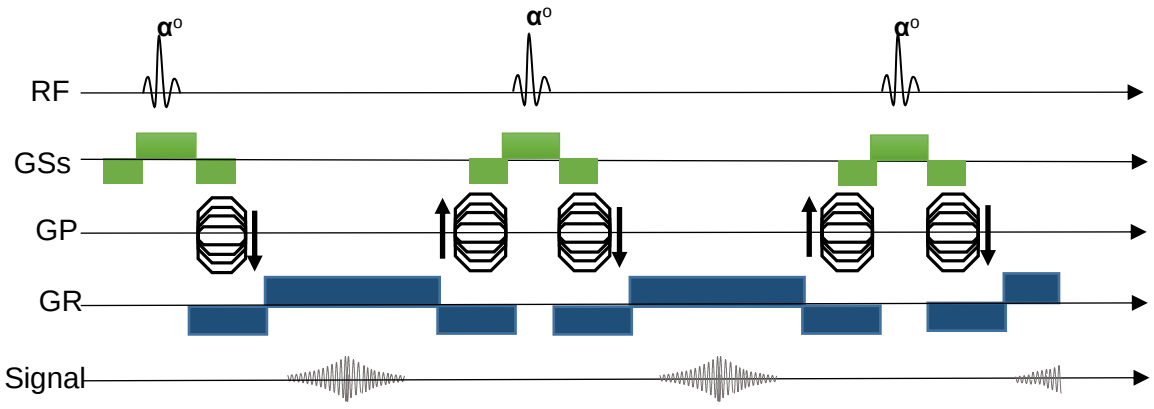


Figure 1.19 Pulse sequence diagram for the FIESTA sequence. RF- radiofrequency excitation pulse (**α**º – user defined flip angle), GSs- slice select gradient, GPh- phase select gradient, GR- readout gradient.

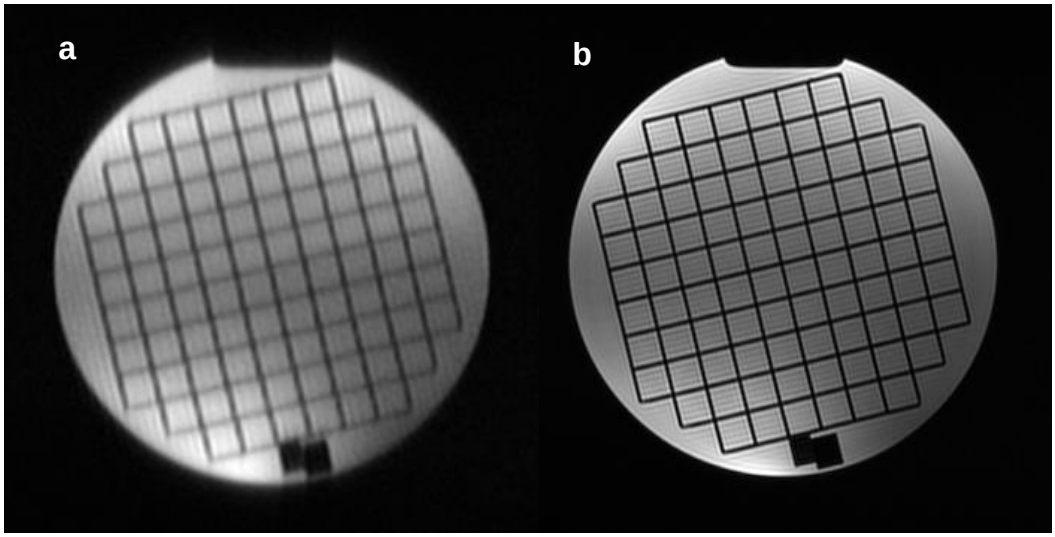


Figure 1.20 Comparison of ssFSE (a) and FIESTA (b) images of a phantom acquired at the same slice position. Blurring can be clearly seen in the ssFSE image due to the long echo train.
Image a; ssFSE acquired using, TR 2000, TE120, ETL180 FOV 34x32cm, Matrix 256x256, Slice thickness 4mm. Image b; FIESTA acquired using, TR 4.2, TE 2.3, FOV 38x34, Matrix 384x256, Slice thickness 4mm.

Balanced gradients of equal magnitude and duration (determined by flip angle and TR) but of opposite polarity are alternately applied with the initial cycle of excitation and magnetisation inducing the FID signal. The second, opposite polarity, as well as producing

transverse magnetisation, acts as a refocusing pulse for residual magnetisation from the previous cycle, in the same way the refocusing pulse does in a spin echo sequence consequently producing an echo. The FID and SE signal are sampled at the same time resulting in a very high SNR.

Because of the ultrashort TR used, contrast is not based on the T1 and T2 relaxation times of tissues but rather on the ratio of T1 to T2. Signal from muscle and other tissues appears dark but the very high signal of both liquids and fat appear bright, as they have similar T1/T2 ratios but very different T1 and T2 relaxation times (132). This contrast mechanism means that the FIESTA is excellent at demonstrating CSF and tissue boundaries of the fetal brain but provides limited contrast between the different components within the brain, particularly as there is very little resultant contrast between grey and white matter (133) . Therefore, as ssFSE sequences are truly T2 weighted, they provide better tissue contrast of the developing fetal brain) (29). The contrast differences of the ssFSE and the FIESTA sequences within the fetal brain are demonstrated in Figure 1.21. The ability of each sequence to distinguish between the different tissue types within the fetal brain can also be defined quantitatively by calculating and comparing the contrast to noise ratios (CNR). This was possible by selecting two regions of interest on the images acquired in-vivo and displayed on the vendor workstation (Advantage Workstation, VolumeShare 7 version 4.6, GE Healthcare, WI, USA). Two regions of interest (ROI, sub-plate and intermediate zones) were selected on an image acquired using a ssFSE sequence and the signal for each region recorded (shown in Figure 1.21a). A region of interest was also placed within the field of view but in an area void of signal and the standard deviation of the signal displayed by the workstation also recorded. CNR was then calculated by subtracting the arbitrary signal of one region of interest (S1) from the signal of the other ROI (S2). This was then multiplied by the SD noise value (SDN) i.e. CNR = S1-S2/SDN.

This calculation was then repeated for the FIESTA sequence using an equivalent imaging slice and ensuring the size and positioning of the ROI was identical to the one used for the ssFSE measurements. This resulted in four arbitrary signal values- two each for the ssFSE and FIESTA (Table 3).

The CNR was calculated for each sequence and are shown in Table 3. The results demonstrate that the CNR in the ssFSE is three times higher than the CNR of the FIESTA highlighting the superior ability of the ssFSE for showing the tissue characteristic of the fetal brain.

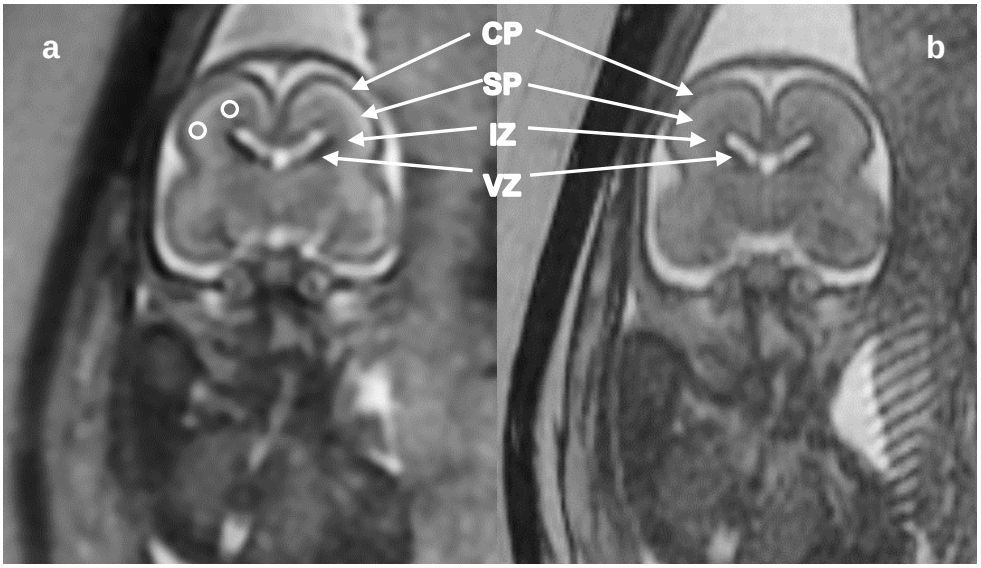


Figure 1.21 Coronal images of a fetus at 21 weeks gestation comparing the resultant contrast of the T2 weighted ssFSE (a) and FIESTA (b). Although the layers of the cortex (CP cortical plate; SP subplate; IZ intermediate zone; VZ ventricular zone) can be seen in the images using both sequences they are more clearly defined by the ssFSE. (Circles in (a) demonstrate the positioning of ROI for CNR calculations).

Table 1.3 Comparison of signal intensity, background noise and CNR of two regions of the fetal brain measured invivo. (Arbitrary units)

	Signal measurement of the sub plate (SP)	Signal measurement of the intermediate zone (IZ)	Differences in signal (SP - IZ)	Standard Deviation of Background noise	CNR of the SP and IZ
ssFSE	99.49	83.94	15.55	15.39	1.01
FIESTA	94.51	90.98	3.53	11.39	0.31

While FIESTA has the advantage of higher SNR, lower SAR due to smaller flip angles, less blurring and faster acquisition compared to ssFSE, it does have limitations. Banding artefacts, a distinct feature of the FIESTA sequence, are caused by field inhomogeneity interfering with phase coherence of the transverse magnetisation from the multiple TRs. If the timing of the TRs are not in phase they cancel each other out rather than combining resulting in signal void and manifest as banding artefact. Therefore, a uniform magnetic field is essential (131). Although the very short TR makes the FIESTA sequence less sensitive to field inhomogeneity, banding artefacts are usually prominent at air/tissue interfaces (Figure 1.22). Slice thickness is often restricted in the 2D FIESTA sequence due to the limitations of the gradients, particularly as oblique imaging is required to image each anatomical orientation of the fetal brain. A larger field of view (FOV) is also necessary to ensure that the banding artefacts do not obscure the area of interest.

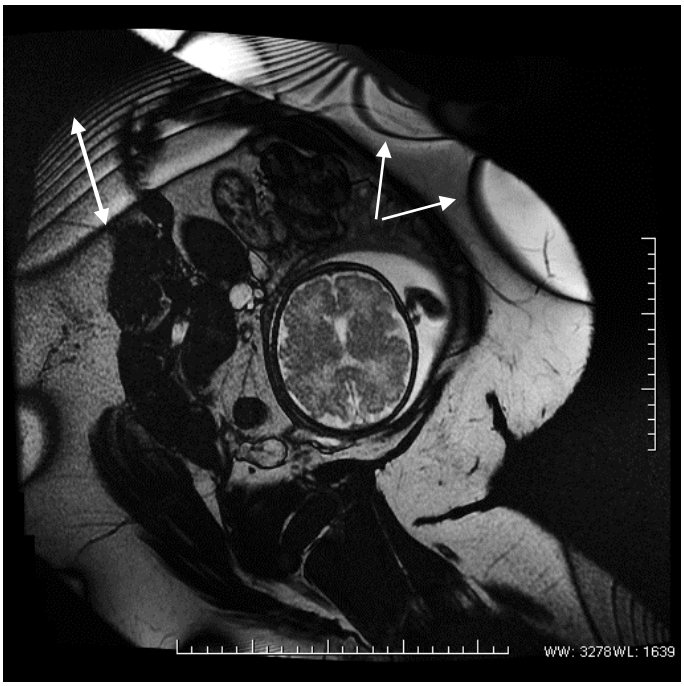


Figure 1.22 FIESTA image showing banding artefacts at air/tissue interface due to signal void (white arrows)

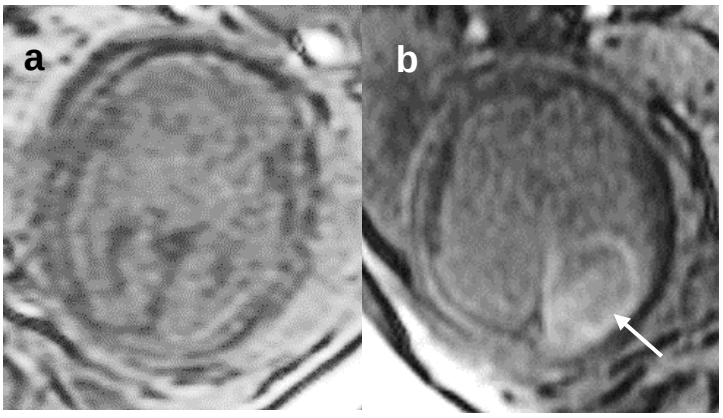


Figure 1.23 Axial T1 iuMR images typical of the limited contrast achieved. Axial T1 of the normal fetal brain (a) and a fetal brain with posterior bleed (arrow, b). MR parameters: TR 12, TE ,6, flip angle 40, bandwidth 31, preparation time 2000, slice thickness 5mm, Matrix 192x128

To produce T1W images of the fetus remains a challenge due to the high water content of the developing brain, resulting in poor contrast differentiation between grey and white matter (Figure 1.23a). T1W images are achieved by using ultrafast gradient echo sequences but are more prone to movement artefact than ssFSE due to longer acquisition time. Resolution is also limited in order that scan time can be kept to a minimum. Because of this, T1W images are used to make gross assessment rather than delineate smaller anatomical structures. For example, T1W sequences still adequately demonstrate haemorrhage (Figure 1.23b), fat and calcification (57). Girard *et al* (100) also highlight the need for T1W imaging in the third trimester to demonstrate signal changes from the myelination process, particularly when it is abnormal, as it manifests sooner on T1W images than T2W images.

A fast fluid attenuated inversion recovery sequence (FLAIR) may also be useful to image the fetal brain as it suppresses signal from CSF, increasing contrast between CSF spaces and adjacent structures (Figure 1.24). FLAIR can sometimes provide T1 information and be useful in clarifying areas of signal change, but like T1 imaging it has a long acquisition time and therefore tends to be affected more by movement (57).

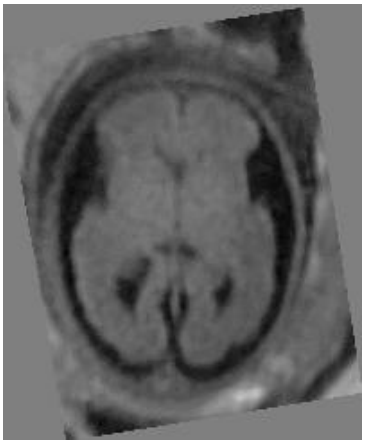


Figure 1.24 Axial FLAIR fetal brain image acquired using TR 2700, TE 122, bandwidth 41, echo train length 240, inversion time 2000, NEX 0.5, slice thickness 5mm, matrix 224 x 224

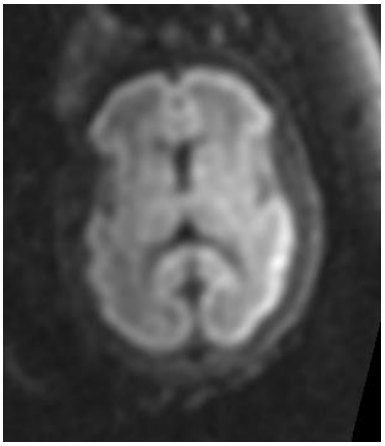


Figure 1.25 Axial diffusion weighted (b700) image acquired using TR 4000, TE 109, bandwidth 250, Nex 4, slice thickness 4mm and 0.5mmgap, matrix 128 x 128, b-value 700.

Diffusion weighted imaging (DWI) (Figure 1.25) is sensitive to the random thermal Brownian motion of water molecules within tissues. Water molecules are usually free to move in any direction, but structures such as cell membranes, macromolecules, and fibres will restrict diffusion. The apparent diffusion coefficient (ADC) provides a measure of the magnitude of this diffusion process (i.e. the mean displacement of a molecule in a given time) and differs for different body fluids and tissues (134). Pathological processes such as tumours, abscesses and ischaemia may not always be clearly identified on routine structural MR imaging, but have been shown to alter normal diffusion. Normal ADC values for the developing fetal brain have been established (135) and consequently changes in diffusion demonstrated through signal change in DWI MR sequences highlight pathology (131).

The sequences described so far are part of our routine iuMR imaging protocol to assess the fetal brain. Developing and extending the range of MR sequences may provide further clinically relevant information about fetal brain development and improve detection of abnormalities.

1.5.3 MR Safety

The potential hazards of MR imaging are well established for any person being exposed to the MR environment, and provided safety screening procedures are adhered to, then MR is considered ‘safe’. This assumption cannot be made for the developing fetus as it may be particularly vulnerable during the first trimester when organogenesis occurs (136). Exposure to the static magnetic field during an MR scan in the adult population may cause mild sensory effects such as vertigo, nausea and taste sensations which are harmless. The time varying magnetic field may also cause transient peripheral nerve stimulation which may be uncomfortable but does not cause adverse effects, although the effect on the fetus, if any, is unknown (137).

The consequences of exposure to the MR environment during pregnancy are difficult to assess as the true effect on the fetus cannot be measured directly. The two main areas of potential concern that have been highlighted are exposure to the loud noise generated during the scan, and possible heating due to energy deposition caused by the radiofrequency (RF) pulses. The acoustic noise generated during an MR scan can reach over 100 decibels due to the switching of the gradients. The anatomical structures required for hearing are fully formed by 20 weeks gestation, and the fetus has been shown to respond to noise from this time point (138). Although difficult to replicate experimentally it is thought that amniotic fluid may reduce the sound by 30-50%, as described by Glover *et al* (139), who used a hydrophone in a volunteers stomach filled with water to record sound intensities during an MR scan. The experiment was designed to replicate the acoustic environment a fetus experiences in the uterus. However, it assumed that water has the same attenuation properties as amniotic fluid, and did not model the environmental changes experienced by the fetus over the full 9 months. The results should therefore be viewed with caution. The most conclusive evidence to support the view that the fetus' hearing is not adversely affected by noise during MR scanning come from studies which performed follow up hearing tests on children exposed to MR *in utero* and found no significant hearing impairments (140-142).

This evidence was confirmed by Reeves (143), who retrospectively reviewed outcomes of the hearing tests routinely performed on neonates and found no significant differences between those exposed to iuMR and a control group which was not.

Another safety concern related to iuMR is the potential heating caused by the absorption of energy from the electromagnetic RF pulses. The amount of RF energy absorbed per unit of mass of an object is known as the specific absorption rate (SAR) and is measured in watts per kilogram (W/Kg). Several studies have reported that an increase of fetal temperature of more than 1 degree Celsius over 24 hours is potentially teratogenic (144) and can cause neural tube and facial defects (145, 146), with the central nervous system (CNS) being considered particularly vulnerable (136). The thermoregulatory response of pregnant women is potentially compromised during pregnancy, and that of the fetus is unknown, although it is thought that the amniotic fluid surrounding the fetus permits effective heat dispersion (147).

Despite concerns, there has been no conclusive evidence to suggest that iuMR imaging of the fetus has any detrimental effects. Consequently the Medicines and Healthcare Products Regulatory Agency (148) and the International Commission on Non-ionising Radiation Protection (149) state that MR imaging can be performed when the benefit is considered to outweigh any risk and the information obtained from iuMR cannot be obtained by any other non-ionising means (e.g. USS). It is also recommended that MR exposure should be kept to a minimum. Whole body SAR exposure should be limited to normal operating mode. This restricts exposure to 2 W/Kg and prevents a core temperature rise of more than 0.5 degrees. This guidance is adhered to for all iuMR imaging performed in the Academic Unit of Radiology, hence all fetal imaging acquired and shown in this thesis did not exceed recommended SAR limits.

In practical terms, SAR is determined by the sequences and parameters selected by the operator as well as by field and gradient strength. For example, due to the additional RF

pulses they use, fast single-shot spin echo sequences produce a higher SAR than gradient echo sequences (150). Structuring an MR protocol so that all the information required is achieved with minimal SAR should be investigated. The use of a single 3D acquisition to replace 2D sequences in each anatomical plane may have the potential to reduce SAR. To date, there appears to be little research into this aspect of iuMR imaging.

1.6 Measures of Diagnostic Performance

Diagnostic tests are a fundamental part of healthcare, enabling clinicians to make a diagnosis, assess the severity of disease and guide clinical decision making and disease management. Before any diagnostic test is accepted into routine clinical use its diagnostic performance must be determined by examining every aspect to ensure it is clinically relevant and useful in the context to which it is applied (151).

Fryback and Thornbury (152) defined a hierarchal model containing six levels which outline the different elements of diagnostic efficacy (Figure 1.26). This model considers all elements of the diagnostic pathway, acknowledging that diagnostic performance cannot be measured by a single factor but is dependent on the efficacy at each level. Diagnostic performance of a test at a higher level is influenced by and dependent on performance at a lower level, so if technical efficacy is poor it will reduce performance at all other levels.

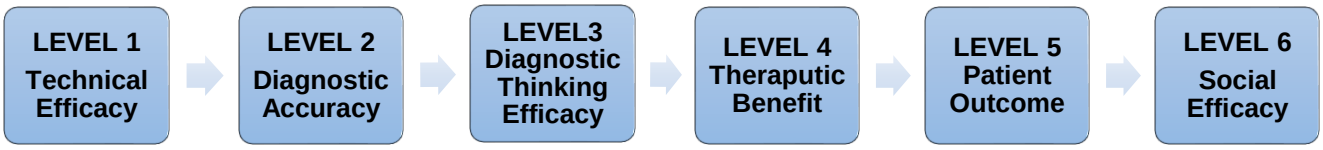


Figure 1.26 Hierarchal model of diagnostic performance as proposed by Fryback (1991)

Level 1 encompasses the performance of the technical aspects of a test. This is the ability to physically measure information with precision and reproduce that information reliably (153). For diagnostic imaging, this includes the quality and abilities of equipment used, aspects of image quality such as resolution, contrast, sharpness, artefacts and the ability of the technologist to use the equipment effectively.

Diagnostic accuracy, at Level 2, is usually measured as a binary outcome by comparing the results of the new test to the true condition status as determined by a reference standard, with results frequently presented as percentages. This simplistic evaluation of diagnostic accuracy fails to provide any meaningful statistical analysis or take into account the significance of false positive and false negative results and may overestimate test performance (154). A more thorough analysis is achieved using a 2 x 2 contingency table which takes into account not only true positives and negatives, but also false positive and negatives to determine sensitivity and specificity (155). Measures of sensitivity and specificity do not determine the severity or anatomic extent of a disease, but calculates the proportions of correct and incorrect positive and negative diagnoses made by the diagnostic test compared to an outcome reference diagnosis. The positive and negative predictive values are also useful measures of diagnostic test accuracy, providing the probability that the diagnostic test will correctly identify those with or without the condition under investigation (156).

At Level 3, diagnostic thinking efficacy links how the information provided by the diagnostic test at Level 2 influences patient management at Level 4, and addresses the question ‘does the information influence the clinician’s thinking about the disease likelihood enough to affect patient treatment’? (153). Diagnostic thinking efficacy is difficult to measure quantitatively, and instead relies on subjective or empirical measures such as the clinician’s estimated probability of a diagnosis before and after a test, often referred to as diagnostic certainty or confidence (152). When diagnostic confidence is examined it is usually as a separate entity

rather than as an integral part of the diagnostic pathway, simply measuring confidence before and after any given test (157). Ng and Palmer (158) point out that this fails to take into account the effect of wrong diagnoses. They propose a framework in which diagnostic accuracy and diagnostic confidence are amalgamated to examine how each of these aspects influence clinical management whilst taking into account eventual outcome (correct or incorrect diagnosis). This framework, (shown in Chapter 3, Figure 3.1) assigns a 'route score' according to impact on the patient ranging from +4, representing where the test under investigation had a positive contribution which was beneficial to the patient, to -4, where the test has a detrimental influence. Where the test has no impact, a score of 0 is assigned. Examining diagnostic confidence is a concept rarely considered when investigating diagnostic performance, yet it is fundamental to clinical decision making. A clinician who is highly confident of a diagnosis is more likely to act upon that diagnosis than if confidence is low (159). This directly affects clinical management in that if the confidence is misplaced, it can cause treatment to be either given when not needed or withheld when required, and can have detrimental consequences for the patient (160).

At Level 4, therapeutic efficacy deals with how a diagnostic test and its interpretation impacts on the patient's treatment, in terms of how therapy planned before a test is altered by the results of that test (152). It is possible that a diagnostic test can perform well at lower levels but if it has no impact or influence on the management of disease then it may simply become a means to reassure the clinician, although this may be of benefit in itself. For example, if iuMR adds nothing to the information obtained by ultrasound, it is unlikely to impact on patient management. It could be argued that although no further information is obtained, it still provides reassurance that the original diagnosis is correct. This may be equally important, particularly when decisions are being made which have significant consequences, such as termination of pregnancy.

The ultimate goal of a diagnostic test is to benefit the patient, a consideration at Level 5 in Fryback's hierarchical model. Patient efficacy is defined as the end result due to the test; for example patient deaths avoided, or change in quality of life, regardless of the sensitivity and specificity of a test (161). In fetal imaging this can be significant. If iuMR imaging excludes a severe brain abnormality previously diagnosed by USS then a decision regarding termination of the pregnancy may be reversed, with a resulting successful pregnancy.

The final Level, 6, is societal efficacy which relates to the cost-effectiveness of a new test. Resources are limited, and allocation is often prioritised for those services for which the benefit is significant enough to justify the expense. This aspect of diagnostic performance is often difficult to quantify as diagnostic imaging technologies, unlike medical drugs or treatments, rarely have direct measurable long term patient outcomes (162). As a result, strategies for cost-effective analysis of technologies have been introduced. Reference case analysis uses the calculation of quality-adjusted life years (QALY), the cost of funding the new technology and the consequences for the wider patient population (163).

This hierarchical model provides a guide by which to comprehensively assess a diagnostic test. Although diagnostic accuracy is an essential aspect to consider when investigating a new technology, such as iuMR, in order to assess its true performance all elements need to be incorporated by thorough study design.

Chapter 2

A Systematic Literature Review and Meta-Analysis to Determine the Contribution of MR Imaging to the Diagnosis of Fetal Brain Abnormalities *In Utero*

2.1 Summary

In order to fulfil the first aim of this thesis it was necessary to establish the ability of iuMR to improve the diagnostic accuracy over ante-natal USS for the detection of fetal brain abnormalities as evidenced by previous research. This chapter, therefore, reports the systematic literature review and meta-analysis undertaken to fulfil this aim. The overall conduct and execution of the review was the responsibility of DJ. This included;

- Writing the review protocol
- All literature searches
- Selection and exclusion of articles at all stages of the screening process.
- The assessment of methodological quality for included articles
- Collation of data and analysis of results
- Writing the manuscript which was published in the peer reviewed journal European Radiology:-

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 fetal brain abnormalities In Utero. European radiology. 2017;27(6):2367-80.

The systematic review was conducted by DJ over a 2 year period and represents a significant portion of this time span (approximately 500 hours). Staff at ScHARR (School of Health and Related Research, University of Sheffield) provided support and assistance with the review. This included advice on systematic review methodology (Judith Cohen, Diana Papaioannou), literature search planning (Anthea Sutton), statistics (Mike Bradburn) and preparation of the manuscript for publication. Cara Mooney undertook the role of second reviewer for the screening, selection of appropriate studies to be included in the review, data extraction and methodological quality assessment.

The purpose of this systematic literature review was to provide a comprehensive appraisal of previous research investigating the diagnostic performance of fetal brain MR imaging when attempting to confirm, exclude or provide additional information to USS after there is a suspicion of fetal brain abnormality. In order to identify relevant studies electronic databases were searched as well as relevant journals, conference proceedings and reference lists of applicable studies. Two reviewers independently identified relevant studies for inclusion in the review. Inclusion criteria were original research that reported the findings of prenatal USS and iuMR imaging and findings in terms of accuracy as judged by an outcome reference diagnosis for fetal brain abnormalities.

The inclusion criteria were satisfied by 34 studies, allowed diagnostic accuracy to be calculated in 959 cases, all of which had an outcome reference diagnosis determined by postnatal imaging, surgery or autopsy. The systematic review found that iuMR imaging makes a significant contribution to the diagnosis of fetal brain abnormalities increasing the diagnostic accuracy achievable by USS alone but further evaluation with improved methodology is needed to provide definitive evidence.

2.2 Background

USS is the primary diagnostic imaging method for screening of the pregnancy and considered the reference standard for imaging the fetal brain. There are occasions when technical limitations can hinder clear visualisation of the fetal anatomy, which could result in abnormalities being overlooked (164, 165). As previously outlined in the hierarchal model (section 1.5), the satisfactory performance of a diagnostic test in healthcare is essential as the results are necessary for clinical decisions and management of disease. iuMR imaging was introduced as an adjunct to USS to improve diagnostic accuracy and a growing body of literature confirms increasing use of iuMR in detecting fetal brain abnormalities (166-169). Despite this, the true clinical value of iuMR has not been established and previous limited

statistical evidence has been unable to demonstrate, in terms of diagnostic accuracy, any benefit (170).

A systematic review and meta-analysis allows all relevant evidence from individual studies to be combined and evaluated to provide reliable and cohesive proof regarding an intervention and to reduce or eliminate any potentially conflicting evidence. Consequently the results of a systematic review provide a more accurate assessment of effectiveness and are considered more informative for clinical practice than individual studies alone (171) .

There have been only two other recently published systematic reviews by Rossi and Prefumo (172) and Van Doorn *et al* (173) who aimed to clarify the additional benefit of MRI in the diagnostic pathway when used in addition to USS. Rossi and Prefumo reviewed 13 studies and Van Doorrn *et al* selected 27 studies for review. Despite similar aims and inclusion criteria only 7 studies were included in both reviews. This could, along with date differences for searches, be due to the differences in exclusion criteria. The criteria used by Rossi and Prefumo excluded studies without an outcome reference diagnosis (ORD), non-English publications and those where the data were reported in graphs or percentages. Van Doorns review excluded studies with a sample size of less than 20 and studies where diagnoses were inadequately described. The analysis of the results within Rossi and Prefumo's review were also fundamentally flawed, which is discussed later. Consequently we felt a new systematic review was justified in order to improve upon and update these existing reviews, to attempt to limit the number of studies excluded and to identify any other studies which may have been erroneously excluded.

2.3 Study Aims

The aim of this study is to assess iuMR imaging as a technology to aid the prenatal diagnosis of fetal developmental brain abnormalities to answer the question:- Is the diagnostic accuracy of iuMR superior, equivalent or inferior to USS? The diagnostic accuracy of iuMR compared to antenatal USS was assessed through:

a) Measurement of diagnostic accuracy of antenatal USS alone (i.e. prior to iuMR) in relation to an outcome reference diagnosis (ORD- post-natal imaging, surgery or post-mortem examination).

b) Measurement of diagnostic accuracy of iuMR (following antenatal USS) relative to an ORD (post-natal imaging, surgery or post-mortem examination).

The secondary aims were to determine if prenatal counselling and/or management of the pregnancy changes as a result of iuMR imaging and to identify the fetal brain anomalies for which iuMR is most useful.

2.4 Methods

2.4.1 Protocol

The protocol for this research was written in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)(171) and registered with the International Prospective Register of Systematic Reviews (PROSPERO, registration number CRD42015010265). PRISMA are peer reviewed guidelines that provide a robust set of standards to ensure that systematic reviews are undertaken and reported in a manner which removes ambiguity regarding outcomes. These guidelines were chosen as they were judged the most appropriate for the research question and study design and also recommended by the experienced systematic reviewer providing advice for this review.

2.4.2 Eligibility Criteria

All types of study design were considered eligible for inclusion apart from case reports, reviews or commentaries.

Participants

Pregnant women who had undergone, due to suspicion of an abnormality of their fetus' brain, specialist prenatal ultrasound and subsequent prenatal iuMR and with any findings confirmed by an ORD.

Reference standards

Reference standards accepted to confirm the outcome diagnosis were postnatal imaging by transcranial USS, MRI or CT and surgery, or, in cases of fetal demise or neonatal death, autopsy and post mortem MR imaging.

Exclusions

Studies not reported in English were excluded if a translation was unavailable. If an abstract was available in English these were scrutinised for relevant information but excluded if the information given meant adherence to the inclusion criteria could not be certain.

2.4.3 Search Methods

All studies were identified in which iuMR imaging was used to supplement USS for imaging fetal brain abnormalities in utero. In order to retrieve as many relevant studies as possible a sensitive search strategy was compiled and applied to all relevant data sources, adjusting truncation and wildcard terms of the search strategy for each database as necessary. Medical subject heading (MeSH) terms such as *"magnetic resonance imaging", "ultrasound" and "fetus"* were used and combined with other free-text terms related to fetal brain abnormalities such as "*agenesis of the corpus callosum" or "ventriculomegaly".*

Databases searched included Medline (via OVID) (1966 to present), EMBASE (1980 to present), Cochrane Register of Diagnostic Test Accuracy Studies (accessed 18/03/2015 and 02/10/2015), and Web of Science (1900 to present). The search strategy as applied to the MEDLINE online database is shown in Table 2.1.The reference lists of appropriate articles were also scanned for any other suitable studies that were not highlighted by the searches.

Websites of the relevant obstetric, feto-maternal medicine, and general radiology journals were searched including: Neuroradiology, Radiology, Journal of Ultrasound Medicine, Prenatal Diagnosis, Journal of Magnetic Resonance Imaging, Journal of Perinatal Medicine, Journal of Ultrasound in Obstetrics and Gynaecology, Paediatric Radiology, Neurology and the American Journal of Neuroradiology. In addition, conference proceedings were searched

for applicable studies and authors contacted for relevant data. These included the Radiological Society of North America (RSNA), the British Society of Neuroradiologists (BSNR), European Society of Neuroradiologists (ESNR), American Society of Neuroradiologists (ASNR), European Society of Paediatric Radiology, The Fetal Medicine Foundation world congress and the Asia Pacific Perinatal Imaging Symposium.

Electronic searches were conducted in March 2015 without date restriction and later updated to identify all relevant reports up to the end of September 2015. Initial searches of all data sources and removal of duplicates was undertaken by one reviewer (DJ).

2.4.4 Data Collection

Selection of Studies

The screening and selection of appropriate studies was carried out in three stages and each performed independently by two reviewers (DJ, CM).

Stage 1. Titles of all material generated by the searches were screened and excluded if it was clear the inclusion criteria had not been met.

Stage 2. Titles and abstracts of citations remaining after stage one were reviewed and those that appeared to meet the inclusion criteria or studies where there was uncertainty regarding applicability were selected for stage 3.

Stage 3. Full reports were located either through online resources or by hand searches and reviewed for applicability against the inclusion criteria. Those that met the inclusion criteria were selected for final inclusion in the systematic review.

Any disagreements or ambiguity during each stage of the selection process were resolved by consensus. Where only abstracts were available attempts were made to contact the authors for full reports. If the same data had been published in more than one publication, only the most up to date or complete study was selected. A PRISMA flowchart was used to document and report any decisions made during the study selection process (174) (Figure 2.1).

Table 2.1 Medline Search Strategy

"Table reproduced from: Jarvis D, Mooney C, Cohen J, et al. (2017) A systematic review and meta-analysis to determine the contribution of MR imaging to the diagnosis of foetal brain abnormalities In Utero. Eur Radiol 27:2367-2380."

	Database: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily, Ovid MEDLINE(R) and Ovid OLDMEDLINE(R) <1946 to Present> Search Strategy:-	RESULTS *n* =
1	Brain/ (381902)	381902
2	Abnormalities, Multiple/	36708
3	1 and 2	1518
4	(brain adj5 abnormalit$).mp.	6920
5	Ventriculomegaly.mp.	1506
6	"Agenesis of Corpus Callosum"/	1882
7	corpus callosum.mp.	15290
8	agenesis.mp.	10526
9	7 and 8	2720
10	Arnold-Chiari Malformation/	2609
11	Chiari malformation.mp.	3070
12	Dandy-Walker Syndrome/	895
13	dandy walker.mp.	1258
14	3 or 4 or 5 or 6 or 9 or 10 or 11 or 12 or 13	16031
15	Fetus/ or Pregnancy/	720818
16	Prenatal Diagnosis/	31148
17	f?etus.mp.	115409
18	f?etal.mp.	306437
19	pregnan$.mp.	787645
20	in utero.mp.	21043
21	or/15-20	927013
22	Ultrasonography, Prenatal/ or Ultrasonography/	86794
23	ultraso$.mp.	313296
24	22 or 23	313296
25	Magnetic Resonance Imaging/	279781
26	(magnetic resonance imag$ or MRI).mp.	368017
27	25 or 26	368017
28	14 and 21 and 24 and 27	338
29	Comment/	584249
30	Letter/	840238
31	Editorial/	355577
32	(comment or letter or editorial).pt.	1331667
33	case reports.pt.	1686033
34	29 or 30 or 31 or 32 or 33	2843406
35	28 not 34	204

2.4.5 Assessment of Methodological Quality of Included Studies

Included studies were assessed independently for methodological quality (DJ and CM) using the Quality Assessment of Diagnostic Accuracy Studies (QUADAS 2) tool (175). The QUADAS assessment was done in addition to data extraction in order to assess the quality of each study and their relevance to the review question. As recommended by the QUADAS guidelines, the data collection form was tailored to make the wording and the signalling questions specific to this review. The methodological quality of each study was rated in terms of the risk of bias using signalling questions to score the four key domains. These included: Patient selection, Index tests, Reference standard and Flow and Timing. Studies were scored as “Yes”, “No” and “Unclear” for each of the four items. Additional signalling questions for this review were introduced for both study design and index tests. These were questions to determine prospective versus retrospective study design and details regarding USS and iuMR technique and reporting as these were elements considered likely to introduce bias (Table 2.2). The answers to the signalling questions were reviewed and an overall score of “Low risk” “High risk” or “Unclear” given for each of the four domains. The risk of bias for each domain was decided according to the number of positive answers to the signalling questions; where all 4 or 3 responses were positive (yes) the domain was categorised as low risk and if there were 2 or less positive responses the domain was categorised as high risk. If the study did not report the answer to one of the signalling questions or a question could not be answered definitively then the domain was scored as unclear.

Three domains (Patient selection, Index tests and Flow and timing) for each study were also examined to determine if there was any concern regarding applicability to the review question. This was judged by a single question for each of the three domains. Exclusion criteria stated within the review protocol were applied before questions were answered yes (Low concern) or No (high concern). When detail reported was insufficient to answer the signalling question an Unclear score was given.

TABLE 2.2 Questionnaire to Assess the Quality and Applicability of included studies.
QUADAS 2 ASSESSMENT: Answer Y=yes N= no U=unclear
Does the paper report diagnostic accuracy?
Is the paper relevant to the review question?
If the answer is yes to both questions continue with assessment, if no consider excluding from the review.
DOMAIN 1: Patient Selection
Bias Assessment
1.1. Were selection criteria clearly described?
1.2. Was a consecutive or random selection of patients enrolled?
1.3. Was case-control avoided?
1.4 Was the study prospective?
Overall what is the likelihood the selection of patients introduced bias? (High, Low Unclear)
Applicability
1.5. Do the patients included match the review question?
Yes score Low, No score High and Unclear or not reported score unclear
DOMAIN 2: Index Test(s)
Bias Assessment
2.1. Was the execution of US explained in enough detail to allow its replication?
2.2. Was the execution of MR explained in enough detail to allow its replication?
2.3. Was the US performed and interpreted by a specialist/fetal maternal expert?
2.4. Was the MR performed and conducted by a specialist/ experienced radiologist?
Overall what is the likelihood the conduct of the index tests have introduced bias? (High, Low , Unclear)
Applicability
2.5. Did the flow of patients match how USS and iuMR are used in clinical practice?
Yes score Low, No score High and Unclear or not reported score unclear.
DOMAIN 3: Reference Standard
Bias Asssessment
3.1. Was the reference standard interpreted without knowledge of the results of the index tests?
3.2. Did all participants have a reference standard?
3.3. Did all participants receive the same reference standard?
3.4. Was the reference standard used one specified in the review protocol?
Overall what is the likelihood the reference standard, its conduct or its interpretation introduced bias? (High, Low , Unclear)
Applicability
3.5 Is there concern that the target condition as defined by the reference standard does not match the review question?
Yes score Low, No score High and Unclear or not reported score unclear.
Domain 4: Flow and Timing
Bias Assessment
4.1. Was MRI performed within 2 weeks of Ultrasound in all cases?
4.2. Was the reference standard conducted within the timeframe specified in the review protocol?
4.3. Were all participants included in the analysis?
4.4. Were withdrawals from the study explained?
What is the likelihood the flow of patients could have introduced bias? (High, Low Unclear)

2.4.6 Data Items and Analysis

Study characteristics and outcomes of the included studies were extracted independently by DJ and CM and documented using a custom designed data collection form (Table 2.2). This was piloted on 3 citations to ensure that all the relevant information for analysis was captured. Characteristics noted for each study were: date of publication and objective, study design and setting, sample size, details of USS and iuMR and time lapse between the two. The number of correct and incorrect diagnoses made by both USS and iuMR were also recorded as judged by the outcome reference diagnosis confirmed by postnatal imaging, autopsy or surgery. Clinical examination was discounted as a reference standard as it is rarely able to confirm or refute a diagnosis as the majority of structural brain abnormalities are not apparent externally. Where studies reported the results of imaging from multiple anatomical areas, only the results of the fetal brain were included.

It was anticipated that all studies would recruit only (or predominantly) fetuses with a brain abnormality diagnosed by USS, meaning the sensitivity and specificity of the imaging modalities could not be estimated due to the lack of fetuses without brain abnormality. Therefore, the analysis defined diagnostic accuracy for each modality as the percentage of cases where the diagnosis was confirmed by ORD. In fetuses with multiple abnormalities a primary diagnosis was identified as the abnormality with the most detrimental clinical outcome. In cases where both modalities identified the primary diagnosis but one provided a more specific diagnosis and/or additional information without fundamentally changing the primary diagnosis, our analysis assumed both modalities were correct but the nature of disagreements was subsequently investigated.

A meta-analysis of the diagnostic accuracy of iuMR in relation to USS was conducted using the Stata statistical analysis software (176). For each study the odds ratio for the paired iuMR and USS accuracies and its standard error were computed using the method of Becker and Balagtas, using a 0.5 correction for zero cells (177, 178). Odds ratios were combined using a random effects model and the I^2 statistic was used as an indicator of heterogeneity

within the included studies (179, 180).

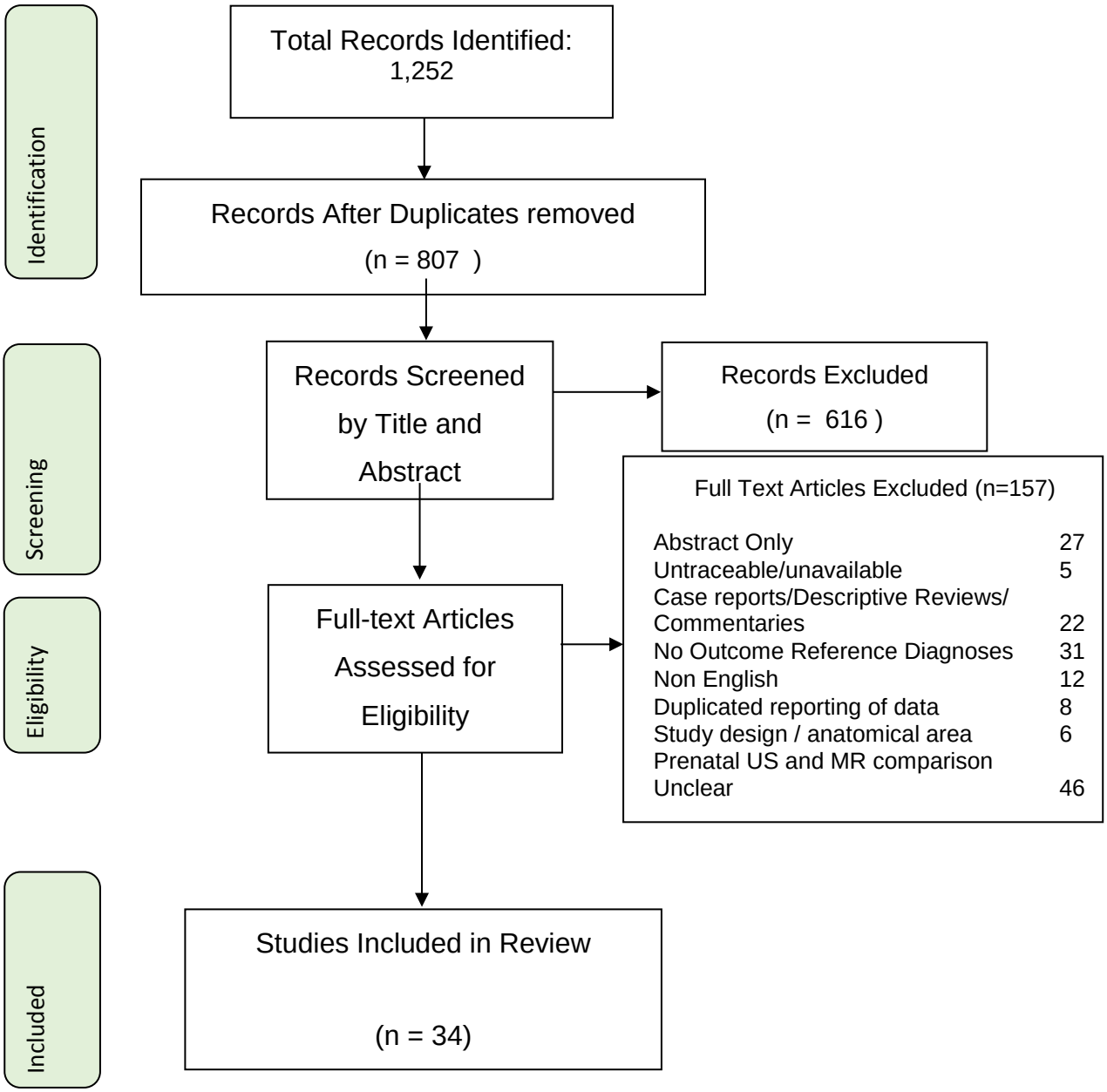
Table 2.3 Data Items Recorded For Each Study
Author, Year
Title and Objective
Publication Type
Country of Study
Language of Publication
STUDY CHARACTERISTICS
Target Population
Method of Selection
Retrospective (R) Prospective (P)
TOTAL Number in Study
Number Excluded + Reasons
FINAL Number Included in Review
ULTRASOUND DETAILS
Age range of Fetus' at USS (weeks)
Level of USS- Routine (R) or specialist (S)
Was USS equipment and technique described? (2D, 3D, TV etc)
Experience of Sonographer
Problems Encountered? If yes specify
iuMR DETAILS
Age of Fetus' at iuMR
Time delay between USS and iuMR
Was iuMR Technique and equipment described?(Magnet strength, use of sedation, sequences used etc)
Fetal iuMR experience of reporting radiologist
Was the radiologist blinded to USS report?
Problems Encountered? If yes specify
OUTCOME DETAILS
Reference Standard Used
Within 6 months?
ANALYSIS - numbers confirmed by outcome reference diagnosis
iuMR and USS agreed and correct
iuMR and USS agreed but both wrong/missed significant finding
iuMR changed diagnosis (USS wrong)
USS additional information to iuMR (USS more exact)
USS changed diagnosis (iuMR wrong)
Number Where iuMR Changed Counselling
Number Where iuMR Changed Management
Specific Abnormalities where iuMR was most accurate
Specific Abnormalities where iuMR was inaccurate

2.5 Results

Our initial searches generated a total of 1,250 potential studies with 807 remaining for additional scrutiny after duplicates were removed. Further screening resulted in 34 published studies for final inclusion in the review (17, 21, 81, 83, 120, 181-209), Categories for exclusion of full papers reviewed but rejected are listed in the PRISMA flowchart (Figure 2.1).

Figure 2.1 PRISMA Flowchart of Study Selection

"Image reproduced from: Jarvis D, Mooney C, Cohen J, et al. (2017) A systematic review and meta-analysis to determine the contribution of mr imaging to the diagnosis of foetal brain abnormalities In Utero. Eur Radiol 27:2367-2380."



2.5.1 Study Characteristics

The 34 studies were published over a 20 year period (1994-2014) as listed in Table 2.4. With regard to study design 19 studies (21, 83, 120, 181, 183, 185, 188, 191, 192, 198, 202, 207, 209-214) were prospective and 12 retrospective (17, 81, 84, 184, 187, 190, 195-197, 203, 206, 215) but this was not specified in 3 studies (189, 200, 216). All studies selected a consecutive cohort of patients with either a remit to investigate all fetal brain abnormalities (24 studies (120, 165, 181, 184, 188-191, 195-199, 202-205, 209, 214, 217-221)) or to investigate a more specific brain abnormality e.g. ventriculomegaly, corpus callosum anomalies (10 studies (17, 21, 81, 182, 192, 194, 200, 201, 222, 223))

USS was performed in a tertiary centre and/or conducted by fetal medicine experts in 21/34 studies (17, 83, 84, 120, 184, 185, 187, 188, 190-192, 195, 198, 204, 206, 207, 209, 210, 212, 214, 224), in 12/34 (21, 181, 183, 189, 197, 200, 202, 203, 207, 211, 215, 216) it was either unclear or not specified, and in 1 study (196) USS was performed in a routine clinical setting. Clear details regarding USS technique (transabdominal or transvaginal imaging views obtained) and equipment (manufacturer, transducer) were provided in 21 studies (17, 21, 83, 120, 181-183, 185-189, 191-193, 195, 199-201, 206, 224). The remaining 13 studies provided minimal information or the details were not given (184, 194, 196-198, 202-205, 207-209). 3/34 acknowledged technical difficulties in some cases which limited the USS including fetal lie, maternal obesity and oligohydramnios (189, 201, 207). The age range of fetuses reported across studies was 13-41 weeks gestation. Time delay between USS and iuMR was less than two weeks in 19/34 (83, 120, 181, 183, 186, 188, 190, 191, 193-196, 198, 202, 203, 205-208), not specified in 13/34 studies (21, 81, 182, 184, 187, 189, 192, 197, 199-201, 204, 209) and in 2 studies there were cases in which the time delay was greater than 2 weeks (15 and 17 days (17, 185)).

Details regarding the experience of the clinician reporting the iuMR study were only available in 10/34 studies (17, 83, 185, 191, 194, 195, 198, 201, 207, 208), half of these quantified this in terms of years (between 1 and 15) and for the remaining a description of ‘experienced’

was given. In 2 studies, the reporting radiologist was unaware of USS findings (17, 198). Details regarding MR imaging technique was reported in all papers including manufacturer, sequences and types of receiver coils used. Fast T2 weighed sequences were performed in all studies with some using an additional range of imaging sequences (T1, DWI, 3D and FLAIR). Early studies reported the use of fasting and sedation in order to achieve optimal imaging (21, 211).

2.5.2 Methodological Quality

The results of the methodological quality assessments using the Quadas 2 criteria are presented in Figure 2.2. Risk of bias for patient selection and applicability was low in 31/34 (91%) studies (17, 21, 81, 83, 84, 120, 181, 184, 187, 188, 190-192, 195-198, 200, 202, 206, 207, 209-215, 218, 222), high in 1 (6%) (203) and unclear in 2 (12%) (189, 216) with high risk of bias due to patient selection criteria not being defined and retrospective study designs. The risk of bias due to conduct and interpretation of the index tests was low risk in 15/34 (44%) studies (17, 81, 83, 84, 120, 187, 191, 195, 198, 206, 207, 212, 214, 218), high risk in 4/34 (12%) studies (184, 196, 197, 203) and unclear in 15/34 (44%) (21, 181, 188-190, 192, 200, 202, 209-211, 213, 215, 216, 222). Assessment of potential bias introduced by the reference standard was considered low risk in 19/34 (56%) studies (84, 120, 184, 187-189, 196, 198, 200, 206, 207, 209, 211-213, 216, 218, 222), high risk in 9 (26%) (21, 181, 190, 191, 197, 203, 210, 214, 224) and unclear in 6/34 (18%) (17, 83, 192, 195, 202, 215), as there were a proportion of cases within the study that did not have a confirmed outcome diagnosis or it was determined by clinical examination. Bias in the flow and timing as judged by timing between USS and iuMR imaging or due to methods used for analysis of findings was deemed low in 14/34 **(**41%) (83, 120, 181, 183, 185, 188, 202, 203, 206, 207, 214-216), high in 12/34 (35%) (17, 21, 84, 184, 187, 190, 192, 195, 197, 198, 209, 224) and unclear in 8/34 (24%) (189, 191, 196, 200, 210-213). The majority of the studies posed no concern regarding applicability for each of the three domains, with only 3% posing high and

6% unclear concern regarding index tests and 3% unclear applicability regarding patient selection.

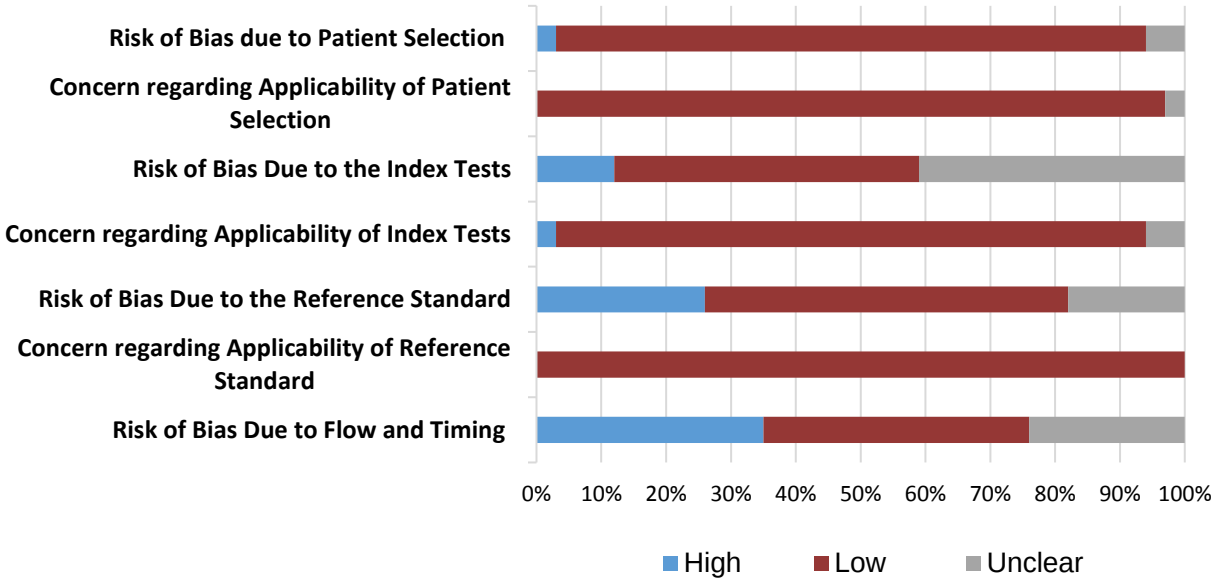


Figure 2.2 QUADAS 2 Risk of Bias and Applicability Assessment Results

2.5.3 Diagnostic Accuracy of USS and MRI

The 34 included studies reported a combined total of 2530 fetuses (Median 32.5, Range 10-834) but of these 62% (n=1,571) were excluded as they did not have an iuMR (n=796), 542 did not have an ORD, were non-brain pathology (n=159) or other exclusions (n=74). Consequently this systematic review reports on the outcomes of 959 fetuses. In 6/34 studies (188, 196, 207, 212, 213, 216), all fetuses had an ORD and when combined contributed 186/959 to the analysis in this review (median 24.5, Range 12-72). The remaining 773/959 (median 38, Range 10-834) fetuses were from the outstanding 28 studies (17, 21, 81, 83, 84, 120, 181, 183-185, 187, 189-192, 195, 197, 198, 200, 202, 203, 206, 207, 209-211, 214, 215).

The overall diagnostic accuracy combined across 34 studies were 75.2% for USS and 91.0% for iuMR (overall odds ratio=3.10, 95% CI 1.98 to 4.86, p<0.0001; Figure 2.3). Although individual studies were heterogeneous (I^2 = 45%; p=0.002), nearly all reported an improvement in diagnostic accuracy following iuMR. The data is also represented in the form of a L'Abbe plot (Figure 2.4) in which the diagnostic accuracies of iuMR and USS are presented as percentages, with the different sample sizes being represented by size of the plotted circles.

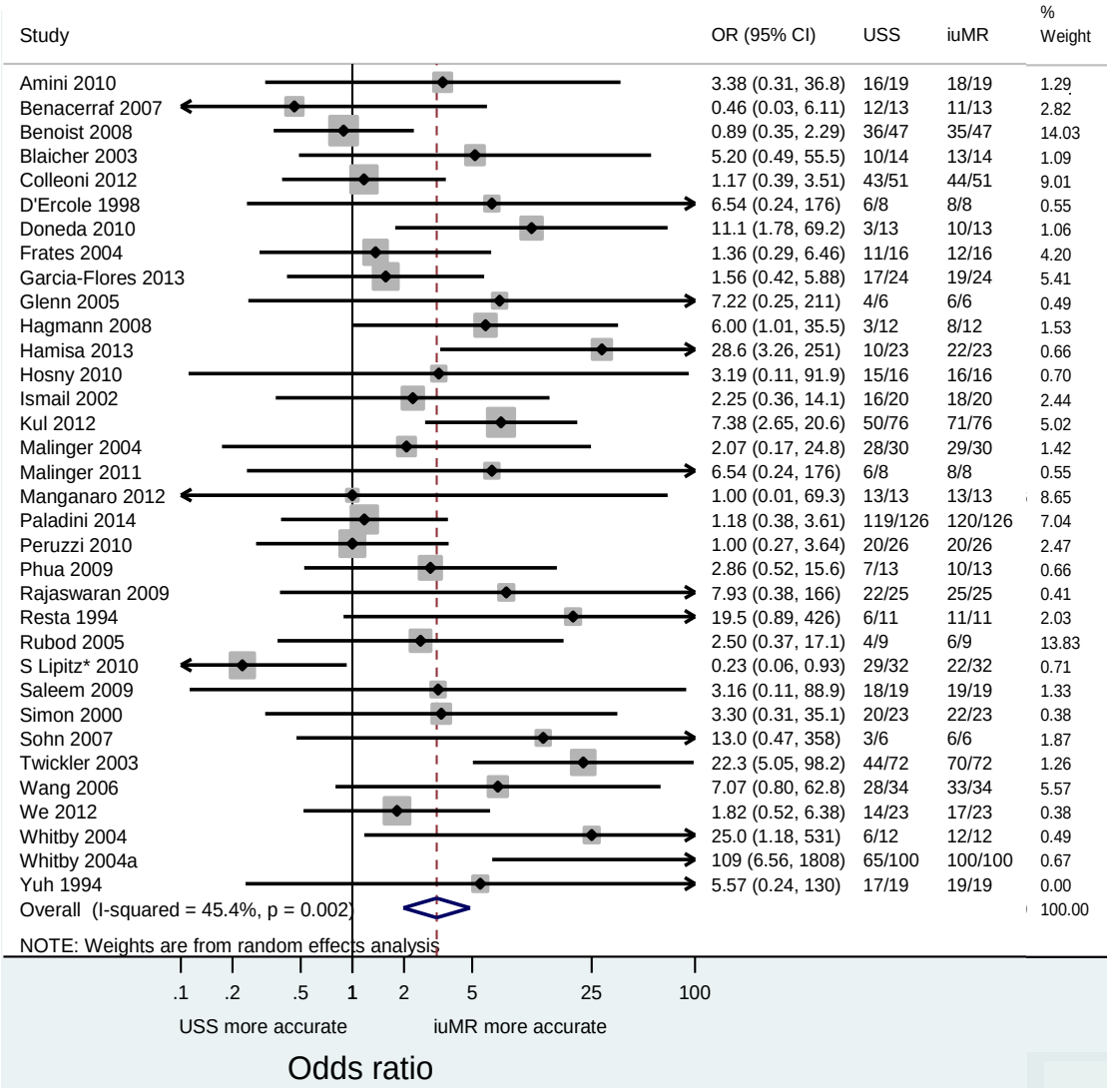


Figure 2.3 Forrest Plot Showing the Odds Ratios of diagnostic accuracy for all studies (First Author and Date only) and overall effect Odds Ratio with Confidence Intervals.

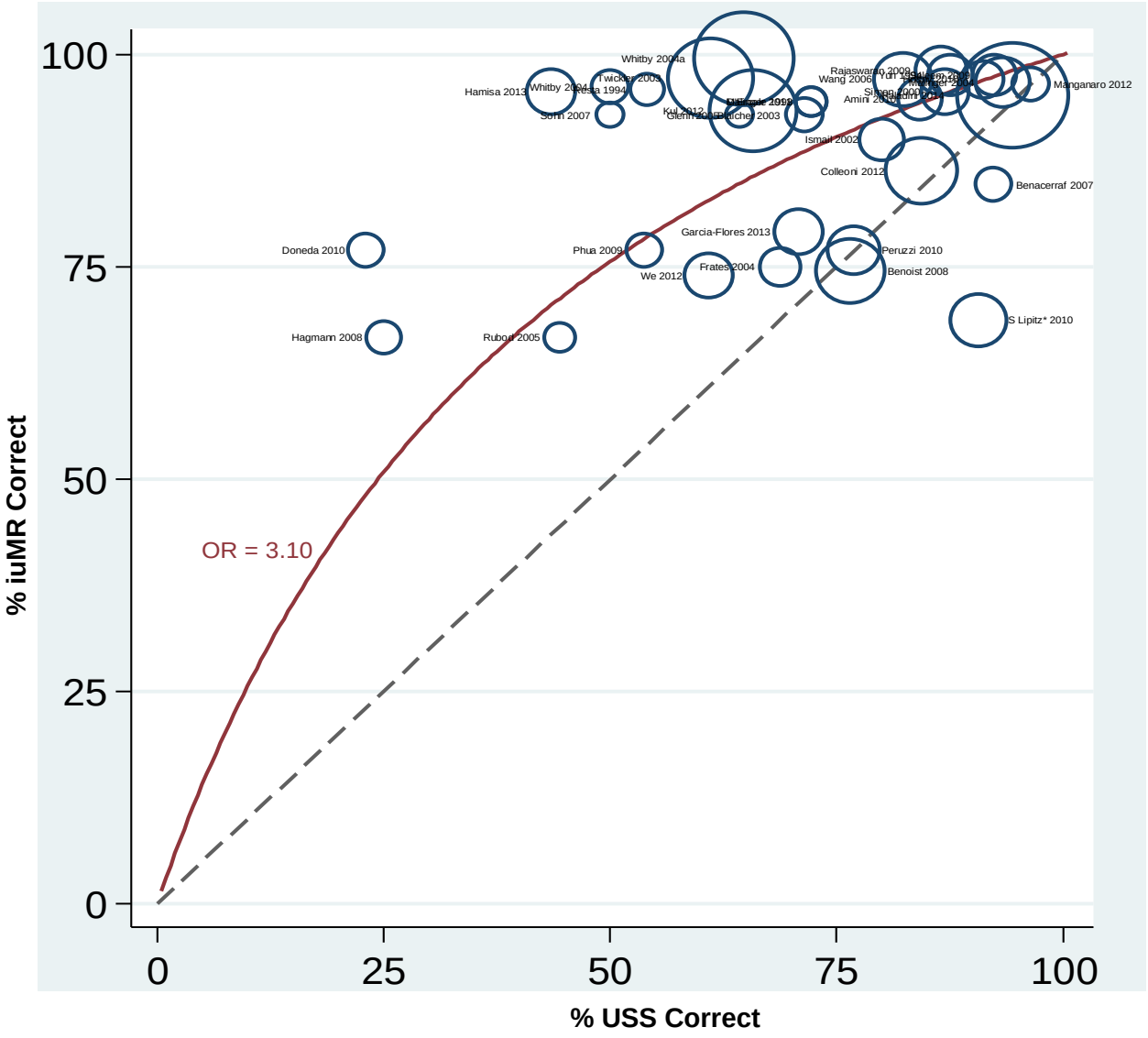


Figure 2.4 L'Abbe plot of diagnostic accuracy of USS and iuMR. Circle size is proportional to sample size of each study. The dotted line indicates equal diagnostic accuracy between USS and iuMR and the solid line is the overall odds ratio line and represents a ratio of 3.1, estimated by pooling the results from all studies

"Image reproduced from: Jarvis D, Mooney C, Cohen J, et al. (2017) A systematic review and meta-analysis to determine the contribution of mr imaging to the diagnosis of foetal brain abnormalities In Utero. Eur Radiol 27:2367-2380."

Agreement between USS and iuMR

The reports from USS and iuMR were in agreement and agreed with the ORD in 527/959 (55%). USS and iuMR were in agreement but discordant with the ORD in 52/959 (5.5%) fetuses (Table 2.5 1a, 1b)

In 160/959 (16.5%) fetuses iuMR and USS were in agreement regarding the primary diagnosis but additional information was added- either secondary diagnoses or a more concise/confident primary diagnosis given. In this category iuMR provided additional information in 146/959 (15%) and USS provided additional information in 14/959 (1.5%) cases as confirmed by ORD.

Disagreement between USS and iuMR

The diagnoses on iuMR and USS disagreed in 222 (23%) cases. Of these, the iuMR was in agreement with the ORD in 186 (19%), the majority of which were abnormalities undetected by USS (139/186, 75%). The remaining 47/186 (25%) were abnormalities reported by USS but correctly excluded by iuMR. In 34 cases the USS diagnosis was incorrectly overturned by iuMR, 10 of which were abnormalities wrongly excluded or missed by iuMR and 24/34 were abnormalities diagnosed by iuMR but not found by USS or on the ORD (Table 2.5 2b and 3b).

Table 2.6 presents the discordant diagnoses between USS and iuMR according to category of abnormality. The most frequent areas of disagreement were midline (24%) and posterior fossa abnormalities (21%). In particular agenesis of the corpus callosum and the Dandy Walker spectrum of abnormalities were frequently missed or, less frequently, wrongly identified on USS. The most frequently misdiagnosed anomaly on both USS and iuMR were cortical formation abnormalities (17%) such as hemimegalencephly, lissencephaly and heterotopia.

Changes in Counselling and Management

Eleven studies, (120, 187, 189, 190, 196, 206, 207, 209, 212, 213) reporting on 186 fetuses, specified the benefit of iuMR in terms of changes to counselling of parents or management of the pregnancy. These changes as a result of findings on iuMR affected 78/186 (41.9%) fetuses.

Table 2.4 Details of the 34 studies included in the review, listed as first author and date

Author, Year	Title/objective	Country of Study	Target Population	Method of Selection	Retrospective (R) Prospective (P) Not Specified (NS)	TOTAL Number in Study	FINAL Number included in Review
AMINI, H.*et al* 2010	The clinical impact of fetal magnetic resonance imaging on management of CNS anomalies in the second trimester of pregnancy.	Sweden	Fetuses with suspected CNS abnormality on USS	Consecutive	P	29	18
BENACERRAF, B. *et al* .2007	What does magnetic resonance imaging add to the prenatal sonographic diagnosis of ventricidomegaly?	USA	Fetuses with VM on USS	Consecutive	P	26	13
BENOIST, G., *et al* 2008	Cytomegalovirus-related fetal brain lesions: Comparison between targeted ultrasound examination and magnetic resonance imaging.	France	Fetuses with CMV infection	Consecutive	R	49	47
BLAICHER, W.*et al* 2003	Magnetic resonance imaging in foetuses with bilateral moderate ventriculomegaly and suspected anomaly the corpus callosum on ultrasound scan.	Austria	Fetuses with suspected VM and ACC on USS	consecutive cases with VM and ACC	P	41	14
COLLEONI, G. *et al* 2012	Prenatal diagnosis and outcome of fetal posterior fossa fluid collections.	Italy	Fetuses with posterior Fossa abnormality on USS	Consecutive fetuses with Posterior Fossa Abnormalities	R	105	51
D'ERCOLE, C.*et al* 1998	Prenatal diagnosis of fetal corpus callosum agenesis by ultrasonography and magnetic resonance imaging.	France	Fetuses with suspected ACC on US	Consecutive	P	14	8
DONEDA, C.*et al* 2010	Early cerebral lesions in cytomegalovirus infection: Prenatal MR imaging.	Italy	Fetuses with CMV infection	Consecutive	P	38	13
FRATES, M.*et al* 2004	Fetal anomalies: comparison of MR imaging and US for diagnosis.	USA	fetuses with abn detected at US	Consecutive	P	27	16
GARCIA-FLORES, J.*et al* 2013	Fetal magnetic resonance imaging and neurosonography in congenital neurological anomalies: Supplementary diagnostic and postnatal prognostic value.	Spain	Fetuses with cns abn	Consecutive	R	28	24
GLENN, O. A.*et al* 2005	Fetal magnetic resonance imaging in the evaluation of fetuses referred for sonographically suspected abnormalities of the corpus callosum.	USA	fetuses with suspected CC abn	consecutive cases selected of fetuses with suspected CC abn	R	10	6
HAGMANN, C. F *et al* 2008	Foetal brain imaging: ultrasound or MRI. A comparison between magnetic resonance imaging and a dedicated multidisciplinary neurosonographic opinion.	UK	comparison of stand US, specialist US and MRI accuracy + change in management	Consecutive	R	51	12 (comparison of specialist US and MRI only)

Author, Year	Title/objective	Country of Study	Target Population	Method of Selection	Retrospective (R) Prospective (P) Not Specified (NS)	TOTAL Number in Study	FINAL Number included in Review
HAMISA, M.*et al* 2013	Magnetic resonance imaging versus Ultrasound examination in detection of prenatal fetal brain anomalies.	Eygpt	Fetuses with suspected Brain abnormality on USS	Consecutive	P	23	23
HOSNY, I. A. & ELGHAWABI, H. S. 2010	Ultrafast MRI of the fetus: an increasingly important tool in prenatal diagnosis of congenital anomalies.	Eygypt	Fetuses with suspected Brain abnormality on USS	Consecutive	NS	25	16
ISMAIL, K. M.*et al* 2002	Fetal magnetic resonance imaging in prenatal diagnosis of central nervous system abnormalities: 3-year experience.	UK	Fetuses with suspected Brain abnormality on USS	Consecutive	R	27	20
KUL, S.*et al* 2012	Contribution of MRI to ultrasound in the diagnosis of fetal anomalies.	Turkey	Fetuses with suspected Brain abnormality on USS	Consecutive	P	184	76
MALINGER, G.*et al* 2004	Fetal brain imaging: A comparison between magnetic resonance imaging and dedicated neurosonography.	Israel	Fetuses with suspected Brain abnormality on USS	Consecutive	P	42	30
MALINGER, G.*et al* 2011	Can syndromic macrocephaly be diagnosed in utero?	Israel	fetuses with suspected macrocephaly on US	Consecutive	R	98	8
MANGANARO, L.*et al.* 2012	Role of foetal MRI in the evaluation of ischaemic-haemorrhagic lesions of the foetal brain.	Italy	Fetuses with ischaemic-haemorrhagic lesions	consecutive with inclusion criteria	P	271	13
PERUZZI, P.*et al* 2010	Magnetic resonance imaging versus ultrasonography for the in utero evaluation of central nervous system anomalies.	USA	Fetuses with suspected CNS abnormality on USS	Consecutive	R	26	26
PHUA, H. *et al* 2009	Magnetic resonance imaging of the fetal central nervous system in Singapore.	Singapore	Fetuses with suspected CNS abnormality on USS	fetuses who had an mri	R	31	13
RESTA, M. *et al.*1994	Magnetic resonance imaging in pregnancy: study of fetal cerebral malformations.	Italy	Fetuses with suspected CNS abnormality on USS	Consecutive	P	15	11
RUBOD, C.*et al* 2005	. Role of fetal ultrasound and magnetic resonance imaging in the prenatal diagnosis of migration disorders.	France	fetuses with suspected migration abn on US	Consecutive	NS	14	9
SALEEM, S. N.*et al* 2009	Fetal MRI in the evaluation of fetuses referred for sonographically suspected neural tube defects (NTDs): Impact on diagnosis and management decision.	Eygypt	fetuses with suspected NTD on US	Consecutive	P	19	19

Author, Year	Title/objective	Country of Study	Target Population	Method of Selection	Retrospective (R) Prospective (P) Not Specified (NS)	TOTAL Number in Study	FINAL Number included in Review
SIMON, E. M.*et al* 2000	Fast MR imaging of fetal CNS anomalies in utero.	USA	Fetuses with suspected CNS abnormality on USS	Consecutive	p	73	23
SOHN, Y.*et al* 2007	The usefulness of fetal MRI for prenatal diagnosis.	Korea	Fetuses with suspected CNS abnormality on USS	Consecutive	R	30	6
TWICKLER, D. M.*et al* 2003	Second-opinion magnetic resonance imaging for suspected fetal central nervous system abnormalities.	USA	Fetuses with suspected CNS abnormality on USS	Consecutive	P	72	72
WANG, G.*et al* 2006	Fetal central nervous system anomalies: Comparison of magnetic resonance imaging and ultrasonography for diagnosis.	China	Fetuses with suspected CNS abnormality on USS	Consecutive	NS	34	34
WE, J. S.*et al* 2012	Usefulness of additional fetal magnetic resonance imaging in the prenatal diagnosis of congenital abnormalities.	Korea	Fetuses with suspected Brain abnormality on USS	Consecutive (8yrs)	R	81	23
WHITBY, E. H.*et al* 2004**A**	Comparison of ultrasound and magnetic resonance imaging in 100 singleton pregnancies with suspected brain abnormalities.	UK	Fetuses with suspected CNS abnormality on USS	Consecutive	P	101	100
WHITBY, E. H.*et al* 2004	Corroboration of in utero MRI using post-mortem MRI and autopsy in foetuses with CNS abnormalities.	UK	fetuses with prenatal US and iuMRI and who underwent PM MRI	Consecutive	P	12	12
YUH, W. T.*et al* 1994	MR of fetal central nervous system abnormalities.	USA	Fetuses with suspected CNS abnormality on USS	Consecutive	P	22	19
Rajaswaran et al 2009	Ultrasound versus MRI in the diagnosis of fetal head and trunk abnormalities	India	Fetuses with suspected head or trunk abnormality on USS	Consecutive fetuses with head or trunk abn	P	40	30
S. LIPITZ *et al* 2010	Value of prenatal ultrasound and magnetic resonance imaging in assessment of congenital primary cytomegalovirus infection	Israel	Fetuses with CMV infection	Consecutive	P	38	35
D. PALADINI *et al* 2014	Accuracy of neurosonography and MRI in clinical management of fetuses referred with central nervous system abnormalities	Italy	Accuracy of US and MRI	Consecutive	R	834	126

TABLE 2.5 Results of the number (n=) and percentages (second column) of fetuses within each category of outcome.

		n=	%
1a	iuMR and USS agreed and Correct	527	55
1b	iuMR and USS agreed but Incorrect	52	5.5
2a	iuMR more exact/ additional Info to USS	146	15
2b	iuMR changed incorrect USS diagnosis	186	19
3a	USS more exact/ additional Info to iuMR	14	1.5
3b	iuMR incorrectly changed correct USS diagnosis	34	4
	TOTAL	959	

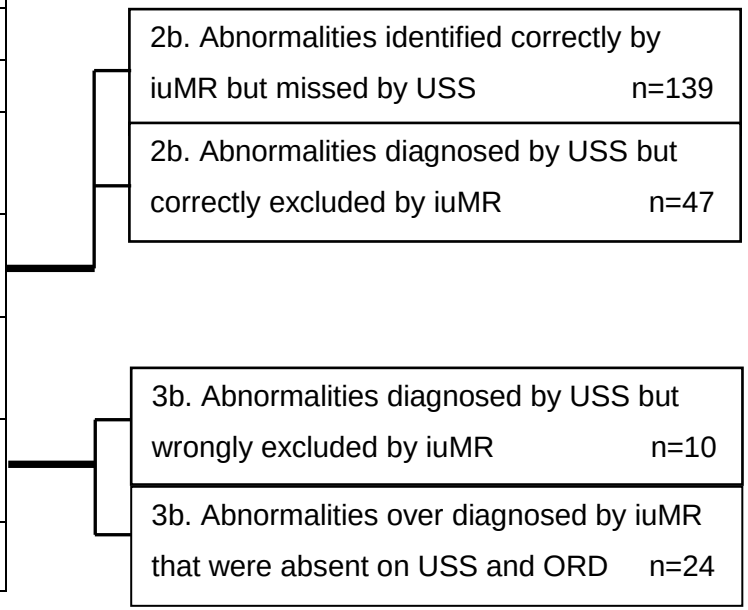


TABLE 2.6 Discordant diagnoses according to abnormality detected						
Abnormalies Identified	Abnormalities identified correctly by MRI but missed by US	Abnormalities diagnosed by US but correctly excluded by MRI	Abnormalities diagnosed by US but wrongly excluded by MRI	Abnormatilies over diagnosed by MRI that were absent on US and ORD	US and MRI diagnoses both wrong (either missed or overdiagnosed)	All Groups
VENTRICULAR SYSTEM Ventriculomegaly Aqueduct stenosis	5	10	1	1	6	23
NEURAL TUBE DEFECTS Anencephaly Encephalocoele Mylomeningocoele	5	5	0	1	1	12
CORTICAL FORMATION ABNORMALITIES Hemi/Megalencephaly Schizencephaly Lissencephaly Heterotopia Microcephaly	21	3	3	5	14	46
MIDLINE ABNORMALITIES Holoprosencephaly Agenesis/Hypogenesis of Corpus Callosum Absent Cavum Septum	39	15	2	1	7	64
POSTERIOR FOSSA ABNORMALITIES Mega Cisterna Magna Blakes Pouch Cyst Dandy Walker or Variant Cerebellar or Vermian Hypoplasia	28	13	2	2	12	57
VASCULAR ABNORMALITIES Haemorrhage Haematoma Dural Fistula Aneurysm	17	0	1	1	1	20
DESTRUCTIVE OR MASS CEREBRAL LESIONS Tumours, Cysts, PVL Other Lesions, Dysplasias	24	1	1	13	11	50
TOTALS	139	47	10	24	52	

2.6 Discussion

This systematic review and meta-analysis demonstrate that using iuMR to support USS in the diagnosis of fetal brain abnormalities increases diagnostic accuracy by 16% (75% for USS alone and 91% for iuMR as an adjunct). The heterogeneity of the included studies was moderate (I^2 = 45%, p=0.002) according to the definitions of Higgins *et al* (225), suggesting there was methodological and clinical variability and inconsistency in the measurement of outcomes within each study. This heterogeneity is also reflected in the results of the QUADAS assessment of the included studies with the highest proportion of studies being scored as having a high risk of bias in the Reference Standards and Flow and Timing categories. This was mainly due to the time delay between USS and iuMR, exclusion of cases from analysis and failure to report details regarding outcome reference diagnosis.

Although investigation of heterogeneity as part of a meta-analysis is recommended (225), the ability to do so within this review is compromised by the lack of reporting (and indeed quantification) of all the ways in which studies differ. The performance of both diagnostic tests is influenced by many factors and a limitation of this review was incomplete reporting of characteristics that would potentially influence diagnostic performance such as operator experience (specified in just a third of included studies) and technical difficulties (three studies) (165, 189, 212). iuMR is not without its limitations and our review demonstrated that iuMR overestimates the presence of abnormalities more frequently than failing to identify them. This could be explained by the nature of fetal iuMR in which the need for fast imaging compromises image quality. To the untrained eye artefacts from maternal breathing, fetal movement and image aliasing may potentially mimic or obscure pathology (57). It is for this reason ‘experience’ should perhaps be defined more specifically, for example by the number of fetal brain examinations reported.

The timing of USS in relation to iuMR imaging is also relevant in the assessment of both tests. The fetal brain develops rapidly and significant delay between the two examinations may influence the ability to diagnose accurately either because of natural brain development, increase in size of critical anatomical structures or because of disease progression. 13/34 studies failed to report any delay time, making an overall analysis of effect from this criteria unreliable and another area that suggested an element of bias within those studies.
The extent to which iuMR ultimately contributes to changes in management or in counselling regarding the pregnancy is also unclear as this was only reported in a small proportion of studies. Equally the impact of a wrong diagnosis made by iuMR was not defined in any study despite it occurring in 14/34 studies (84, 120, 181, 187, 188, 190, 192, 195, 196, 198, 202, 206, 213, 215, 218).

Our review builds on the systematic reviews undertaken by Rossi and Prefumo (172) and Van Doorn *et al* (173). Rossi and Prefumo identified 2323 potential studies published between years 2000 and the end of 2012 and reviewed 13 studies (710 fetuses), having excluded 2293 by title and abstract. Van Doorn *et al* searched for publications between years 1990 and March 2014 and identified 2748 and excluded 2577 by title and abstract with 27 studies (1184 abnormalities detected by USS but only 454 with ORD) reviewed. The differences of search dates and of exclusion criteria, described earlier, appear to be the factors resulting in the variation of studies reviewed by each study. An important difference between the two is that Rossi and Prefumo restricted studies to those where outcomes were confirmed by a reference diagnosis, although chose to accept clinical examination as an ORD whereas Van Doorns selection criteria did not require an ORD. A strength of our review was the requirement of an ORD for any outcomes included in the meta- analysis. As previously stated we excluded clinical examination as an ORD. Although this significantly reduced the number of outcomes available we felt this was justified as most structural brain abnormalities, and consequently diagnostic accuracy, cannot be determined with certainty on clinical examination alone.

Our analysis included 34 studies, of which, 15 were additional to those included in the previous reviews due to more recent searches and differences in selection criteria such as unlimited year of publication or sample size within studies. Although Van Doorns searches were unrestricted by non-English publications or the requirement of an ORD our review included more studies. This may be due to the limitation of sample size of >20 by Van Doorn, resulting in 6 additional studies in this review, and the requirement of 'adequate description of diagnoses' which was not clearly defined by Van Doorn.

Even with subtle differences in methods between all the reviews, findings were similar. Rossi reported that iuMR was accurately able to identify brain abnormalities in 94•3% of included fetuses, Van Doorn reported 80% and our study 91%, an increase of 15-20% when compared to USS alone. Both Rossi and Van Doorn reported the highest proportion of disagreement between USS and iuMR was related to midline abnormalities, particularly the posterior fossa. iuMR was better able to diagnose abnormalities in this anatomical region, also consistent with the findings of this systematic review which incorporates a further 4 studies published since 2012. One significant flaw, but acknowledged as such by Rossi and Perfumo was to undertake pooled sensitivity and specificity analysis of iuMR results as part of their review. Whilst ideally this analysis should be performed to adequately assess diagnostic performance it was inappropriate in this instance as none of the studies included cases that were true or false negative, having all been referred from USS with a suspected brain abnormality.

The statistical methods required for a meta-analysis differ from standard methods with contribution to analysis weighted according to size of study and data pooled to provide an overall measure of diagnostic accuracy and the heterogeneity amongst studies. Rossi and Van Doorn did not quantify heterogeneity, although both reviews highlighted the inadequate reporting of study characteristics, which may compromise the findings of all three systematic

reviews. In order to adequately assess the accuracy of a diagnostic test and determine its true benefit in clinical practice optimal study design is necessary [52].

Replication of the previous reviews is both justified and necessary- it reassures that the minor differences in inclusion and exclusion criteria, both at study selection and data extraction, do not change the outcomes significantly, thus adding weight to the current evidence base. In spite of the different nature of all the studies the diagnostic accuracy of iuMR was clearly superior across the studies but the heterogeneity identified may compromise these findings. The moderate level of heterogeneity acknowledged by our review warranted further investigation but was prevented by insufficient reporting of study characteristics. Despite its increasing use in clinical practice poor study design has previously brought into question the diagnostic capabilities of iuMR above that which is achieved by USS and its benefit in terms of guiding the management of pregnancy. Further prospective studies with adequate sample size and unbiased assessment of diagnostic accuracy are needed.

2.7. Conclusion

When fetal brain abnormalities are suspected on USS, iuMR imaging is able to contribute significantly to the diagnostic pathway, both by clarifying findings and increasing significantly the detection rate of abnormalities, particularly in midline and posterior fossa abnormalities. The moderate methodological heterogeneity of the studies included suggests that further investigation is still required in order to clarify the full impact of iuMR.

Chapter 3

MERIDIAN: A Study to Investigate the Additional Value of iuMR Imaging for the Diagnosis of Fetal Brain Abnormalities

3.1 Summary

The systematic review highlighted significant methodological weaknesses within previous studies, therefore to address those limitations and thoroughly evaluate the role of iuMR imaging in the diagnosis of fetal brain abnormalities further research was necessary. Previous studies also failed to consider all elements of diagnostic test performance consequently the full impact of iuMR had not been established. This chapter presents key findings from the MERIDIAN study a large multicentre prospective study that aims to provide a comprehensive assessment of iuMR imaging as an adjunct to prenatal ultrasound when fetal brain abnormalities are suspected. The MERIDIAN protocol is published at http://www.nets.nihr.ac.uk/projects/hta/090601 (226).

The concept, planning and protocol development was completed before DJ worked in the Academic Unit of Radiology but timing was such that DJ was involved before commencement of recruitment and was named on the proposal as a principal researcher. The principle investigator for MERIDIAN is Professor Paul Griffiths, who is also supervisor of this work. Project management, administrative support and all statistical analysis for the study were undertaken by ScHARR. Patient recruitment was undertaken by feto-maternal experts and midwives at sites participating in the study. Funding for MERIDIAN was provided by the NIHR, which also funded 60% of working hours for DJ, whose role within MERIDIAN has been:

- Lead MR radiographer undertaking approximately 500 of the MR scans in Sheffield (500 hours)
- Answering queries from study midwives from the referring centres regarding suitability of possible participants. This included 3 queries requesting more detailed information about the scanning process and establishing the MR safety for 6 patients with implants.

- Entering data onto the central database for approximately 60 cases, and 'data cleaning'. This involved reviewing and correcting any erroneous information entered by others (20 hours work).
- Primary analysis of the processed data to calculate diagnostic confidence score with CM and PDG. This entailed reviewing the outcome data for each participant and on a case by case basis evaluating each using the diagnostic confidence framework to determine the confidence score (60 hours work).
- Contributing to the preparation of both the primary and secondary manuscripts accepted by The Lancet and Clinical Radiology as listed below. This included reading the manuscript, correcting grammatical and typographical errors and making suggestions with regard to content.

Publications arising from this work.

1) 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.

2) Griffiths PD, Bradburn M, Campbell M, Connolly D, Cooper C, Jarvis D, *et al*. Change in diagnostic confidence brought about by using in utero MRI for fetal structural brain pathology: analysis of the MERIDIAN cohort. Clinical Radiology. 2017;72(6):451-7.

3.2 Background

The results of the systematic review and meta-analysis demonstrated that iuMR imaging gave an overall improvement in diagnostic accuracy of 16% when used as an adjunct to USS. Although this finding is clinically significant, the review highlighted substantial

methodological limitations and moderate heterogeneity of the studies reviewed, which limits the validity of the results.

Whilst diagnostic accuracy is fundamental to diagnostic performance it is also necessary to consider how the additional information provided influences the clinicians, the patient and ultimately the management of the pregnancy. Changes in prognosis and perceptions of referring clinicians and the pregnant women involved were not considered in any of the studies included in the systematic review and the majority (23/34 studies) also failed to report if there were changes in the management of pregnancies as a result of iuMR imaging. The MERIDIAN study was designed to provide a comprehensive assessment of the diagnostic performance of iuMR for fetal brain abnormalities and address the limitations of previous research in order to inform the future role of iuMR

3.3 Primary Aims

The primary aims of MERIDIAN, and the focus of this chapter, cover two aspects of the study; the diagnostic accuracy and the diagnostic confidence of iuMR imaging in comparison to the performance of prenatal USS in relation to an outcome reference diagnosis and the influence these had on the management of the pregnancy. The MERIDIAN study also sought to determine the clinical impact of the inclusion of iuMR imaging in the diagnostic pathway. This aspect of the study was covered by measuring the referring clinician's perception of changes in the prognosis of pregnancies due to iuMR. The opinions of the pregnant women involved were also sought, through questionnaire and interview, with regard to their experience and perceived benefits or drawbacks of iuMR. However, as I was not involved in this work it was excluded from this report.

Aim 1. To assess the diagnostic accuracy of iuMR compared to antenatal USS through:

a) Measurement of the diagnostic accuracy of antenatal USS alone (i.e. prior to iuMR) relative to a reference diagnosis (post-natal imaging (CT, MRI or trans cranial USS) or post-mortem examination).

b) Measurement of the diagnostic accuracy of iuMR (following antenatal USS) relative to a reference diagnosis (post-natal imaging or post-mortem examination).

Primary Hypothesis

Null

The diagnostic accuracy achieved by iuMR imaging following detailed antenatal USS for suspected brain abnormalities is no greater than that achieved by ultrasound alone.

Aim 2. To assess the change in clinical diagnostic confidence before and after iuMR imaging and its influence on the management of pregnancy.

Secondary Hypothesis

Null

The diagnostic confidence achieved by iuMR imaging following detailed ante-natal USS examination for suspected developmental brain abnormalities is no greater than that achieved by USS alone.

3.4 Methods

3.4.1 Study Design and Ethics Approval

This is a prospective, observational, cohort study of diagnostic accuracy and diagnostic confidence undertaken in accordance with the Medicines for Human Use (Clinical Trials) Regulations 2004 and with ethics approval through the Integrated Research Application System (62734). The study was designed to include all brain abnormalities suspected or diagnosed, at antenatal USS by feto-maternal experts. Selection bias was minimised by

prospectively recruiting participants from 16 sites incorporating approximately 44% of the UK population, ensuring a wide geographic and socio-economic base. Participants were able to withdraw from the study at any time without their clinical care being affected. Consistency of data collection across all sites was ensured by providing a central electronic database, access to which was password protected to safeguard confidentiality. Each subject was assigned a study number to ensure anonymity.

The conduct of the study was overseen by three groups: a Trial Steering Committee, a Data Monitoring and Ethics Committee, both of which were independent of the study, and a Trial Management Group, consisting of researchers who were part of the study team.

3.4.2 Calculation of Sample size

It was estimated that the study would recruit from a possible referral base of 564,333 pregnancies, of which 0.3% were predicted to have a fetal brain abnormality and therefore eligible for inclusion (1). The study aimed to recruit a minimum of 750 pregnant women in order to provide 504 complete cases in which a definitive reference outcome diagnosis was available. It was estimated that fetal brain abnormalities are accurately diagnosed by USS in approximately 70% of cases and it was predicted the addition of iuMR would increase this to over 80%. This increase was considered clinically important, potentially leading to changes in fetal prognosis and management in approximately 5% of cases. Consequently 504 complete datasets would enable a greater than 10% increase in diagnostic accuracy to be detected with 90% power and 95% confidence. This figure also allowed for recruitment of a sub-group of 336 women (2:1 ratio) of up to and including 23 weeks gestation in whom the management of the pregnancy had been determined before this point. 23 weeks is a key date within UK law governing abortion and is therefore considered a significant time-point in pregnancy. Based on outcomes of previous studies, data excluded due to loss to follow up or lack of outcome data was expected to be 30% (10% of fetuses ≤23 weeks gestation and

20% of fetuses ≥24 weeks gestation). A 4% loss of participants was also predicted due to non-attendance or failed MRI because of claustrophobia or contraindications (227, 228).

3.4.3 Participants

Pregnant women in whom the fetus had been diagnosed of having, or was suspected of having, a brain abnormality diagnosed by USS and who fulfilled the following criteria;

Inclusion criteria

1. The pregnancy was in the late second or third trimester of pregnancy, the fetus being greater than 18 weeks gestation at the time of iuMR imaging;
2. The fetus had, or was suspected of having, a developmental brain abnormality following detailed specialist USS.
3. Had a singleton or multi-fetal pregnancy.

Exclusion Criteria

Pregnant women were excluded from the study if any of the following criteria were present:-

1. Unable to give informed consent
2. MRI was contraindicated due to:

a) Safety concerns, e.g. the participant had a pacemaker, recent surgery with metallic sutures or implant, electronic or metallic implant at risk of malfunctioning or heating due to the magnetic field or intra-orbital metallic foreign body;

b) Previous experience of severe anxiety or claustrophobia in relation to MR imaging;

3. Unwilling or unable to travel to one of the five specialist MR imaging centres;
4. Unable to understand English where a satisfactory translation service was unavailable;
5. The participant was under 16 years of age.

3.4.4 Recruitment

Initial assessment included a detailed USS evaluation of the fetus performed by a fetal medicine expert who had significant experience in imaging and assessing fetal brain development. This was performed on pregnant women in whom the fetus was thought to have a brain abnormality, identified by routine second trimester screening as part of their routine clinical care.

It was left to the judgement of the fetal medicine expert to assess whether participation in the MERIDIAN study should be offered. If it was judged participation in the study was clinically inappropriate or would delay management of the pregnancy, then participation in the study was not offered. Where a pregnant women fulfilled the inclusion criteria, written information (Appendix 1) and a full verbal explanation of the study was given to ensure participants understood what their participation would entail. Written informed consent (Appendix 2) was obtained either by the fetal medicine expert or, where the pregnant woman needed more time to consider participation, consent was taken by the neuroradiologist before iuMR examination.

The full details of the USS were recorded by the fetal medicine expert on the relevant section of the online database (Form D, Appendix 3). This included demographic details, technique used (2D, 3D) and difficulties encountered, such as fetal position, body habitus etc. All structural brain abnormalities detected were recorded and the fetal medicine expert assigned a score which denoted how confident they were for each diagnosis made. This is described in detail later in this chapter. The participants were then referred to one of the nominated specialist imaging centres for iuMR imaging.

MR Imaging was carried out at the primary site (Sheffield) or at one of five secondary sites- Newcastle, Leeds, Birmingham, Belfast and Nottingham. The secondary sites scanned their own recruits and local Radiologists provided the iuMR report and completed the study documentation according to their findings. MR imaging was performed at any time point after

18 weeks, ideally within two weeks of the specialist USS due to the evolving nature of the fetal brain and the possibility of changes which might skew the diagnostic accuracy data. Exceptions to this time limit were permitted when there was a clinical need for information at a specified time point. These cases were excluded from the primary analysis. All centres used a 1.5 Tesla MR scanner and the imaging protocol used was determined locally by the reporting radiologist according to clinical indication. As a minimum requirement this included T2 weighted images in all 3 anatomical planes relative to the fetal brain and an axial T1W sequence with a maximum slice thickness of 5mm. No sedation was used for either the fetus or mother, and sequences were repeated as required in order to achieve clinically diagnostic images, but with a maximum on table time of 40 minutes. The imaging sequences used in Sheffield are described in Chapter one and in Chapter five. Radiologists reported the iuMR scan with full knowledge of the USS findings and level of diagnostic certainty. Each structural diagnosis identified by USS was either excluded or confirmed, and any new pathology identified which was not seen on USS was also recorded. The radiologist also recorded details such as the date of the MR examination, the age of the fetus and any adverse events or problems (Form E, Appendix 4). A clinical report was also issued to the referring centre as per routine radiology protocol.

Participants returned to their referring hospital for the results of the iuMR imaging according to each referral centre's standard clinical follow up protocol. The clinicians were asked at this point to record any changes in prognosis, management of the pregnancy, and changes in counselling as a result of iuMR, using a clinical feedback form (Form G, Appendix 3)

3.4.5 Pregnancy Outcome Reference Diagnosis

The diagnoses made by USS and iuMR were compared to an outcome reference diagnosis (ORD) in order to calculate the diagnostic accuracy of both modalities. Reference standards used were different according to pregnancy outcomes as outlined below.

i) In cases of termination of pregnancy, intra uterine death or neonatal death, information was gathered from the results of autopsy or post mortem MR imaging;

ii) Where the pregnancy was successful, with a live fetus, outcome information was derived from post-natal imaging which consisted of MR, CT or transcranial USS performed within 6 months of birth (term corrected in cases of premature birth).

Where USS and iuMR had shown isolated VM, the outcome reference diagnosis of resolved VM was permitted based on either third trimester USS or the post-natal imaging.

3.4.6 Diagnostic Accuracy Data Analysis

Each case was individually reviewed by an independent panel comprised of two neuro-radiologists. Their role was to decide if there was complete agreement between USS, iuMR and the ORD. In cases where the fetus had more than one brain abnormality, the neuro-radiologists were also asked to identify the primary diagnosis, which was judged as the one likely to have the worst prognosis. Where there was complete three way agreement (USS, iuMR and the ORD agreed on the diagnosis) no further action was necessary. If there was any disagreement about diagnosis anywhere in the data (USS diagnosis compared to iuMR diagnosis or, USS and/or iuMR diagnosis compared to the ORD) it was referred to an expert panel for review. This panel consisted of three independent consultants (fetal medicine specialist, paediatric neuroradiologist and paediatric neurologist), and who did not recruit or report for the study. The independent expert panel were blind to the origin of the prenatal diagnosis (USS or iuMR; anonymised as scan 1 or scan 2) as far as possible. It was asked to decide if either scan 1, scan 2 or neither agreed with the outcome reference diagnosis. Secondly, the panel were asked to decide which imaging modality diagnosed the most severe clinical outcome. Once a decision had been made, the database was un-blinded by the study team so that diagnostic accuracy and diagnostic confidence assessments could be carried out.

Diagnostic accuracy of iuMR compared to ultrasound was the primary outcome for the study and was measured by:

a) The diagnostic accuracy of antenatal USS alone (i.e. prior to iuMR) relative to, the outcome reference diagnosis (post-natal imaging or post-mortem examination).

b) The diagnostic accuracy of iuMR relative to the outcome reference diagnosis (post-natal imaging or post-mortem examination).

In cases where a fetus had more than one brain abnormality, diagnostic accuracy assessment was based on the primary diagnosis identified by the independent neuro-radiologists. Diagnostic accuracy, with 95% confidence intervals, is reported as a primary outcome with the difference between USS and iuMR ($DA_{MR} – DA_{US}$) also stated. McNemar's test was used to assess the significance of differences in diagnostic accuracy achieved with and without iuMR imaging.

3.4.7 Assessment of Diagnostic Confidence

Diagnostic confidence is fundamental to clinical decision making. A clinician who is highly confident in a diagnosis is more likely to act upon that diagnosis than when confidence is low. Assessing diagnostic confidence was essential to determine if the information provided by iuMR influenced the clinician's thinking about the likelihood of disease enough to affect patient management. As part of MERIDIAN, diagnostic confidence was used as a measure to assess the clinical effectiveness of iuMR imaging by determining the relationship between the diagnostic confidence of both USS and iuMR in relation to diagnostic accuracy.

A basic approach used to examine diagnostic confidence is to measure changes before and after a diagnostic test, calculated as C_2-C_1, i.e. at USS (C_1) and after iuMR (C_2) (157, 229). Although this gives the percentage change in confidence, it fails to take into account any

change in pre-test to post-test diagnosis. One attempt to address this simply excludes cases where a change in diagnosis occurs but this bias prevents the true influence of the diagnostic test under investigation being appreciated (229). Omary, Kaplan (230) attempted to correct for change in pre-test to post-test diagnoses. They did this by not only using the conventional C_2-C_1 method but also, in cases where the pre-test confidence is high and there is a diagnosis change post-test, by calculating diagnostic confidence as (C_2-[100-C_1])%. The disadvantage of the Omary correction method is that it assumes the diagnostic test is accurate.

In order to assess the impact of diagnostic confidence on the MERIDIAN cohort we used the method proposed by Ng and Palmer (158), as it seeks to define the ultimate bearing the diagnostic test may have on the patient. Ng and Palmer developed a score based weighted average (SWA) method which is determined by the application of a framework on a case by case basis and allocates a route label and score for each case. It recognises that the diagnosis made by the test under scrutiny may be wrong, the diagnosis made may be more or less severe than the correct diagnoses or the diagnostic test may introduce deleterious effects which can have a range of consequences for the patient. Ng and Palmer developed the SWA assessment to overcome the limitations of other methods and to assess the influence of computed tomography (CT) on the diagnostic confidence of clinicians managing the treatment of patients presenting with acute abdominal pain. In order to adapt the framework for our analysis we replaced any reference to ‘initial diagnosis’ or ‘initial confidence’ with USS which was our initial diagnostic method. The diagnostic test under scrutiny in Ng and Palmers study, CT, was replaced with iuMR the diagnostic test we were scrutinising. All other aspects of the framework were kept the same.

Once each case was complete (comprising USS diagnosis and associated confidence score, iuMR diagnosis and associated confidence score and confirmed ORD) it was assessed using the framework. The framework (Figure 3.1) determines a route label and associated

score by taking into account the level of confidence (high or low), any change in confidence level and any change in diagnosis (more or less severe, no change or excluded) between USS and iuMR, as well as the ultimate accuracy of the diagnosis (as determined by the outcome reference diagnosis and judged by the independent panel). The framework covers 36 possible outcomes, with associated route label and a score allocated on a 9 point scale from -4 to +4 dependent on the positive or negative contribution iuMR made, as shown in Table 3.1. The scores closer to zero represent the reducing influence, either beneficial or detrimental, iuMR may have had on the diagnostic pathway for the patient.

TABLE 3.1 Diagnostic Confidence Framework Possible Outcome Scores

USS		MR		Score	
Result	Confidence	Result	Confidence	If reference diagnosis positive	If reference diagnosis negative
+	High	+	High	0	-1
+	High	+	Low	-1	0
+	Low	+	High	1	-2
+	Low	+	Low	0	-1
+	High	-	High	-4	3
+	High	-	Low	-3	2
+	Low	-	High	-3	2
+	Low	-	Low	-2	1
-	High	+	High	4	0
-	High	+	Low	3	-2
-	Low	+	High	3	-1
-	Low	+	Low	2	-1
-	High	-	High	-2	0
-	High	-	Low	-1	-1
-	Low	-	High	-3	1
-	Low	-	Low	-2	0

When the confidence framework is applied, the highest and lowest scores are only assigned in two scenarios. The highest score of +4 is assigned when the diagnosis made by iuMR is correct (as determined by the ORD), was made with high confidence and changed the highly confident but wrong diagnosis made by USS to a more severe diagnosis e.g. USS diagnosed VM but iuMR diagnosed ACC which was confirmed postnatally. Contrary to that is

the scenario where a highly confident diagnosis made by iuMR was incorrect, underestimating the correct highly confident diagnosis made by USS and consequently assigned a score of -4. A neutral score of zero was assigned when the contribution of iuMR was deemed to have neither a positive nor negative influence. As shown in Figure 3.1, this was allocated in six different situations; - where the iuMR diagnosis is correct and emulates USS, or where the iuMR diagnosis is incorrect but made with a lower certainty than the diagnosis made by USS.

In order to apply the diagnostic confidence framework to determine the route score in MERIDIAN, clinicians were asked to indicate their diagnostic certainty of any diagnoses made. This was done immediately after USS by the fetal maternal specialist and by the reporting radiologist immediately after iuMR examinations. Diagnostic confidence scores were indicated using a 5 point Likert rating scale (231) which allowed a range of responses with a percentage value assigned which best represented the degree of certainty the clinician had in the diagnosis they made.

- Diagnosis excluded (iuMR only, scored as 90% certainty)
- Very unsure (10%),
- Unsure (30%),
- Equivocal (50%),
- Confident (70%)
- Highly confident (90%).

The confidence scores allocated by clinicians were then divided into two sub groups for analysis:-

- High confidence: - Confident (70%) and highly confident (90%)
- Low confidence: - Equivocal (50%), unsure (30%) and very unsure (10%)

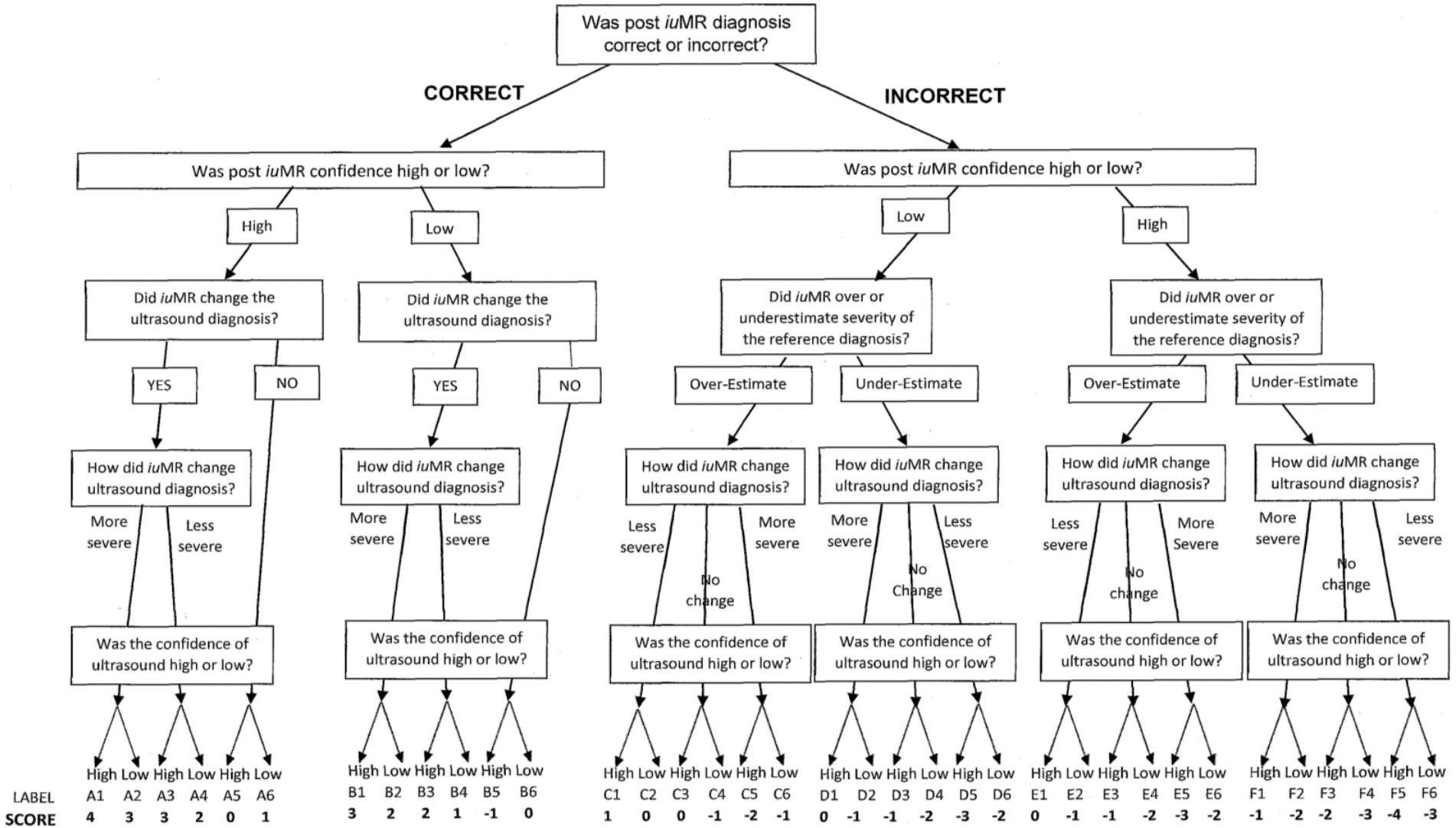
The rationale for the division into two groups was that a confidence score of 50% or less was unlikely to have any clinical impact, whereas confidence scores of 70 or 90% were more likely to lead to a change in management or the instigation of treatment.

The SWA method was used to measure the diagnostic impact of iuMR imaging within the study and to provide a subjective assessment of the influence of diagnostic confidence on clinical management of the patient. All cases where an ORD was confirmed were assessed using the SWA flowchart on a case by case basis to determine a route label and score. Where a case had more than one diagnosis, the confidence score of the primary diagnosis identified by the independent panel was used for analysis (e.g. the confidence score of ACC would take precedence over the confidence score of VM). The results of the SWA method were also compared to the integer scores as a result of conventional assessment of diagnostic confidence and with the Omary correction method described earlier. To do this the changes in diagnostic certainty were converted to the same integer 9 point scale as the SWA method. For example:

Conventional method- 90% (C_2) – 50%(C_1) = 40% = +2
Omary Correction (diagnosis change) = (90%(C_2) – [100-90%(C_1)])%= 90-10%=80%= +4

The frequency of each integer score for all three types of analysis was tabulated and described in terms of the number of cases in which iuMR reported with greater confidence (positive scores) and the number of cases with reduced confidence (negative scores). The mean and standard deviations of the score and 95% confidence intervals were calculated and one sample t-tests were carried out to test the hypothesis that the expected calculated scores were zero.

Figure 3.1 Flow Diagram of Diagnostic Confidence Framework Showing the Possible Routes and Ultimate Scores as Adapted from Ng and Palmer (2007)



3.5 Results

A total of 1101 pregnant women with 1109 fetuses were recruited over a three-year period (2011-2014) who met the inclusion criteria and consented to participate. After exclusion of ineligible or declined participants (n=198), incomplete MR examinations (n=80), patients with incomplete outcome data (n= 191) and exclusions due to more than two weeks between USS and iuMR there were 570 fetuses with complete datasets for inclusion in the analysis. The flow of patients through the study is shown in Figure 3.2. Final numbers within the study exceeded those required for the power calculations (Table 3.2)

64% of participants underwent iuMR imaging at the University of Sheffield's Academic Unit of Radiology and the remaining 36% were scanned at one of the five collaborating centres. Five patients, representing 0.45% of the whole study cohort, could not tolerate the iuMR, four because of claustrophobia and one due to physical discomfort. These patients were excluded from the analysis as no useful imaging data was acquired. Two further patients were also excluded as the iuMR examination was terminated due to the demise of the fetus between the USS and iuMR examinations. Consequently, there were a total of 823 (99%) completed iuMR examinations from a total of 830 women. Of these, 570 fetuses fulfilled the inclusion criteria, having both iuMR within 2 weeks of USS and an ORD. The final 570 cases comprised 502 completed pregnancies and 68 that resulted in termination of pregnancy (TOP). Of the 570, 369 (65%) were in the 18 weeks to ≤23 weeks group (110% of required) and 201 (35%) in the ≥24 week group (120% of required).

Figure 3.2 Flow of participants through the study

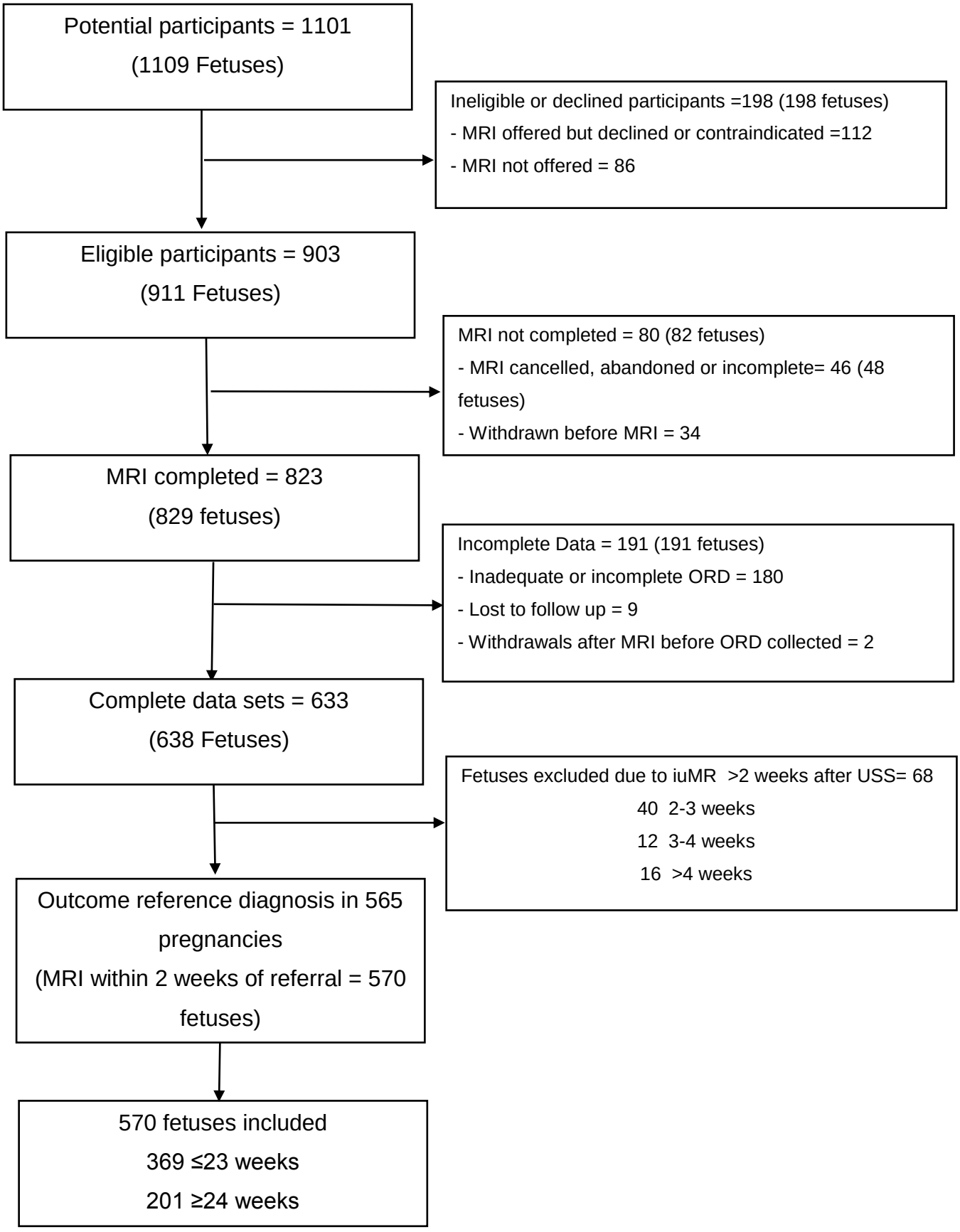


Table 3.2 Details regarding participants predicted and number in final cohort		
	Numbers required by the power calculation	Actual numbers in the study
Had a successful iuMR examination	720 fetuses	830 fetuses
Had an outcome reference diagnoses	560 fetuses	638 fetuses
Of those, iuMR within 2 weeks of USS	504 fetuses	570 fetuses
18-23w gestation at the time of iuMR	336 fetuses	369 fetuses
≥24w gestation at the time of iuMR	168 fetuses	201 fetuses

Table 3.3 Characteristics of Participants in the Primary Cohort and in Those Excluded			
	ORD available (N=570)	ORD unavailable (N=176)	Excluded (N=81)
Gestational age at iuMR (weeks)			
Mean (SD)	24·5 (4·5)	23 ·9 (4·2)	25·7 (3·6)
≤23 weeks	369 (65%)	127 (72%)	35 (43%)
≥24 weeks	201 (35%)	49 (28%)	46 (57%)
Time from USS to iuMR (days)			
Mean (SD)	5·8 (3·5)	5·3 (3·3)	22·6 (8·6)
<1 week	403 (71%)	134 (76%)	0
1-2 weeks	167 (29%)	42 (24%)	0
>2 weeks	0	0	81 (100%)
iuMR site			
Sheffield	380 (67%)	121 (69%)	31 (38%)
Birmingham	75 (13%)	34 (19%)	15 (19%)
Newcastle	66 (12%)	6 (3%)	9 (11%)
Leeds	34 (6%)	12 (7%)	11 (14%)
Nottingham	12 (2%)	3 (2%)	1 (1%)
Belfast	3 (1%)	0 (0%)	14 (17%)
Pregnancy type			
Singleton	539 (95%)	166 (94%)	78 (96%)
Multiple	31 (5%)	10 (6%)	3 (4%)

3.5.1 Diagnostic Accuracy

Overall of the 570 completed cases, USS gave an accurate diagnosis for 68% and iuMR gave an accurate diagnosis for 93%, an improvement of 25% (95% CI 21-29%). USS and iuMR were in agreement and correct in 385 cases (68%) but incorrect in 39(7%). Incorrect diagnoses made by USS were corrected by iuMR in 144 cases (25%) and USS gave a correct diagnosis in two fetuses (<1%) for which iuMR gave an incorrect diagnosis. The diagnostic accuracy of iuMR was similar for both age groups, but USS was less accurate in the 24 weeks or older gestational age group than in the younger group (Table 3.4). IuMR identified additional abnormalities in 387 (49%) of 783 cases without an ORD, of which 201 (52%) were apparent on follow up USS. These results did not require an ORD as additional abnormalities were not used for the primary analysis of overall diagnostic accuracy.

Table 3.4 Results of the diagnostic accuracy of both USS and iuMR.

	USS Correct *n* (%)	iuMR Correct *n* (%)	Percentage Difference (95% Confidence Interval)	P value*
18-23 Weeks (n=369)	258 (69.9%)	341 (92.4%)	22.5% (17.8%, 27.2%)	<0.0001
24+ Weeks (n=201)	129 (64.2%)	188 (93.5%)	29.3% (22.6%, 36.1%)	<0.0001
Combined (n=570)	387 (67.9%)	529 (92.8%)	24.9% (21.1%, 28.7%)	<0.0001

The most common diagnoses made at USS were;

-isolated ventriculomegaly (306 (54%) of 570 fetuses);

-abnormalities within the posterior fossa (83 (15%) of 570 fetuses);

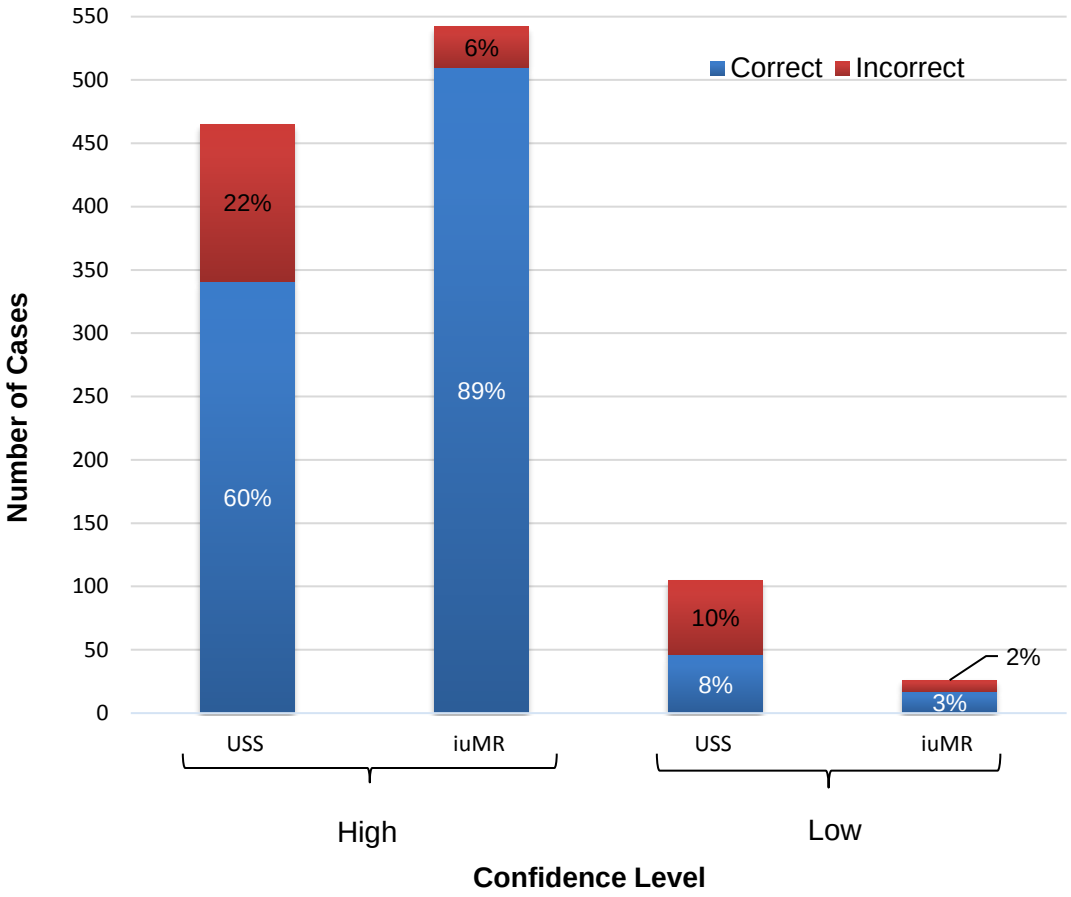
-failed commissuration (ie agenesis or hypogenesis of the corpus callsosum; (79 (14%) of 570 fetuses).

The fetal medicine expert felt that iuMR provided additional diagnostic information in 387 (49%) of 783 cases. In just over half (52%) any further anatomical abnormalities were apparent at subsequent USS**.** This additional information, being based on the opinion of the fetal medicine experts did not require an ORD, therefore results are based on 783 of 823 cases (95%). The other 40 cases were excluded due to lack of follow up data, incomplete information or withdrawal from the study.

3.5.2 Diagnostic Confidence

USS reported the primary diagnosis (as identified by the panel of independent experts) with high confidence in 465 (82%) of 570 cases, of which 124 (22%) of 570 cases were found to be incorrect. iuMR reported the primary diagnosis with high confidence in 544 (95%) of 570 cases, an increase of 13% compared to USS. iuMR made an incorrect diagnosis with high confidence in 32 (6%) of 570 cases. USS made more diagnoses with low confidence than iuMR, 105 (18%) and 26 (5%) respectively and of these had a higher proportion of incorrect diagnoses, Figure 3.3.

Figure 3.3 Relationship Between Diagnostic Accuracy and Diagnostic Confidence



The frequency for each of the integer scores as a result of the application of the score-based weighted average method and the integer scores using both the C_2-C_1 and Omary corrected methods applied to each of the 570 cases, are displayed in Table 3.5.

Analysis of the SWA method revealed that iuMR resulted in an appropriate increase in diagnostic confidence (scores +1 to +4) (i.e. iuMR was more confident and/or corrected a wrong USS diagnosis) in 178 (31%) of cases. A negative score, indicating a potential detrimental influence by iuMR, was recorded in 41 (7%) (i.e. iuMR made an incorrect diagnosis with high confidence or made a correct diagnosis with low confidence).

Table 3.5 Results of Diagnostic Confidence Analysis using all 3 methods			
Route Score	Score Weighted Method	Conventional C_2-C_1	Omary Corrected C_2-C_1
+4	59	16	73
+3	42	24	64
+2	43	53	57
+1	34	91	70
0	351	331	276
-1	30	38	22
-2	10	11	7
-3	1	4	1
-4	0	2	0

The mean difference in confidence on the -4 to +4 ordinal scale was +0·75 (95% CI 0.63 to 0.87, p<0·0001, Table 3.6).

When the 570 cases were analysed using the conventional method the Mean difference was +0.44 in favour of iuMR (95% CI 0.35 to 0.54, p<0·0001; Table 3.6) with a difference in confidence level of any degree in 42%, of which 32% were made with greater confidence following iuMR, rather than USS (10%).

The Omary corrected method resulted in a much higher mean difference on the -4 to +4 ordinal scale at 1.10 in favor of iuMR (95%CI 0.98 to 1.25, p<0·0001; Table 3.6).

A difference in confidence levels of any degree was present in 52% of all cases, 47% were more confident on iuMR and 5% more confident on USS.

Table 3.6 Changes in diagnostic confidence using the conventional method in the first row, with Omary correction in the second row and the SWA in the third row.				
	Difference in confidence, Mean (SD)	95% Confidence for Mean difference	Test statistic, t	*p* value
Conventional analysis	0·44 (1·20)	(0·35, 0·54)	8·87	<0·0001
With Omary correction	1·10 (1·57)	(0·97, 1·23)	16·75	<0·0001
Score-based method	0·75 (1·50)	(0·63, 0·88)	11·96	<0·0001

3.5.3 Clinical Management

With regard to the influence of iuMR on final clinical management, iuMR was felt to have 'no value' in 95 (12%), 'minor influence' in 419 (53%), 'significant' influence in 201 (26%), 'major' influence in 49 (6%) and 'decisive' in 19 (3%) of cases. This information was based on 783 of 823 cases (95%) as no ORD was required.

Out of the 17 cases where the iuMR diagnosis was made with low confidence (Figure 3.4) 14 cases had a significant influence on final clinical management and 3 were considered to have a major influence. There were no cases, made with low confidence, where the influence of iuMR was considered decisive. Of the 252 cases where the iuMR diagnosis was made with high confidence, 187 were considered to have a significant influence, 46 a major influence and 19 a decisive influence on the final choice of management (Figure 3.4)

Figure 3.4 Relationship Between iuMR Diagnostic Confidence and Influence on the Final Choice of Management of the Pregnancy

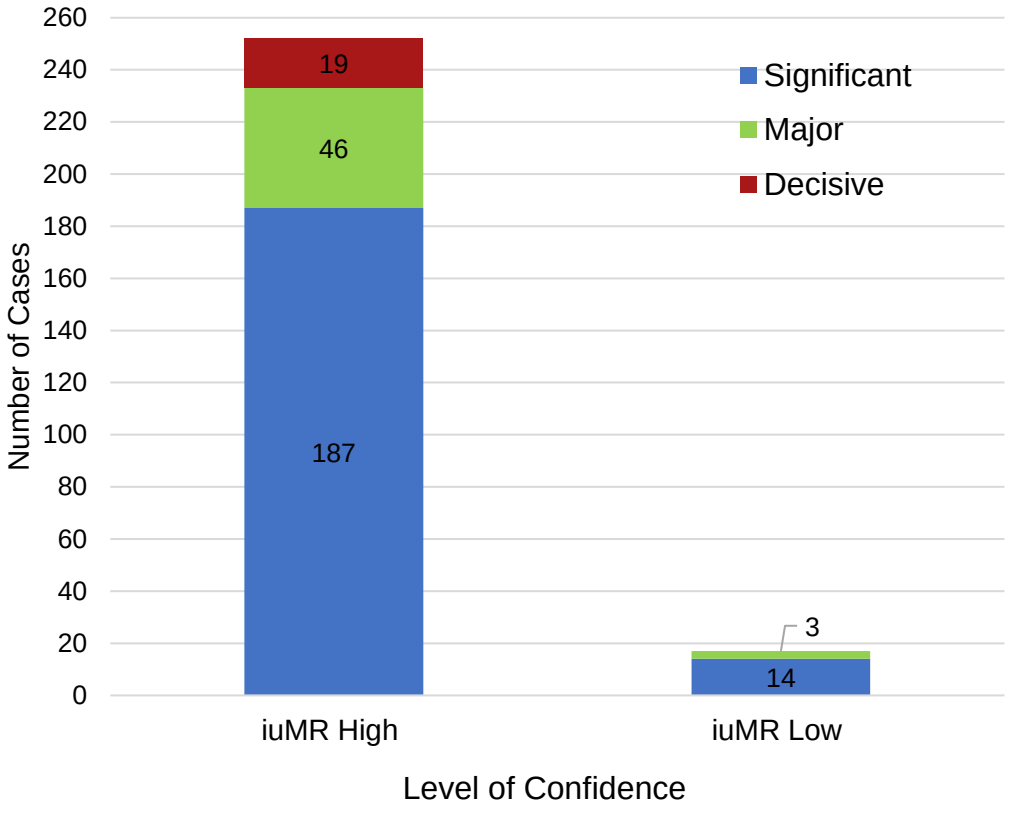


Figure 3.5 Frequency of Relationship Between Integer Scores and Influence on Final Clinical Management

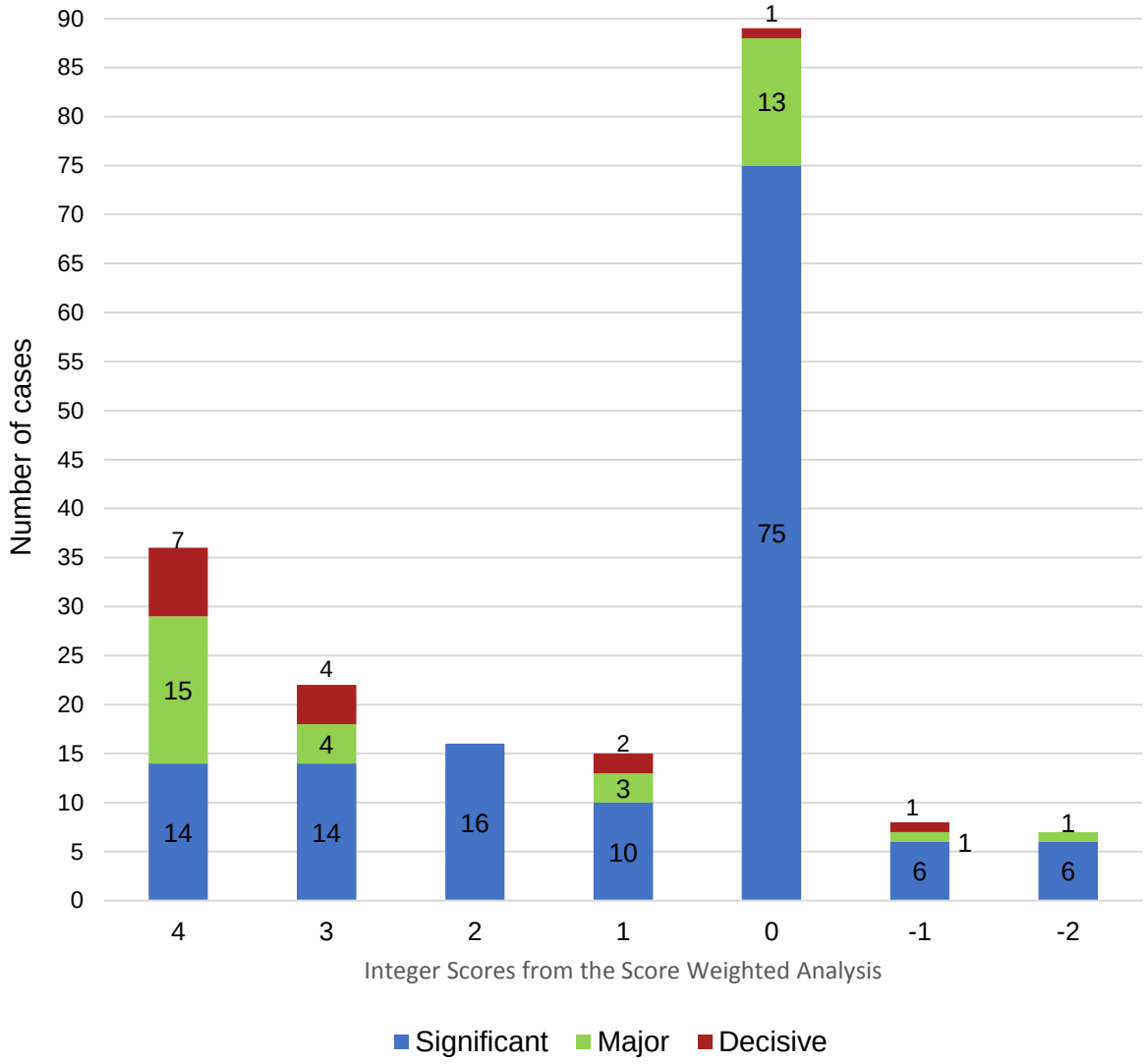


Figure 3.5 displays a histogram of the integer scores as a result of the SWA analysis in relation to influence on final clinical management. They consist of 295 (59%) of the 507 complete cases in the three most influential levels (significant, major and decisive) and also have an ORD, as a requirement of the SWA method. The highest number of cases scored as major and decisive occurred when the influence of iuMR was highest (integer +4), with 7 decisive, 15 major and 14 significant cases.

3.6 Discussion

In order to address the primary aim of this thesis a thorough assessment of the diagnostic performance of iuMR for diagnosing fetal brain abnormalities was necessary. Multiple studies, a large number of which were included in the systematic review, have demonstrated that MRI improves diagnostic accuracy when brain abnormalities are suspected by USS. However, poor study design, due to inconsistencies and methodological weaknesses has limited the validity of findings (119). These were addressed by MERIDIAN as the study was appropriately powered, did not exclude any type of brain abnormality, women were recruited prospectively, and diagnostic accuracy calculations were based on only those cases where iuMR was performed within 2 weeks of USS and the ORD was known. MERIDIAN also provided a more full assessment of the diagnostic performance of iuMR by also investigating its impact in terms of improvement in diagnostic confidence, therapeutic efficacy and patient outcome.

903 women were recruited, resulting in 823 women who underwent MR imaging, providing 570 (63%) complete datasets which exceeded the numbers we predicted or were required for adequate powering of the study. This may have been because eligible subjects were motivated by the desire to gather more information about their pregnancy and hence were more willing to participate, or due to an under estimation of either the total number of pregnancies or the percentage of fetuses with brain abnormalities in the referral population, the figures for which are not yet available.

To substantiate USS or iuMR findings, a confirmed outcome diagnosis was crucial to this study, particularly when there was discrepancy between the two. We estimated that in 20% of recruits an ORD would not be available, this figure being based on the findings of previous studies (120, 191, 215). This figure was a realistic estimate as final calculations confirmed an ORD was unavailable in 21.7% of the fetuses who underwent iuMR. Obtaining an ORD for all cases is difficult. Postnatal imaging is not required clinically for a 'normal' child, so was

unlikely to be offered routinely, and when a pregnancy is terminated autopsy is not performed in a high percentage of cases in the UK. A further 68 (10.6%) cases were excluded from the primary analysis as the time between USS and iuMR was greater than 2 weeks. This limitation was necessary to ensure any changes in diagnosis were due to the accuracy of either USS of iuMR rather than anatomical changes due to the rapidly changing nature of the developing fetal brain.

When safety guidelines are adhered to, iuMR imaging is a safe alternative method for visualising the developing fetus in utero with no detrimental biological or physical effects on the fetus or mother being reported to date. Claustrophobia is considered a limitation of MRI due to the confines of the bore of the magnet and restriction due to the imaging coil. Our study found that MRI was tolerated well by the majority (99.5%) of participants with only five terminating the examination due to claustrophobia or discomfort before adequate data was obtained. It is hard to judge if this is similar to previous comparable studies as most do not include this aspect in their reports, but the failure rate of MRI due to claustrophobia in a general adult population has been reported as 1-3% (232).

The results of the study showed the diagnostic accuracy achieved by iuMR, following detailed ante-natal USS for suspected brain abnormalities, was greater than that achieved by USS alone, regardless of the gestational age of the fetus ($p<0.0001$). When examining this improvement in diagnostic accuracy by gestational age, iuMR was able to give an accurate diagnosis in 92% of fetuses at 23 weeks gestation or under and in 94% of older fetuses representing a 22% and 30% increase respectively over USS. The lower accuracy of USS at later gestations is frequently a problem as ossification of the fetal skull and its low position within the maternal pelvis is a known limiting factor for USS performance.

Our results confirmed the findings of our systematic review and the reviews by Rossi and Prefumo (172) and Van Doorne (173), who all found that diagnostic accuracy is consistently

improved when iuMR is part of the diagnostic pathway. This was evidenced by the 80-94% accuracy of iuMR, an increase of 15-20% over the diagnostic accuracy of USS.
There are potentially two shortcomings of our study. Firstly, the radiologists reporting the iuMR examination were not blinded to the findings of the USS examination. Although this could possibly introduce an element of bias to the findings it was felt that conducting the study in this way was justified as it reflects standard clinical practice in the UK and our aim was to assess iuMR as an adjunct to USS rather than to replace it. Secondly, the involvement of collaborating centres meant that women were recruited from all over the UK, but the majority (64%) of the iuMR scans were carried out in Sheffield at the University's Academic Radiology Department where the most experienced radiologist was based. Although all the radiologists had some experience of reporting iuMR, greater experience is likely to influence diagnostic accuracy in favour of iuMR.

The aim of our study was to assess the diagnostic performance of iuMR which is not based on diagnostic accuracy alone. We therefore included an assessment of the improvement of diagnostic confidence as a result of iuMR and its ultimate effect on patient management. We chose to utilise the method proposed by Ng and Palmer (158) as this not only evaluates changes in diagnostic confidence as a result of the new test (iuMR) but also takes into account if that change is 'appropriate'. The resultant score, is assigned according to the ultimate effect the new test may have on patient outcome, whether that be positive, negative, or even neutral (zero score). Conventional scores and Omary corrected scores may ultimately be misleading as they do not take into account whether the diagnosis made by a new test is correct. Our results showed that the conventional method underestimates the true influence of iuMR and the Omary corrected method overestimates it. For example, if a diagnosis of VM was made by USS with 90% confidence, and a diagnosis with a worse prognosis was made by iuMR with 90% confidence, the conventional method (90-90) would result in a score of 0 (no change in confidence), and the influence of iuMR would be missed. Using this scenario with the Omary corrected calculation the resultant score would be (90-

[100-90])=80% or +4, showing a positive influence of iuMR even though the diagnosis might be incorrect. Ng and Palmers method, being based on the results of an ORD and changes in diagnosis and confidence, corrects for these errors.

Our study found that a higher proportion of the diagnoses made by iuMR were made with high confidence than those made by USS (95% vs 86%) and that a higher proportion of those highly confident diagnoses by iuMR were correct (89%, compared to 60% by USS). Although iuMR made 5% of diagnoses with low confidence, this was appropriate as 2% of the 5% were incorrect. The results which concerned diagnostic confidence are more easily appreciated by the results of the SWA analysis which was able to show that iuMR had a positive influence on the diagnostic pathway in 31.2% (178) of cases (scores of +1 to +4). In the majority (61.6%) of cases iuMR were scored as 0, with neither a positive or negative effect on the diagnostic pathway. In 41 (7%) cases the confidence of iuMR was inappropriate with a potential detrimental effect to the patient.

The relationship between diagnostic confidence and the influence of iuMR on the management of pregnancy is not definitive and can only be surmised. This is primarily because although the fetal maternal experts were asked specifically to indicate the level of influence iuMR findings had on the management of the pregnancy, they were not asked if the level of confidence with which the diagnosis made by iuMR contributed to that influence. In over half the cases (59%) that had an ORD, iuMR was considered to have either a significant, major or decisive influence on management of pregnancy. Even when iuMR was made with low confidence there were still 3 cases where iuMR had a major influence and 14 where the influence was significant. The highest number of cases where iuMR was thought to be major or decisive occurred in those cases where the SWA was +4. When reviewing the cases where the SWA was zero, the influence of iuMR on management was considered to be significant in 75 cases, major in 13 cases and decisive in 1 case. This suggests that iuMR

provided positive reassurance in a high proportion of cases even though the diagnosis or confidence did not change after iuMR.

3.7 Conclusion

iuMR makes a positive contribution in a high proportion of cases when included in the diagnostic pathway if fetal brain abnormalities are suspected. Both accuracy and the confidence of findings are improved to such an extent that iuMR should be used routinely to inform decisions about the management of pregnancy when a brain abnormality is suspected on USS.

Chapter 4

The MERIDIAN Add-On Study.

4.1 Summary

This chapter reports the findings of the MERIDIAN 'Add-on study', which was an adjunct to the primary MERIDIAN, study, by providing a normal control group. This prospective cohort study aimed to recruit 200 fetuses in whom no abnormalities had been detected on USS. The purpose of this was to determine the false negative rate of fetal brain abnormalities in this group and thus complete the assessment of the diagnostic performance of 2D iuMR imaging for the primary aim of this thesis.

The Add-on study was supported and funded by the NIHR-HTA as an extension to the primary MERIDIAN study, and conducted under the same ethics approval and clinical trials regulations. The principle investigator (PDG) undertook the design and planning of the study, and the MERIDIAN team at ScHARR undertook the management of the study. With regard to MERIDIAN as a whole the Add-on study has been the focus of the author's time and contribution. This has consisted of –

- Explaining the study to approximately 30 participants in order to obtain informed consent
- Performing 200 of the MR scans (200 working hours)
- Showing resultant MR images and giving an overview of their babies brain anatomy to some participants (n=40).
- Analysis of findings from the study

This chapter will form the basis of a manuscript for submission to a peer-reviewed journal in late 2017.

.

4.2 Introduction

The results of the systematic review and the MERIDIAN study demonstrated that iuMR imaging when undertaken following USS significantly improves the detection of fetal brain abnormalities. This improvement in diagnostic accuracy has significant implications for clinical practice, but using overall accuracy as a measure of test precision may overestimate its performance (154). Overall accuracy is calculated by counting the number of correct answers against the number of incorrect answers, but the intrinsic value of a diagnostic test is not only its ability to detect an abnormality when one is present (sensitivity) but to also correctly exclude the possibility of an abnormality when a patient is healthy (specificity). Whilst sensitivity and specificity define the characteristics of a test, positive and negative predictive values may be more useful to a clinician as they provide an indication of the likelihood a test will give an accurate diagnosis (156). The calculation of positive and negative predictive values requires a sample with both 'diseased' and 'non-diseased' participants. The primary MERIDIAN study, and all studies investigating the accuracy of iuMR for diagnosing fetal brain abnormalities as part of the systematic review, have only recruited women in whom the fetus had a brain abnormality suspected on USS. It therefore appears that no previous study has investigated the negative predictive rate in this group. Recruiting a cohort of normal fetuses would, when used in conjunction with the results from MERIDIAN, enable the positive and negative predictive values of both iuMR and USS to be calculated. This would provide a more precise analysis of the diagnostic performance of both USS and iuMR and of their significance in the diagnostic pathway.

4.3 Methods

The Add-on study aimed to recruit 200 women in whom the fetus was not thought to have any form of abnormality either of the brain, or somatic, based on antenatal USS examination in order to answer the question 'Does iuMR detect any fetal brain abnormalities in fetuses judged to be developing normally on USS?' This information would be used in combination with the results of the primary MERIDIAN study to determine both the positive and negative

predictive values of USS and iuMR. Confidentiality of participants data was safe guarded by the use of a password protected database, described in Appendix 3, and anonyminity ensured by allocation of participant numbers.

4.3.1 Participants and Recruitment

Study participants for this prospective cohort study were recruited from UK maternity units, (through contact with MERIDIAN study midwives), or by publicity through posters, leaflets and press coverage. Contact details for the Academic Unit of Radiology in Sheffield were provided which pregnant women could use if they were interested in participating in the study. At this point, a patient information leaflet (Appendix 7) giving full details of the study was sent by email or post to the potential participant. A follow-up telephone call by a member of the study team enabled any queries to be answered and initial screening questions to be completed (Appendix 8). Eligibility for the study was initially based on verbal confirmation during the screening process. A copy of the USS report was then obtained at a later time point to confirm the normal development of the pregnancy and background information recorded (Appendix 9).

Upon satisfactory completion of initial screening, eligible participants were offered an appointment to attend the Academic Unit of Radiology in Sheffield for the MRI scan. The aim was to perform the iuMR within 1 week of USS, although participants were accepted regardless of the interval between ultrasound and iuMR imaging. A participant was deemed eligible to participate in the study if the following inclusion criteria were met:

- The participant had undergone prenatal USS and there were no brain or somatic abnormalities suspected regarding the fetus;
- The participant had no history of previous pregnancy with an abnormal fetus;
- The fetus would be a minimum of 18 weeks gestation at the time of iuMR imaging.

A participant was excluded from the study if she met any of the following criteria:

1. Had a past history of a fetal brain anomaly in a previous pregnancy;
2. Was unable to give informed consent;
3. Had a cardiac pacemaker, intra-orbital metallic foreign body, or recent surgery with metallic sutures or implant;
4. Had previously experienced or was likely to suffer severe anxiety or claustrophobia in relation to MR imaging examination;
5. Was unable or unwilling to travel to Sheffield for specialist MR imaging;
6. Was unable to understand English (except where satisfactory translation services were available);
7. Was under the age of 16 years;
8. Was unwilling for her GP to be informed about the study and given copies of scan reports.

Upon arrival at the Unit written informed consent was taken (Appendix 10) after full explanation of the MR procedure, this included the discussion of potential risks, her right to withdraw from the study at any time and an explicit explanation given that an abnormality may possibly be shown by MR imaging that wasn't previously seen by USS. Part of the consent procedure was also to ensure the willingness of participants to allow their GP to be informed that they were taking part in the study and to have a copy of the MRI report. iuMR examinations were performed at the Academic Unit of Radiology, University of Sheffield on a 1.5T whole body scanner (HDx, GE Healthcare, Milwaukee) or on a 3T whole body scanner (Ingenia, Philips, Netherlands). The iuMR imaging was of the fetal brain only and the protocol followed was that used for the primary MERIDIAN study (Table 1.1, Chapter 1). In addition, all fetuses were imaged using the 3D volume acquisition outlined in Chapter 5. After the scan the woman and her companion(s) were shown the MR images, given some immediate feedback regarding the development of the fetus and offered the opportunity to capture iuMR images of the baby using their own camera. None of the participants were paid

for volunteering for the study but travel expenses incurred by both the participant and her partner, friend or relative to attend the unit in Sheffield for the iuMR scan were reimbursed.

A copy of the USS report was requested from the participant's maternity centre (if the participant had this information in her hand held maternity notes, a copy of this was taken on attendance for iuMR). No further participant contact was required after the visit for the MR scan. All iuMR imaging was reviewed by a consultant neuroradiologist with significant experience in fetal neuro imaging (PDG) and findings recorded (Appendix 11). A full report of the scan performed was sent to the participant's GP. If an anomaly was detected, the neuroradiologist made contact with the participant's obstetric consultant and a full clinical report was issued. It was the participant's doctor's responsibility to take appropriate action if further intervention was required in accordance with their own clinical procedures.

4.3.2 Outcome Measures and Statistical Analysis

The decision that a participant's USS was normal was based on either the second trimester anomaly scan, or on a scan performed in the UK by a fetomaternal medicine specialist. The study compared the USS diagnosis with the iuMRI diagnosis prenatally, and no follow up was planned unless an abnormality was diagnosed on iuMR. The outcome of the pregnancy, with regard to brain development, was assumed to be normal unless an abnormality was suspected on iuMR imaging. In this instance, diagnostic accuracy was determined by an ORD as outlined in the primary MERIDIAN study. The positive and negative predictive values of both USS and iuMR were calculated by combining the results of this study with the results from the primary MERIDIAN study. The positive *predictive value* (PPV) refers to the probability that subjects with a positive screening test have the disease in question. The *negative predictive value* refers to the probability that subjects with a negative screening test do not have the disease in question.

The predictive values are calculated by:-

PPV: = (true positive) / (true positive + false positive)

NPV: = (true negative) / (false negative + true negative)

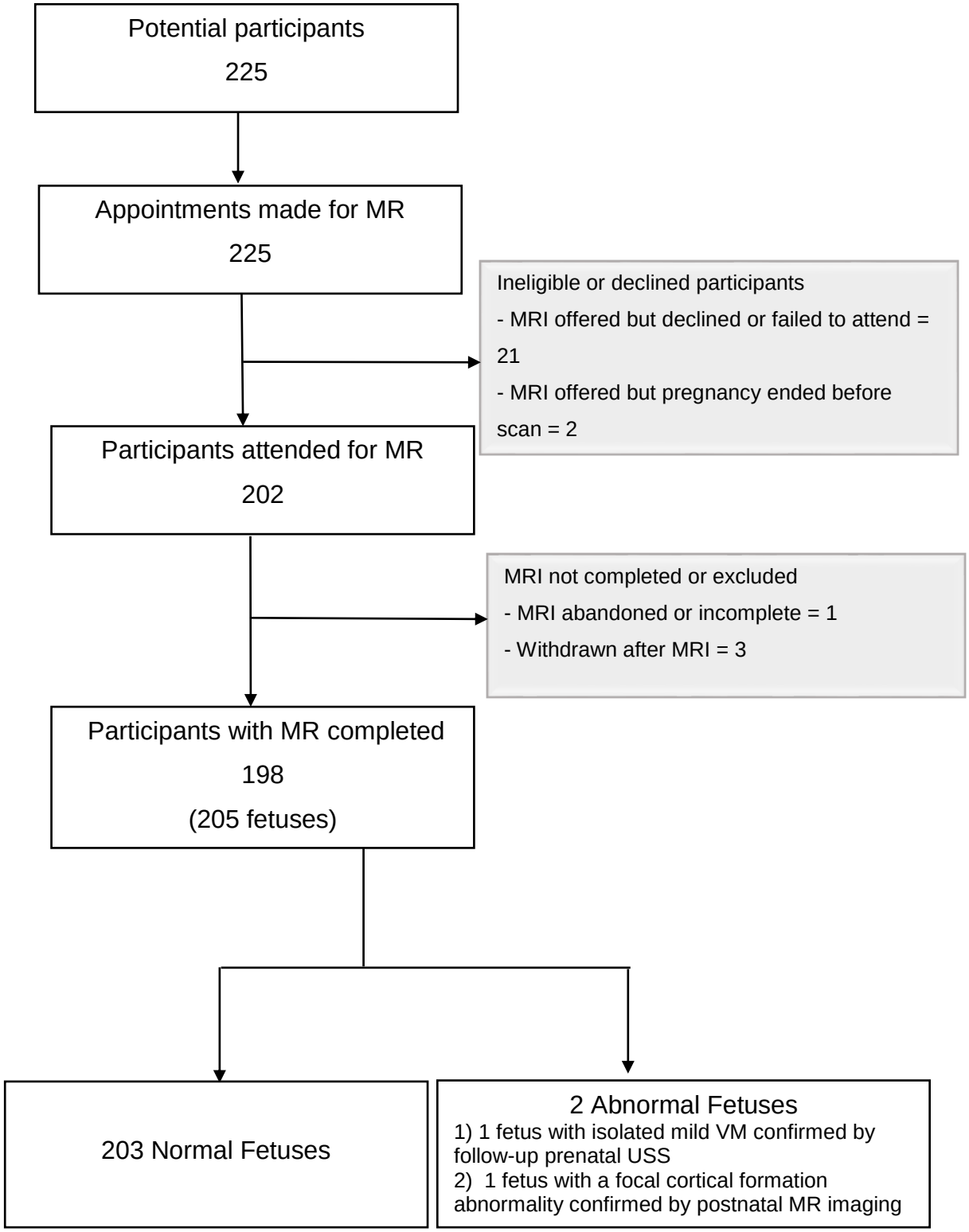
The values are dependent on the prevalence of disease in the sample measured. If all other factors remain constant, the PPV will increase and the NPV will decrease with increasing prevalence (233).

4.4 Results

The study was conducted over a 3.5-year period between November 2013 and May 2017. A total of 225 pregnant women made contact with the unit to enquire about the study, all of whom met initial screening criteria and appointments were made for each to attend for the MR scan. Of this group 21 failed to attend or cancelled their appointment after being screened for the study, and 2 women gave birth before their appointment. Three participants did not meet the inclusion criteria, due to pregnancy complications, and were excluded after the MRI scan had been done. One woman consented to undergo iuMR imaging, but the scan was subsequently abandoned before any relevant data could be captured due to the participant feeling unwell. In total, 198 participants meeting the inclusion criteria (a total of 205 fetuses) were scanned. The flow of participants through the study is shown in Figure 4.1. The final study number included 14 fetuses from twin pregnancies and 191 fetuses from singleton pregnancies. The pregnant women recruited were from a wide geographical area, with 68 (34%) participants living within 18 miles of the Sheffield MR unit and the remaining 137 from outside that area. The furthest distance travelled was 189 miles. The age range of the pregnant women was 20 – 46 years (mean 31.5 years). The number of fetuses grouped by gestational age at the time of iuMR imaging were 54 (26.3%) ≤ 23 weeks and 151 (73.7%) ≥ 24 weeks. A detailed summary of number of the fetuses scanned at each

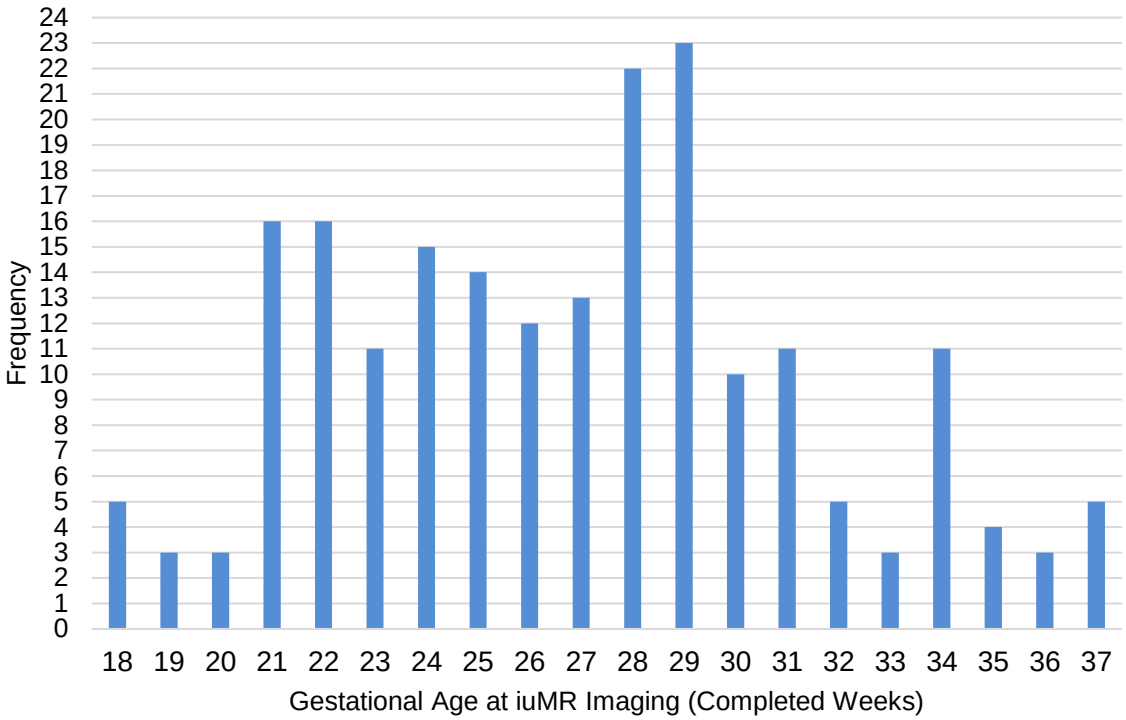
gestational age is shown in Figure 4.2. For all fetuses the normal USS report was based on the routine second trimester screening USS.

Figure 4.1 Flow of participants through the Add-on study



For 203 fetuses the MR scan was performed on a 1.5T scanner (GE HDX Healthcare Milwaukee) and two fetuses were scanned on a 3T scanner (Philips Ingenia, Best, The Netherlands) when the 1.5T was unavailable.

Figure 4. 2 Chart Showing the Number of Fetuses Scanned at Each Gestational Age



IuMR findings were reported as normal for 203 cases but brain abnormalities were reported in two fetuses from separate pregnancies. For both abnormal cases, a formal report was issued and sent to the respective fetal medicine consultants. Table 4.1 and 4.2 show the number and characteristics of correct and incorrect diagnoses made by USS and iuMR according to age category, calculated by combining the results of this study with the results from the MERIDIAN study (234). The positive and negative predictive values of USS and iuMR, showed that both USS and iuMR have excellent NPV (99.0% and 99.5% respectively) but the PPV of iuMR was 93.0%, 25.1% greater than the PPV of USS (Table 4.3.)

Table 4.1 Positive and negative values and predictive values for USS according to gestational age. (Values in red are taken from the MERIDIAN study)			
≤ 23 weeks	ORD +ve	ORD -ve	Predictive values (95% CI)
USS +	258	111	PPV 69.9% (67.6-72.1)
USS -	0	54	NPV 100%
≥ 24 weeks	ORD +ve	ORD -ve	Predictive values (95% CI)
USS +	129	72	PPV 64.18% (59.7-68.5)
USS -	2	149	NPV 98.68 (94.9-99.7)

Table 4.2 Positive and negative values and predictive values for iuMR according to gestational age. (Values in red are taken from the MERIDIAN study)			
≤ 23 weeks	ORD +ve	ORD -ve	Predictive values (95% CI)
MRI +	341	28	PPV 92.4% (CI 90.0-94.3)
MRI -	0	54	NPV 100%
≥ 24 weeks	ORD +ve	ORD -ve	Predictive values (95% CI)
MRI +	190	12	PPV 94.1% (CI 90.2-96.5)
MRI -	1	149	NPV 99.3% (CI 95.5-99.9)
These numbers include the 2 abnormal cases from the Add-on cohort which were added to the MERIDIAN numbers for true positives and 1 case within the MERIDIAN results, where iuMR failed to detect an abnormality identified by an ORD so was moved to the false negative category			

Table 4.3 Total Positive (PPV) and Negative (NPV) predictive values of USS and MR (95% confidence intervals)		
Modality	PPV (95% CI)	NPV (95% CI)
USS	67.9% (65.6-70.2)	99.0% (96.2-99.8%)
iuMR	93.0% (90.9-94.6)	99.5% (96.6-99.9%)
These values combine the results of this study and the primary MERIDIAN study		

iuMR imaging at 26 weeks gestation identified mild VM in one fetus (trigones of the lateral ventricles measuring 10mm and 11mm). This was recorded as an isolated finding and no other brain abnormalities were identified, but linear measurement of biparietal diameter and occipitofrontal diameter indicated a large head size (BPD >97th centile and OFD on the 97th centile) shown in Figure 4.3. Follow up USS confirmed the iuMR findings, and the pregnancy has since been monitored by USS at regular intervals. The pregnancy is ongoing at the time of this report and VM has been confirmed by subsequent USS.

The second abnormal fetus was 35 weeks gestation when iuMR imaging was performed, at which time the examination identified focal increased signal in a gyrus of the right frontal lobe on T2 weighted imaging suggestive of pathology such as a cortical tuber or focal cortical dysplasia (Figure 4.4). Post-natal MR imaging has confirmed the abnormality, but its nature is still unknown and the child is under clinical review.

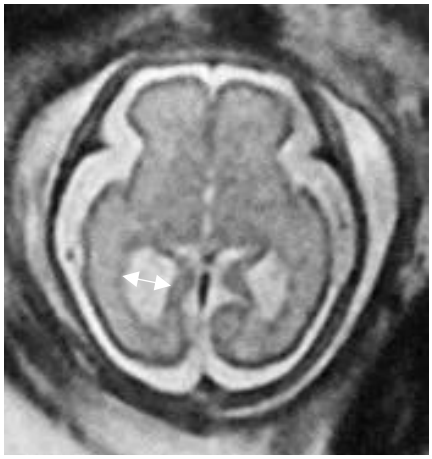


Figure 4.3 Axial T2W ssFSE image showing the VM (arrow, trigone measurement 11mm) in the fetus of 26 weeks gestation

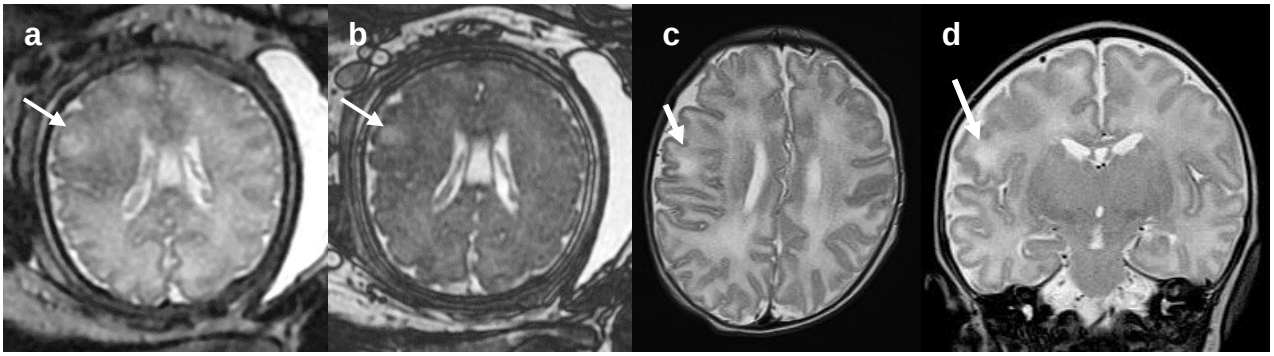


Figure 4.4 (a) Axial T2W ssFSE and (b) Axial 3D FIESTA images showing the increased signal in the right frontal lobe (arrows) in a fetus of 35 weeks gestation. Images (c) axial and (d) coronal of the MR scan of the same baby at 3 weeks old confirm the presence of abnormal signal in the right hemisphere.

4.5 Discussion

The results of the MERIDIAN study and the systematic review demonstrated a significant improvement in diagnostic accuracy when iuMR imaging is used in the diagnostic pathway. This might potentially imply that USS fails to detect significant abnormalities during the screening process. The Add-on study proved that assumption to be incorrect and the results support the role of USS as the satisfactory screening method for imaging during pregnancy in the general population, with the use of iuMR as an adjunct when abnormalities are suspected.

This study successfully recruited a cohort of pregnancies considered on USS to be developing normally. As a result, 205 fetuses were included in our analyses to determine, in combination with the results of the MERIDIAN study, the predictive value for both modalities. Predictive values indicate the precision of a diagnostic test, i.e. how likely the test is to find an abnormality when it actually exists (PPV) or how likely a test is to be negative if no abnormality exists (NPV). They therefore useful to clinicians when making decisions about the use of different diagnostic tests (235). The NPV of USS was high and comparable to that of iuMR (99.02% and 99.51% respectively). The results of the positive predictive values,

(USS 67.89%, iuMR 92.99%), as expected, are in keeping with the overall diagnostic accuracy findings within MERIDIAN (USS 67.89% and iuMR 92.8%), as the same values are used. The exceptions to these findings consisted of two cases in which iuMR correctly identified abnormal appearances that USS judged as normal. These 2 cases were therefore moved into the true positive category of iuMR. There was also 1 case within the MERIDIAN results where iuMR failed to detect an abnormality identified by an ORD. This was therefore moved into the NPV analysis. Neither of these instances, however, significantly affected the results of the calculations significantly. The results of the study also indicated that both USS and iuMR were more likely to be accurate at the younger gestational ages with regard to correctly identifying true negative cases. This demonstrates the advantage of using predictive values to assess a tests diagnostic capability rather than overall accuracy. The MERIDAN results found that iuMR was more accurate overall for fetuses ≥24 weeks gestation (overall accuracy of iuMR ≤23= 92.4% and ≥24= 93.5%) while the Add-on study found that the NPV was slightly higher in the ≤23 age group (NPV iuMR ≤23= 100% and ≥24= 99.33%), providing a more reliable indication of the accuracy of iuMR.

The diagnostic capability of USS has previously been quantified using sensitivity and specificity analysis by reviewing clinical cases that have been scanned as part of the routine screening process during pregnancy. A report by the National Institute for Health and Care Excellence (NICE) (236) described the findings from those studies, showing that whilst the sensitivity of USS was variable (15% to 85%) the specificity was consistently very high (99.4% to 100%). Rossi and Perfumo (172) attempted to define the diagnostic capability of iuMR using similar sensitivity and specificity measures. This was based on 'normal' values defined by a normal ORD but was initially suspected of being abnormal by USS, rather than the recruitment of a normal control group. Review of the literature has not shown that any other study performed has recruited normal pregnancies, (identified by USS screening) which have subsequently undergone iuMR imaging to determine the positive and negative predictive values for these modalities.

In order to estimate sensitivity and specificity with precision, sample size must be adequate (237) therefore sensitivity and specificity could not be reliably calculated for the Add-on study as the sample size was insufficient, the cases confirmed normal by USS being significantly under-represented. There are more than 800,000 pregnancies in the UK each year (238), all of which potentially undergo at least one USS examination. To effectively represent this number to determine specificity with an adequate degree of precision would be extremely difficult and cost prohibitive. Consequently, we chose study design and sample size on a pragmatic rather than statistical basis. As positive and negative predictive values are dependent on disease prevalence within the sample measured they could be reliably calculated and provide a useful measure as to the likelihood that USS and iuMR will give an accurate diagnosis (239). It is interesting to note that the results of the study reported by NICE, being adequately powered were comparable to the NPV in this study. Calculating specificity, however, with the cohort size of this study would give an erroneous value of 52.6%.

There are several possible limitations of the study, which primarily stem from recruiting 'normal' participants. Firstly, there may be an element of bias within the recruitment process as it was reliant on women volunteering for the study. It is unclear if the women who formed our sample were fully representative of the obstetric population, as although they were recruited from a wide geographical area within the UK, we did not record demographics such as ethnicity. Secondly, it was not possible to restrict recruitment to women who could attend for iuMR within two weeks of USS. We were reliant on participant's availability, and appointments were made according to their preferences to limit inconvenience. The longer time period between USS and iuMR, the greater the possibility of abnormalities evolving and hence being visible on MR. This could certainly be true in the fetus diagnosed by iuMR with mild VM, as this can develop at any stage of pregnancy and may not have been present at the time of the 20-week anomaly USS. The advantage to not restricting the time span between USS and iuMR was that a wider age range of fetuses were scanned. In the UK all

pregnant women are offered an anomaly screening USS between 18 and 21 weeks' gestation. If the two-week window was adhered to the age range at iuMR would be 18 – 23 weeks, leading to a biased sample. Thirdly, the diagnostic accuracy of USS for the Add-on study was based on routine USS screening rather than on USS by a feto-maternal expert which was a requirement of the MERIDIAN study. The availability of suitably qualified staff and the cost implications made this criterion unattainable. It is impossible to ascertain whether, in the two cases with abnormalities detected by iuMR if these were not present at USS or if they were missed by USS. In the case of the fetus with VM, there was a 6 weeks delay between USS and iuMR, and there was a delay of 16 weeks between the original USS and iuMR in the second abnormal case. It was therefore possible that the abnormality was not present at the time of the anomaly USS and even if it was, it is impossible to say whether a feto-maternal expert could have identified the cortical abnormality.

The consequences of abnormalities being missed by screening USS during pregnancy are variable. Detecting abnormalities accurately allows further investigations if necessary and instigates additional monitoring of the pregnancy, or, if the abnormality is severe and detrimental to long term outcome allows the option of termination of the pregnancy. Isolated mild VM is a common finding during pregnancy and in this category a very high proportion have a favourable outcome, but iuMR is necessary to identify additional abnormalities (112, 113, 240). This finding therefore is perhaps less significant than the cortical abnormality diagnosed by iuMR in a fetus of 35 weeks gestation. Cortical dysplasia is exceptionally difficult to identify by USS prenatally (39) and can have a range of causes and outcomes. Identifying this abnormality earlier may not have changed the outcome in terms of health of the fetus, but would have provided vital information and allowed the parents to make an informed choice regarding the future of the pregnancy.

4.6 Conclusion

The results of this study confirm the ability of both USS and iuMR to accurately identify when brain development of the fetus is normal. The high negative predictive value of USS confirms the validity of USS as the primary screening imaging method for pregnancy in the general population, and the superior positive predictive value of MR further supports the need for additional iuMR imaging when abnormalities are detected.

Chapter 5

Three Dimensional (3D) MR imaging of the Fetal Brain *in utero*

5.1 Summary

The second aim of this thesis is to report the development, application and clinical evaluation of a 3D volume iuMR acquisition for fetal brain imaging. This aim is fulfilled by the work reported in this and the following two chapters and accomplished using the iuMR imaging data from the MERIDIAN study, but outside the context of the primary study. The review and diagnoses made using the 3D acquisition were carried out by. All other work reported in this chapter was undertaken solely by the author and includes the development of the 3D acquisition over a 6 month period, anonymization of all images ready for neuroradiologist review and the collation and analysis of the results.

This chapter builds on our initial efforts to develop a 3D volume acquisition, which showed potential as a useful method for imaging the fetal brain *in utero.* A pilot study of the first 50 imaging datasets was published in a peer-reviewed journal;

- 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.

The pilot study highlighted the need for further development of the sequence in order to improve image resolution and to reduce acquisition time. In this chapter we report how the sequence was developed and also evaluate the resultant acquisition regarding image quality, diagnostic accuracy and diagnostic confidence. The aim was to assess the 3D MR volume acquisition acquired for each case scanned in Sheffield as part of the MERIDIAN study. Since its development the resultant 3D acquisition has become part of our routine iuMR imaging protocol in Sheffield.

The ability to acquire a 3D data set has been beneficial not only in providing a versatile sequence to aid diagnosis, with a potential reduction in examination time, but also to facilitating the exploration of fetal brain development through both quantitative analysis and electronic and 3D printed surface representations of the fetal brain (reported in Chapters 6 and 7).

5.2 Background

The MR sequences used for imaging the fetus *in utero* described earlier (Chapter 1) were two-dimensional (2D) and usually acquired in all three anatomical planes to provide comprehensive information about fetal brain anatomy which would assist in the diagnosis of abnormalities. Repeated acquisitions were frequently required if image quality was insufficient due to blurring caused by fetal or maternal movement, or through other inherent image artefacts such as image wrap around. This resulted in longer examination times and consequent MR exposure. Although there are no known detrimental effects of iuMR imaging during pregnancy, limiting examination time is recommended in order to protect the developing fetus (148) and to reduce maternal discomfort. An alternative approach to multiple 2D acquisitions is to acquire a 3D MR data set. This is an established method for adult and paediatric imaging, but has not yet been extensively used for fetal imaging.
The inherent characteristics of a 3D volume acquisition allow reconstruction of the raw data into different anatomical planes (including non-orthogonal), potentially reducing the need for multiple 2D acquisitions and hence consequently reducing examination time. Despite these advantages, no commercial or vendor provided 3D MR sequence with short enough acquisition times for imaging the fetus has currently been made available. The evidence within the literature of the development and utilisation of 3D acquisitions for *in utero* imaging by other iuMR imaging centres was also limited. As part of the data extraction process for the systematic review we recorded MR imaging protocol details. These showed that only a

single study, conducted in 2010 (120), recorded the use of a 3D acquisition for fetal brain imaging. However, no details were provided other than the sequence type used (3D-steady-state free precession). In addition, Sun *et al* (241) reported the use of a 3D FIESTA sequence as part of their imaging protocol. By performing volume rendering on the resultant imaging data they were able to display the external anatomy of the fetus. Again, information about their methods and sequence parameters was limited as, although the abstract was in English, translation of the full paper was unavailable. A second paper by the same group (242) extended this work by comparing a 3D FIESTA acquisition and volume rendering of resultant images to 2D ssFSE imaging and 3D USS to determine the diagnostic accuracy of fetal brain abnormalities for each. They found that the 3D FIESTA was more accurate than 2D imaging but less accurate than 3D USS but again only the abstract was available for review. Liu, Glenn (243) proposed a hybrid 3D imaging technique which used radial k-space filling for image formation and time-resolved retrospective image reconstruction. This permitted the acquisition of a 3D dataset in a scan time of 3 minutes. Although the method of acquisition reduced the effects of fetal movement, its use might be limited in practice due to the scan time and the hybrid data acquisition technique. The inherently long scan times of 3D acquisitions often prevent their consideration as viable options for fetal imaging (244, 245).

2D and 3D MR acquisitions both need rigorous optimisation of imaging parameters in order to enhance image quality whilst limiting scan time. There are, however, several factors that make the use of 3D acquisitions more challenging.

3D volume imaging is achieved by the addition of a second phase encoding in the third dimension, perpendicular to the frequency and primary phase encoding. Acquisition time is determined by the number of phase encoding steps in the first dimension multiplied by the number of phase encoding steps in the second dimension multiplied by the TR value. The

partition thickness, determined by the number of partitions of the second phase encoding and their contiguity, must be adequate to provide sufficient visualisation of the anatomy even when the resultant data is reconstructed into different planes. A consideration when planning a 3D acquisition is that image wraparound and truncation artefacts may occur in two directions due to the two phase encodings. Extra partitions in both phase directions are therefore required to ensure that the anatomy outside the volume does not obscure the area of interest. This increases scan time.

To be of practical use for imaging the fetus, which is likely to move during scanning, any 3D acquisition had to be achievable in an ultra-short timescale while still providing high SNR and adequate image resolution. The 2D FIESTA, which is part of our routine fetal imaging protocol, and described in Chapter 1, was initially developed as an ultrafast sequence for cardiac imaging. This enabled rapid acquisitions for demonstration of heart function during suspended respiration (246, 247) and high SNR made it possible to use a 3D FIESTA sequence to visualise the small structures within the central nervous system such as the nerves of the posterior fossa, auditory system and lumbar spine (248-250). This adaptability, in terms of the potential for ultrafast acquisition time and high SNR, was the primary reasons that the FIESTA sequence was used for imaging the fetal brain. Another advantage to using the FIESTA sequence is the lower SAR, due to smaller flip angles and hence less energy deposition to that of the ssFSE. Our initial pilot study found that the SAR of the 3D FIESTA was no greater than that of the ssFSE. In contrast to this Chung *et al (251)* measured the SAR of a steady state gradient echo sequence and found it to be a third lower than that of a single shot T2 weighted sequence.

The 2D FIESTA, like the ssFSE, acquires and reconstructs the data for each imaging slice before acquisition and reconstruction of the next. In contrast to this, a 3D volume is a single acquisition whereby all the data required to fill k-space for the entire volume is acquired before images are reconstructed and displayed. Movement of the anatomy under

investigation at any time during the scan, causes misregistration, with consequent blurring of all resultant images. This, in addition to the inherent acquisition times required for a 3D sequence as opposed those for a 2D scan, meant changes were necessary in order to render the acquisition time acceptable for fetal imaging.

To develop a 3D sequence which could be acquired during maternal suspended respiration and thus eliminate movement artefact from this source, several time saving adjustments were made. These included increasing the receiver bandwidth enabling a shorter TE and TR, and partial Fourier technique which used the conjugate symmetry of k-space to acquire only 0.75 of the phase encoding steps without reducing voxel dimensions. Thus reducing scan time further whilst maintaining resolution. The 3D sequence also had to be of sufficiently high resolution to adequately distinguish the small anatomical structures of the developing fetal brain. 3D volume imaging has inherently high SNR due to the whole imaging volume undergoing excitation at each repetition (as compared to a single slice for 2D imaging). This higher SNR allowed thinner partitions to be sampled thus improving image resolution without significant detriment to image quality (as compared to the equivalent slice thickness used in 2D imaging). The homogeneous excitation across the imaging volume also results in more uniform slice profiles when compared to 2D imaging as partial saturation of signal between slices does not occur. Zero filling of K-space (ZIP) is used to construct new data points from the original acquired data. ZIP averages the signal between two adjacent pixels to create estimated information for a new data point, thereby increasing the spatial resolution. Zero filling in k-space is equivalent to performing linear interpolation in image space.

The 3D FIESTA was acquired in the axial, or (to maximise coverage for larger fetal brains) in an axial oblique plane relative to the fetal brain (Figure 5.1). At the time of iuMR imaging gestational age and consequent size of the fetus and mother was variable so some of the imaging parameters had to be tailored for the individual. The aim for each fetal brain acquisition was to attain full anatomical coverage, with the highest resolution achievable,

within a timescale conducive to maternal arrested inspiration (≈ 20 seconds). This primarily involved altering partition thickness and/or number of partitions. FOV usually remained unchanged unless it was essential to increase it to prevent image wraparound which would obscure fetal brain anatomy. The imaging parameters of the 3D volume are shown in Table 5.1.

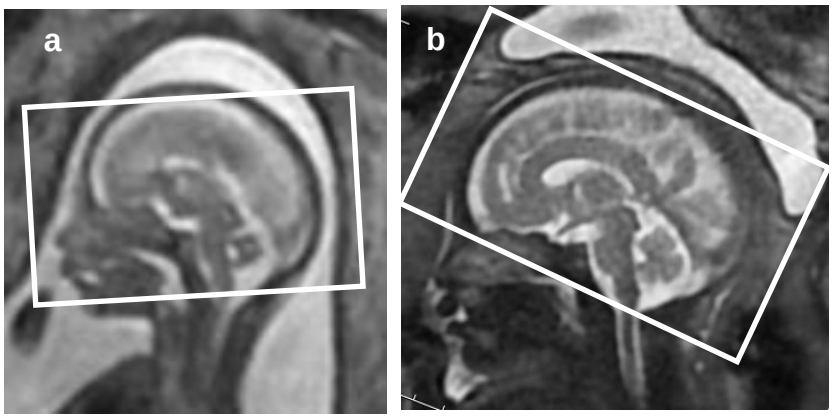


Figure 5.1 Positioning of the volume acquisition dataset for a younger/smaller (a) and older/larger fetus (b) to optimise coverage

Table 5.1 Imaging Parameters for the 3D FIESTA sequence in comparison to the 2D FIESTA Parameters

	Repetition Time	Time to Echo	Flip Angle (degree)	Bandwidth (KHz)	NEX	Partition Thickness/ Slice Gap (mm)	Field of View (mm)	Freq/ Phase Matrix (mm)	Scan Time (s)
3D	Minimum (4.4 ms)	Minimum (2.4 ms)	70	125	0.75	2.0 - 2.6/0	320x256	320/256	20-22
2D	Minimum (4.2 ms)	Minimum (2.2 ms)	70	100	1	4/0	380x340	320/256	25

The 3D FIESTA acquisition was trialled as part of our routine iuMR imaging protocol for pregnant women who attended the AUR MR unit at the University of Sheffield for assessment of their fetus's brain. This included pregnant women who attended as part of the MERIDIAN study.

The inherent differences in acquisition mechanisms between the FIESTA sequence (both 2D and 3D) and the 2D ssFSE as described in Chapter 1 result in different image characteristics, which, along with the difficulties of acquiring a diagnostic 3D dataset, might have ultimately influenced diagnostic accuracy. A retrospective evaluation of the iuMR imaging data acquired as part of MERIDIAN was therefore undertaken. Comparison was made between the 3D acquisition and the routine 2D MR imaging sequences.

5.3 Study Aim

The aim of this research was to compare the diagnostic performance of the 3D FIESTA acquisition to the diagnostic performance of the full routine 2D imaging acquired prospectively for the MERIDIAN study. This work refers to 2D versus 3D throughout. 2D representing the diagnosis made and confidence score given at original MR examination (which included the 3D acquisition) as part of the Meridian study and 3D referring to the isolated 3D FIESTA acquisition reviewed retrospectively and reported here. This research dealt with 3 areas of investigation:-

- Assessment of the image quality of the 3D acquisition;
- The diagnostic accuracy and diagnostic confidence of the 3D volume acquisition compared to the diagnostic accuracy and diagnostic confidence of the 2D iuMR imaging;
- Comparison of ventricular atrial width measurements made using the 3D acquisition with measurements made using 2D imaging when a diagnosis of ventriculomegaly was made;

5.4 Methods

The 3D volume acquisition was separated from the routine 2D MR sequences for each MERIDIAN participant and loaded onto the Advantage Windows workstation (GE Medical Healthcare, Milwaukee). Each data set was anonymised by removing all patient distinguishable information with the only means of identification being the unique MERIDIAN number allocated to each case. A minimum time period of 10 months between evaluation of the 2D imaging as part of MERIDIAN and separate evaluation of the 3D imaging was guaranteed to reduce recall bias. Anonymised documentation of the original clinical referral and ultrasound findings was provided for each case in order to replicate the original reporting conditions of the 2D iuMR examination. To eliminate reader bias each volume data set was appraised by the same neuroradiologist experienced in fetal MR imaging, (PDG) who provided the clinical report for the MERIDIAN 2D iuMR examinations.

The 3D imaging for each participant was evaluated and interpreted and a diagnosis made, as well as a grading of a certainty of diagnosis. All information was recorded by the neuroadiologist using the same Form E to replicate the MERIDIAN protocol as described in Chapter 3 (Appendix 2). The method for scoring and recording the degree of diagnostic confidence for each abnormality, expressed as a percentage, was also identical to that of the MERIDIAN study. The only addition to Form E was an image quality score for the 3D volume. The neuroradiologist assessed each 3D volume acquisition and gave a score of ‘good’, ‘average’, ‘poor’, or ‘non-diagnostic’. This was a subjective assessment based on his experience and took into account anatomical coverage, image artefacts and image resolution. No formal quantitative assessment was made, the rationale being that the primary assessment of the utility of the 3D volume was the ability to make an accurate diagnosis.

Analysis

The diagnosis and associated confidence score attributed to each 3D report was compared to the corresponding original reported 2D diagnosis and confidence score. The diagnoses using both 2D and 3D imaging were compared to the outcome reference diagnosis to determine diagnostic accuracy.

The Null Hypothesis was: The diagnostic accuracy and diagnostic confidence achieved by a 3D volume imaging acquisition is the same as the diagnostic accuracy and diagnostic confidence achieved by 2D MR imaging.

For the purpose of analysis the diagnostic confidence scores were placed into one of two categories, either ‘high confidence’ or ‘low confidence’ as below. This replicated the scheme used in the main MERIDIAN study.

- very unsure (10%),
- unsure (30%),
- equivocal (50%),

} Low confidence

- confident (70%)
- highly confident (90%)
- Diagnosis excluded

} High confidence

Each 3D case was assessed using the score-based weighted average flow chart used for the MERIDIAN study (described in Chapter 3). This was achieved by replacing the results of USS with the outcomes from 2D imaging and replacing the results of iuMR with the outcomes of 3D imaging.

Subgroup analysis of the results was also carried out to assess the influence of gestational age on diagnostic accuracy and image quality. Gestational age was separated into two

groups, comprising fetuses up to and including 23 completed weeks and those of 24 weeks gestation and older. The rationale being that younger fetuses are relatively small and have more freedom to move which may influence the ability to acquire diagnostic datasets. Influence of image quality on diagnostic accuracy was also analysed to determine the relationship between them. In cases where ventriculomegaly was diagnosed, the atrial width measurements made on both 3D and 2D imaging were compared. Ventriculomegaly is usually categorised as mild (atria 10 -12mm), moderate (>12 - 15mm) and severe (>15mm). Although the size of both atria were measured, analysis was undertaken using the larger atrium for each fetus in order to best identify category changes concerning the severity of ventriculomegaly, which was of importance clinically.

Statistical analysis was performed using SPSS software (IBM corp, Version 23.0) with chi-squared used to explore the association of 3D image quality to age of fetus, diagnostic accuracy and diagnostic confidence. McNemars Test was used to compare analysis between 2D and 3D imaging.

5.5 Results

5.5.1 Image Quality

A total of 345 fetuses had a 3D volume acquisition as part of their iuMR examination for the MERIDIAN study at the AUR in Sheffield. The resultant 3D data sets were assessed for image quality. Of these 221 fetuses were scanned at less than 24 weeks gestation, and 124 fetuses at 24 weeks gestation or older. The number of 3D datasets assigned to each category of image quality is shown in Table 5.2, with representative images of each category shown in Figure 5.2. Images were graded as ‘Good’ in 39.4%, ‘Average’ in 34.5%, ‘Poor’ in 15.7% and ‘Non-diagnostic’ in 10.4%. Figure 5.3 shows graphical representation of the image quality categories shown as a percentage for each age group.

TABLE 5.2 Image Quality Assessment of the 3D FIESTA							
			Good	Average	Poor	Non Diagnostic	Total
Gestational Age	≤23 weeks	Count	73	76	41	29	219
		%	33.3%	34.7%	18.7%	13.2%	100.0%
	≥ 24 weeks	Count	63	43	13	7	126
		%	50.0%	34.1%	10.3%	5.6%	100.0%
Total		Count	136	119	54	36	345
		%	39.4%	34.5%	15.7%	10.4%	100.0%

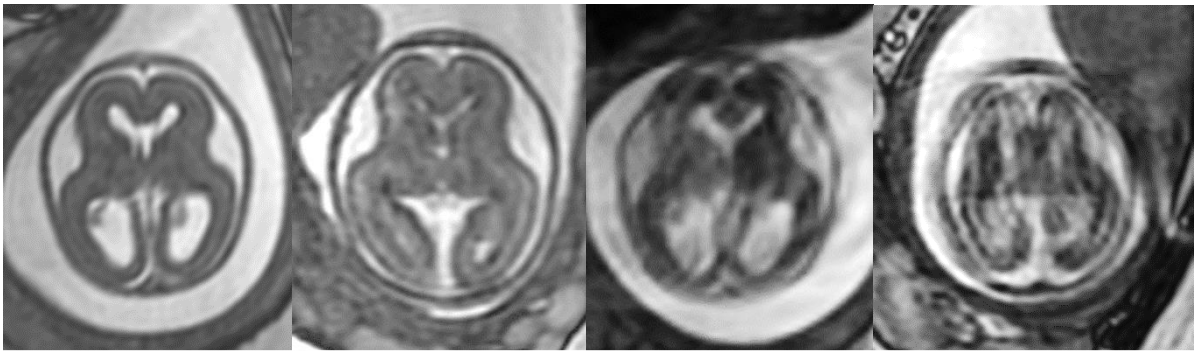
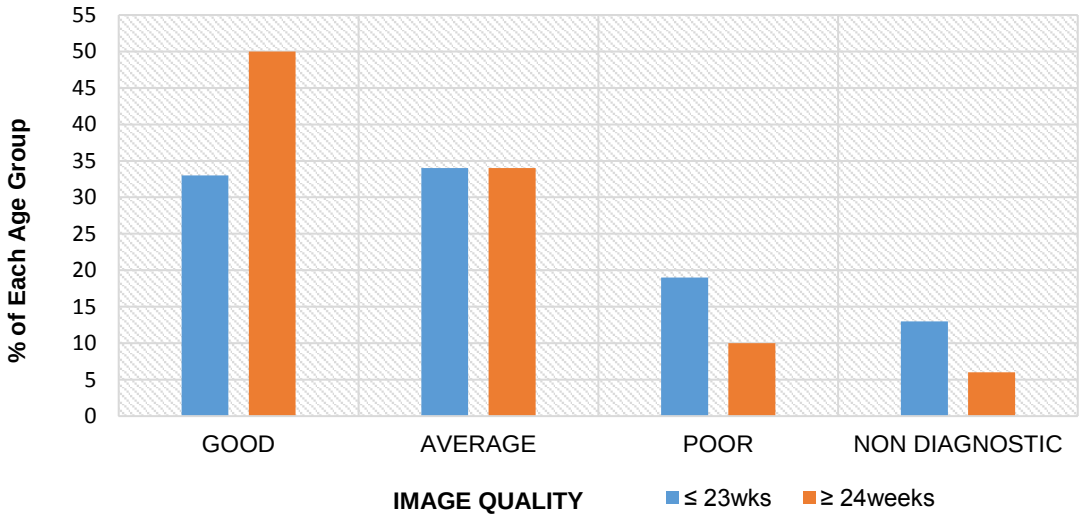


Figure 5.2 Representative 3D volume images for each category of image quality as assigned by the Neuroradiologist

A chi-square test was conducted for association between gestational age and image quality. There was found to be a statistically significant association between gestational age and image quality, $\chi^2 = 13.781$, $p = .003$, with fetuses ≥24 weeks having a higher proportion (84.1%) of datasets scored as 'Good' or 'Average' than fetuses ≤23 weeks (68%).

Figure 5.3 Results of the Subjective Assessment of Image Quality



For the remainder of the analysis, of the 345 datasets, 19 were excluded as there was no outcome reference diagnosis and 36 were excluded as the resultant images were non-diagnostic. This left 290 for further analysis, of which 175 (60.3%) were ≤23 weeks GA and 115 (39.7%) ≥24 weeks gestation.

5.5.2 Diagnostic Accuracy

The diagnostic accuracy of 2D and 3D imaging is shown in Table 5.3. 2D imaging gave a correct diagnosis in 94.5% and 3D imaging was correct in 91.4%, with both 2D and 3D giving a wrong diagnosis in 3.5% (*n*=10). The exact McNemar's test determined that this difference was not statistically significant p=0.078.

A chi-square goodness-of-fit test indicated there was no significant association between diagnostic accuracy and 3D image quality with similar proportions for each category of 'Good', 'Average', and 'Poor' (X^2 = 0.206, p = 0.902). Figure 5.4 shows the number of accurate and inaccurate diagnoses made using the 3D acquisition in relation to the category of image quality. There was also no statistically significant association between gestational

age and diagnostic accuracy for either 2D imaging (X^2 = 1.520 p= 0.218) or for 3D imaging (X^2 1.553 p= 0.213).

Table 5.3 Results of Diagnostic Accuracy of 2D and 3D imaging			
	≤23 wks	≥24wks	Total
2D and 3D Agree and Correct	153 (87.4%)	106 (92.2%)	259 (89.3%)
2D Correct, 3D Incorrect	10 (5.7%)	5 (4.4%)	15 (5.2%)
3D correct, 2D Incorrect	4 (2.3%)	2 (1.8%)	6 (2.1%)
Both Incorrect	8 (4.6%)	2 (1.8%)	10 (3.4%)
Total	175 (100%)	115 (100%)	290

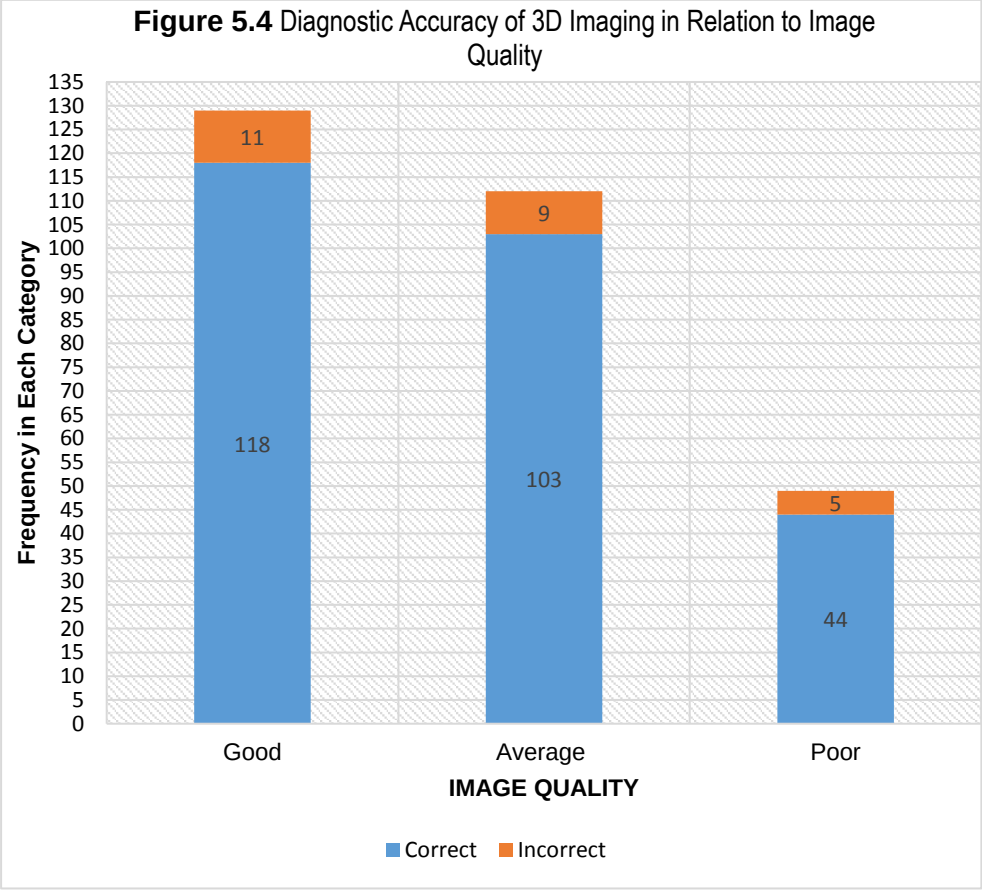


Figure 5.4 Diagnostic Accuracy of 3D Imaging in Relation to Image Quality

A separate review of the incorrect diagnoses made on 3D volume imaging revealed that erroneous measurement accounted for the inaccuracies in 13/15 of cases (Table 5.4). This included head size (case 2), cerebellum and/or vermis (cases 4,5,7,9,11-13) and over or underestimation of the size of the ventricles (Figure 5.7), resulting in pathology being excluded or diagnosed incorrectly.

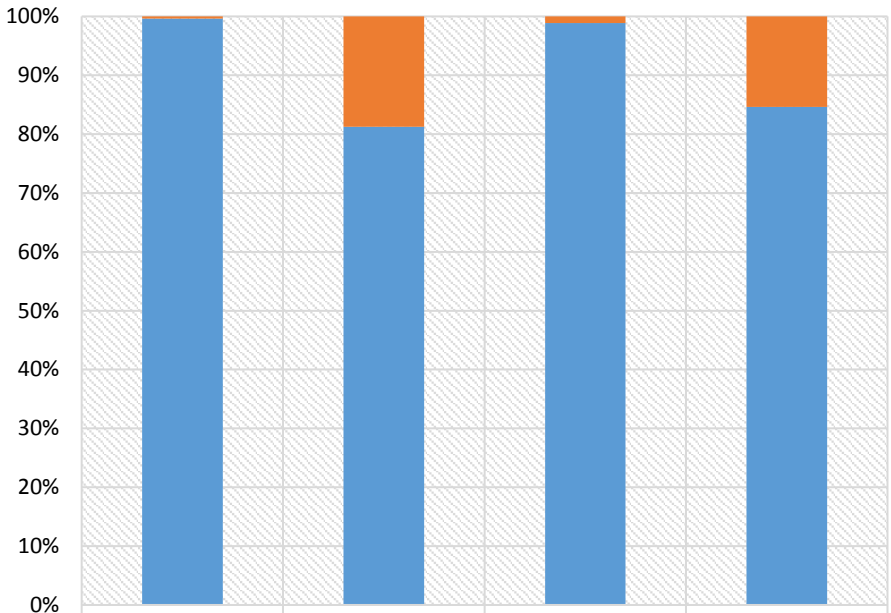
Table 5.4 Comparison of Diagnoses that were Correct with 2D imaging but incorrect with 3D Imaging

Fetus	2D Report (Correct Diagnosis)	3D Report (Incorrect Diagnosis)
1	Normal	VM, mild
2	Microcephaly, delayed sulcation	Normal
3	Normal	VM, mild
4	VM, ACC, germinal matrix cyst	Hypoplasia of the cerebellar vermis, choroid plexus cyst
5	Unilateral VM, cerebellar hypoplasia	Normal
6	Normal	Periventricular calcification (CMV)
7	VM	VM, cerebellar hypoplasia
8	Normal	VM, mild
9	VM, ACC, CFA- polymicrogyria	VM, ACC, cerebellar hypoplasia
10	Absent CSP, heterotopia, VM	VM
11	VM	VM, cerebellar hypoplasia
12	Normal	VM, Blakes pouch cyst
13	Dandy Walker Spectrum	Mega cisterna magnum
14	Normal	VM, mild
15	Aqueduct stenosis	Aqueduct stenosis, cerebellar hypoplasia

5.5.3 Diagnostic Confidence

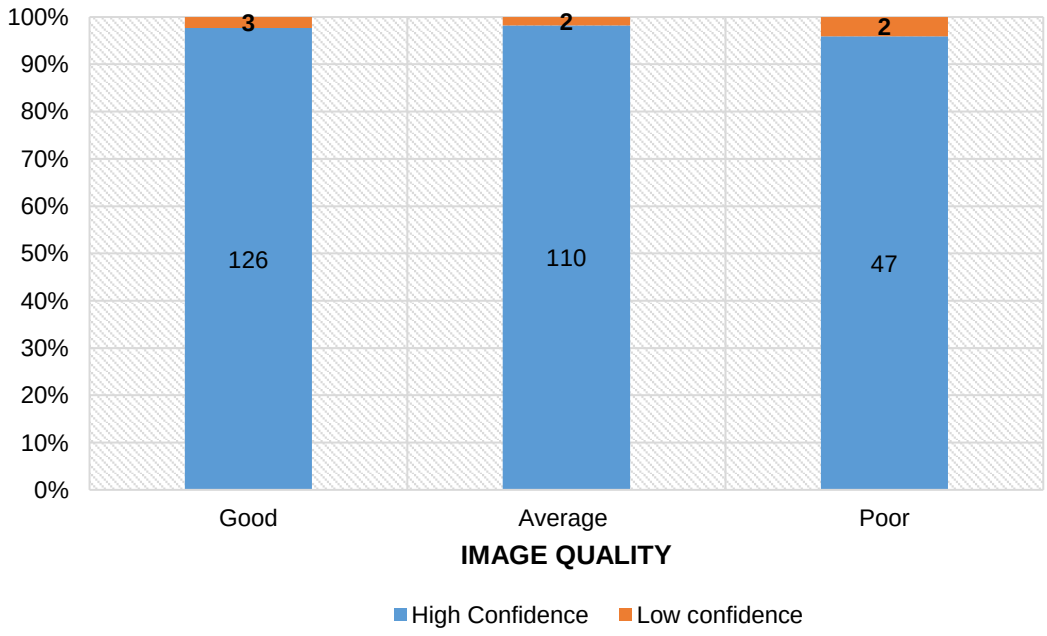
The diagnoses were made with high confidence in the majority (96.2%) of cases on 3D imaging, including those where incorrect diagnoses were given with both 2D and 3D having similar results (p=0.549). Figure 5.5 shows the sample size for the correct and incorrect diagnoses with their associated levels of confidence for both 2D and 3D imaging. The percentage of diagnoses made with low confidence was similar for each category of 3D image quality (Figure 5.6).

Figure 5.5 Diagnostic accuracy in relation to diagnostic confidence
The data table shows the number of fetuses for each category which are also represented as percentages by the bars.



	2D Correct	2D Incorrect	3D Correct	3D Incorrect
Low Confidence	1	3	3	4
High Confidence	273	13	261	22

Figure 5.6 3D Diagnostic confidence in relation to image quality



Results of the analysis of each case using the score-based weighted average flow chart, described in Chapter 3, are shown in Table 5.5. For 163 cases the score was 0, indicating that the level of confidence in relation to findings from the 3D acquisition had no impact, (either positive or negative) compared to 2D imaging. The level of confidence from the 3D acquisition had a positive impact in 7 cases and a negative impact in 20 cases. In 15 out of 20 cases the diagnosis was incorrect but made with high confidence. In the remaining 5, the diagnosis was made with low confidence. In these cases either the diagnosis was correct, or the diagnosis agreed with 2D imaging but was incorrect.

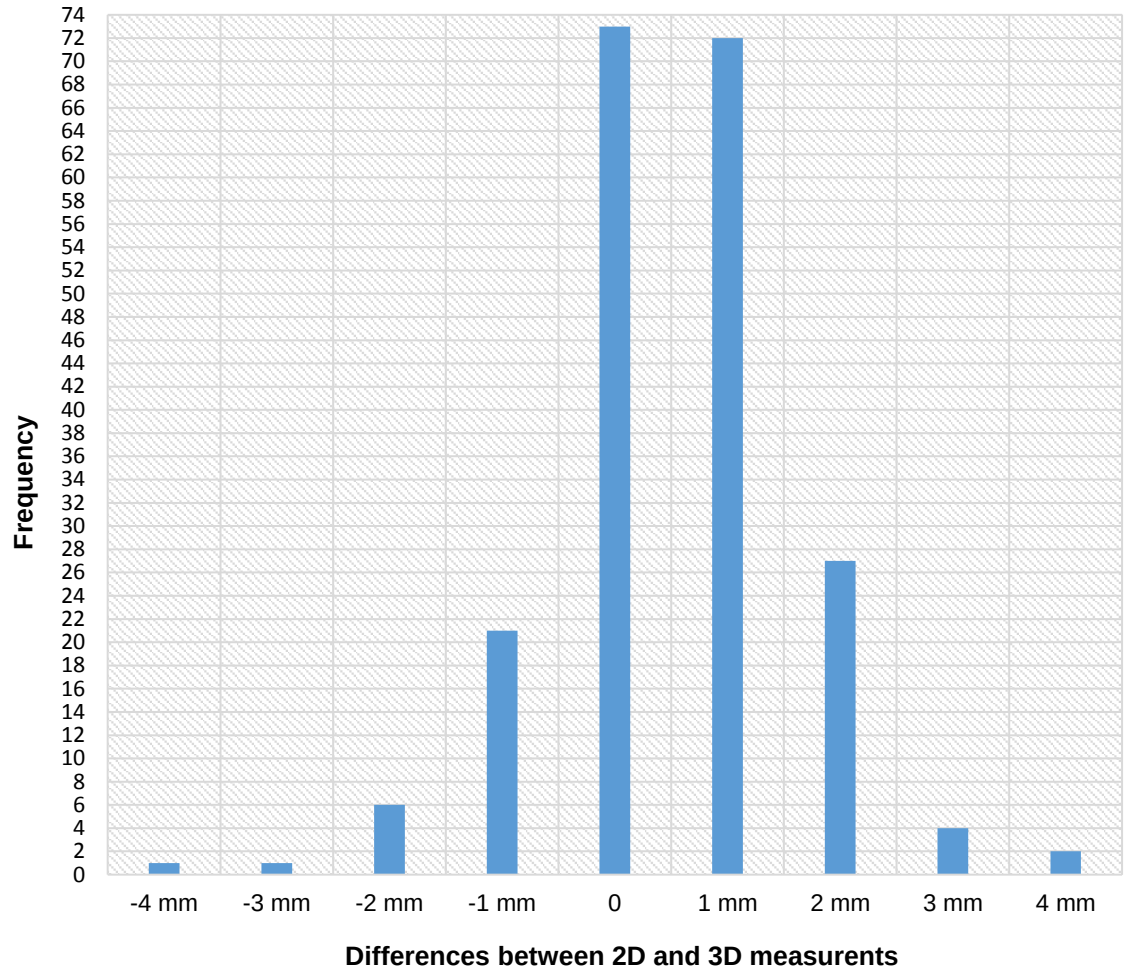
Table 5.5 Scores as a Result of the Analysis of the Influence of Diagnostic Confidence

Number of Cases	Score
163	0
6	3
1	1
7	-1
13	-2

Assessment of cases with ventriculomegaly

Ventriculomegaly was diagnosed in 207 fetuses, either as an isolated finding or in conjunction with other brain abnormalities. In comparison to measurements made on 2D imaging, measurements made using the 3D acquisition were biased towards an overestimation of size (Figure 5.7). Analysis by independent t-test showed there was no significant difference between 2D measurements (mean 12.8, SD 4.0) and 3D measurements, (mean 13.3 SD 4.2), p=0.179 (two tailed).

Figure 5.7 Frequencies of the differences between 2D and 3D acquisitions for atrial width measurements in cases of ventriculomegaly



5.6 Discussion

Evaluation of the diagnostic performance of a new MR imaging sequence is necessary in order to ensure that it is reliable and makes an additional contribution to the established imaging protocol. This is particularly pertinent in the case of fetal imaging, where limiting the exposure of the fetus to the MR environment is recommended. The aim of this research was to develop and assess a 3D acquisition for imaging the fetal brain in utero.

As described in Chapter 1, image quality is an intrinsic part of diagnostic performance. Fryback and Thornbury (152) proposed that adequate technical standards at Level One underpinned the higher levels of the diagnostic efficacy hierarchical model. Technical aspects include the quality of acquired images which is often assessed quantitatively in terms of contrast, resolution, noise and sharpness. These factors are compromised in fetal imaging due to the requirement for ultrafast sequences and are therefore not the most appropriate method by which to assess image quality in this situation. An alternative approach is to measure image quality by its ability to fulfil its intended purpose. Radiologically, this relates to whether the image can be used by the radiologist to solve a specific clinical task, and is measured as diagnostic accuracy (252). Diagnostic accuracy and diagnostic confidence of the 3D imaging in conjunction with the subjective assessment were therefore used as indicators of image quality. The rationale for this was that, if image quality is poor, it is less likely to permit an accurate or confident diagnosis. Results of the analysis of the 3D imaging showed an accurate diagnosis in 91.4% of cases. Although this was lower than the diagnostic accuracy achieved with 2D imaging (94.5%) the difference was not found to be statistically significant. However, the non-diagnostic 3D data sets were excluded from the analysis as it was not possible to determine a diagnosis in these cases. There was also no statistically significant association between the diagnostic accuracy of 3D imaging and related image quality, with equal proportions of inaccurate and accurate diagnoses regardless of category of image quality. Gestational age did not influence diagnostic accuracy significantly but there was a higher proportion of fetuses ≥24 weeks whose images were categorised as 'good' and a higher proportion of younger fetuses whose images were considered of 'poor' quality. This is likely to be due to the small size of fetuses ≤23weeks gestation and the available space they have to move freely compared to older, larger fetuses.

Diagnostic accuracy is influenced by other factors such as the various radiological features of any diagnosed disease, the degree of relevant clinical information given to the radiologist,

and the experience and medical knowledge of the radiologist. These confounding variables were excluded in our assessment of the 3D volume acquisition as the cohort of patients, reporting radiologist and clinical referral details remained unchanged from the original 2D assessments. A significant amount of time was allowed between the original imaging and the later evaluation of the 3D datasets alone. It is acknowledged though, that limitations of this work include the possibility of recognition of the 3D dataset from the original imaging and the recollection of the original diagnosis, both of which may have introduced bias in the reporting of the 3D volume. Despite this, it was felt that this influence would introduce less bias than if a more inexperienced secondary, radiologist undertook the 3D reporting.

The majority of the diagnoses made by both 2D and 3D imaging were made with high confidence regardless of whether the diagnosis was correct or incorrect. In 20 cases, however, diagnostic confidence had a potentially negative impact, indicated by the negative scores using the score-based weighted average assessment. The levels of diagnostic confidence were also unaffected by the quality of the 3D imaging. This, along with the high level of diagnostic accuracy, was surprising when the image quality was considered poor for 15.7% of the 3D datasets. This could be due to the subjective assessment and consequent categorisation of image quality by the radiologist.

The contrast mechanisms inherent in the FIESTA sequence had the potential to limit the ability to distinguish the evolving structures and maturation processes within the brain parenchyma (described in Chapter 1), making neuronal developmental abnormalities difficult to identify. The diagnostic accuracy achieved from the 3D acquisition did not support this suggestion, with the majority of incorrect diagnoses made using 3D imaging relating to the measurement of anatomical boundaries. This was particularly evident with regard to atrial width measurements in cases of ventriculomegaly. The reason for this disparity was not investigated by this study but previous research has demonstrated that discrepancy between

USS and iuMR measurements, as well as inter-observer discrepancies when using fetal iuMR to measure ventricles, is common (115).

5.7 Conclusion

Adequate 3D volume iuMR imaging was achievable in a high proportion of cases. Image quality of the resultant datasets graded ‘Good’, ‘Average or ‘Poor’ had little impact on either diagnostic accuracy or on the confidence with which a diagnosis is made. Whilst the full range of 2D imaging sequences achieved a higher rate of accuracy, the difference was not statistically significant, suggesting that the inherent image contrast of the 3D acquisition had no impact on its diagnostic capability.

Chapter 6

Quantification of Total Fetal Brain Volume Using 3D MR Imaging Data Acquired *in utero*

6.1 Summary

This chapter describes the method for post processing the 3D volume acquisitions introduced in Chapter 5 to determine reference values of total brain volumes. The cases used for determining these volumes were primarily from the Add-on cohort with no abnormalities on antenatal ultrasonography and *in utero* MR imaging. They therefore form the basis of our 'normal' reference data.

This novel work was undertaken solely by the author, which includes

- The post processing of the 3D imaging and manual segmentation of fetal brain anatomy to establish total brain volumes. This represents approximately 800 hours work.
- Writing and preparation of the manuscript that resulted in the publication given below which also forms part of the content of this chapter.

> 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.

Images from 3D volume MR acquisitions of 132 fetuses were used to extract brain volumes by manual segmentation. The accuracy of the method for measuring volumes was assessed by measuring the volumes of 3D printed brain models of known sizes and also by comparison to values reported in the published literature. Reproducibility and reliability of the methodology were assessed by analysis of the brain volume results of two subgroups who had measurements made by both the primary and a secondary observer. These results recently been published in a peer-reviewed journal (253).

Intra- and inter-observer agreement was high, with no statistically significant differences either between or by the same observers ($p= 0.476$ and $p= 0.427$, respectively). The results of the brain volume assessments are presented graphically with mean and 95% prediction

limits alongside estimates of normal growth rates. There was also high agreement between our volume measurements, the volumes of the brain models and the volumes of fetal brains measured at autopsy. We can conclude therefore that fetal brain volumes can be reliably extracted from iuMR imaging 3D datasets with a high degree of reproducibility. The resultant data could potentially be used as a reference tool in the clinical setting.

6.2 Introduction

It has been demonstrated that iuMR imaging is a valuable adjunct to USS in terms of increased diagnostic accuracy and diagnostic confidence. Despite this there is still room for improvement. This was evidenced by the 7-8% error rate for iuMR in MERIDIAN and a detailed analysis of those errors will be performed in late 2017. One possible explanation is the limited anatomical resolution of 2D MR imaging sequences. Acquisition of a 3D MR dataset not only permits reconstruction of the raw data into multiple anatomical planes but also, the ability to acquire thinner slices and their contiguity allows additional post processing techniques. Investigation of the use of the 3D volume was therefore undertaken to explore fetal brain growth and development by measuring brain volume for quantitative analysis.

A routine part of the prenatal assessment of the fetus is to monitor fetal growth and this is currently undertaken by USS. With regard to the central nervous system, measurement of skull dimensions e.g. bi-parietal diameter (BPD), occipital-frontal diameter (OFD) and/or head circumference are routinely used as indirect indicators of fetal brain growth. While fetal biometry is an important part of prenatal screening to assess brain development there may be a disparity between those measurements and brain volume. Quantification of fetal brain volume using USS is possible but is not routinely used in clinical practice. In the literature volumes calculated using USS are more representative of total intracranial volumes which include the ventricles and extra axial CSF (254-256).

The post-processing of imaging data to investigate fetal brain development quantitatively is a relatively new area of research. Previous work initially focused on extracting the fetal brain anatomy from the surrounding tissues using manual segmentation in order to measure fetal brain volumes in small numbers of fetuses (257, 258). Manual segmentation has also been used to extract brain volume measurements in fetuses with growth restriction or with ventriculomegaly, and comparing those volumes to the brain volumes of normal fetuses (259, 260). All these reports used the ssFSE images that were acquired for the clinical evaluation of the fetal brain to extract brain volume measurements.

The ability of ssFSE sequences to acquire images in ultrafast time scales and the resultant high T2 contrast, have made them the preferred choice for post-processing methods. The use of 2D ssFSE images in this way has its limitations. Spatial misregistration can occur as a result of fetal movement between each individually acquired imaging slice. Misregistration, along with the potential for uninterpretable images, could result in the inaccurate estimation of brain volume. To combat this, the development of motion correction methods for retrospective application to the MR data from ssFSE acquisitions have been developed. This uses image registration software that take one image from a single stack of imaging slices as a reference. The boundaries of the anatomy on the other slices are then aligned to the first image to create a complete motion free dataset (261-263). An improvement on this method used a two-step process which, in addition to slice matching, combine several imaging stacks of multiple orientations. This first required each imaging stack and orientation of the fetal head to be aligned by estimating the degree of movement. When combined with signal intensity matching and correction algorithms this created high resolution 3D datasets (264, 265). Despite this new approach, the possibility still existed of missing data due to movement between imaging slices. The resultant reconstruction may therefore not have been a true reflection of the anatomy as interpolation would have been required to fill in the missing data. Further work has sought to try to correct this potential error (266).

Sophisticated computer vision algorithms have also been developed to automate segmentation of fetal brain anatomy. Automatic methods developed for adult brain segmentation have not been successfully applied to the fetal brain. This is due to the unpredictable location of the fetus due to movement, the inherently limited MR contrast of the fetal brain which also changes as the fetal brain matures, and the variation in tissue signal intensities due to the position of the fetal head in relation to the phased array coil and magnetic field bias effects (267).

Several automated methods have been developed which use as a basis the more clearly defined anatomical boundaries produced by higher resolution motion corrected images. In addition, segmentation was based on predefined 3D atlases of fetal brain tissue distribution created using the average shape information from manually segmented 2D iuMR images of normal fetal brains (245, 268-273). These manually defined atlases of fetal brain anatomy were the basis of a number of automated methods. Habas *et al* (268) used them to create a statistical atlas based on the signal intensities of different tissues, and in combination with their location within the brain, automated segmentation algorithms were developed. This method has been used to both automatically segment different tissue regions within the fetal brain (269), the brain as whole, including early folding patterns (268, 274-276) and to study the brains of fetuses with mild ventriculomegaly (277). An alternative method for automatic fetal brain segmentation used templates from predefined atlases created by manually segmented fetal brains at different gestational ages. Using shape and size, rather than tissue signal intensities, new subjects were matched to the most appropriate template. This non-rigid registration method then initiated automated segmentation (262, 272, 278).

In most implementations a certain amount of user input is required to locate the brain within the imaging volume for successful slice to volume reconstruction. However, algorithms have recently been introduced to fully automate the process (279, 280). They combine motion correction with automated segmentation to create images of the fetal brain which are both

anatomically correct and have a high level of detail. There are, however, three potential disadvantages to these methods. Firstly, all the methods used to date utilised imaging data acquired using the ssFSE sequence, and based automated segmentations on predetermined knowledge of the size and shape of a fetal brain at equivalent gestations (templates) determined by manually segmented images. The automated segmentations were based on data which may have been inaccurate due to inter-slice motion and misregistration of data. The templates therefore have to be corrected to ensure accurate data. Secondly, it is unclear how the automated segmentation methods, being based on intensity distributions and growth trajectories drawn from healthy fetuses, could be applied to cases where fetal development is not following normal trajectories of growth and sulcation due to pathological or developmental abnormalities. Even measurements close to normal would be biased by the template, to an extent which is difficult to quantify. The brain abnormalities in which automatic segmentation has been applied successfully are growth restriction and isolated mild VM (277, 281). Neither of these pathologies challenge the accuracy of the automated methods as fetal anatomy and brain contours in these cases are similar to normal brains. Thirdly, the software and expertise to develop the sophisticated computer vision algorithms is rarely available in clinical situations, which precludes the routine application of automated motion correction and segmentation methods.

6.2.1 Study Aims

Having refined a method for acquiring 3D MR data sets of the fetal brain, our aim was to establish a reliable method of measuring normal ranges of fetal brain volume using the resultant imaging data. This would permit the application of these measurements in routine clinical practice and would allow them to be used as a reference for future cases when significant deviation from normal brain development was suspected.

The aims of this research were:-

- To establish reference values of fetal brain volumes derived from a cohort of normally developing fetuses across a wide gestational age range;

- To assess the accuracy of our method for measuring brain volumes by using 3D printed brain models of known volumes and by comparing the brain volumes with those in the published literature;
- To assess the reliability of the resultant fetal brain volumes by inter and intra reproducibility measurements.

6.3 Methods

6.3.1 Participants

Pregnant women whose fetuses had no abnormalities somatic or brain on USS and were at no increased risk of brain abnormalities were recruited from one of two sources: the MERIDIAN Add-on study, or other research studies sponsored by our Institution (282). All participants consented for their imaging data to be used for research and training purposes. The gestational age at which the *iu*MR study was performed is quoted in relation to the estimate of fetal age made on second trimester USS. To confirm normal appearances, the *iu*MR studies were reviewed by a consultant paediatric neuroradiologist (PDG) with over 15 years' experience reporting *iu*MR brain imaging.

6.3.2 Exclusions

Datasets were excluded if the entire fetal brain was not included in the MR imaging volume or if an abnormality was subsequently suspected after review by the neuroradiologist.

6.3.3 Data Acquisition and Image processing

The method for acquiring the 3D MR imaging data sets used for this quantitative analysis are described in Chapter 5. The DICOM datasets from each examination were anonymised and transferred to a standard PC and converted into Analyse format before being loaded, one case at a time, into 3D Slicer, (the image processing and analysis software package, (http://www.slicer.org,(283)) for segmentation. 3D Slicer was chosen as it is a free public

domain software and is relatively easy to use for a variety of image processing applications (the instructions for 3D slicer are outlined in Appendix 12). Anatomical areas of the fetal brain were outlined freehand on the axial images due to the higher in-plane resolution of that orientation, although the coronal and sagittal planes were used for reference to improve accuracy (figure 6.1a-c). The anatomical boundaries of five regions were delineated: cerebral ventricles (including lateral, third and fourth ventricles and cerebral aqueduct), right and left cerebral hemispheres, infratentorial brain (cerebellum and brain stem to the level of the medulla/spinal cord junction) and the extra-axial CSF spaces. Different colour labels were used to differentiate each anatomical area (figure 6.1d-e).

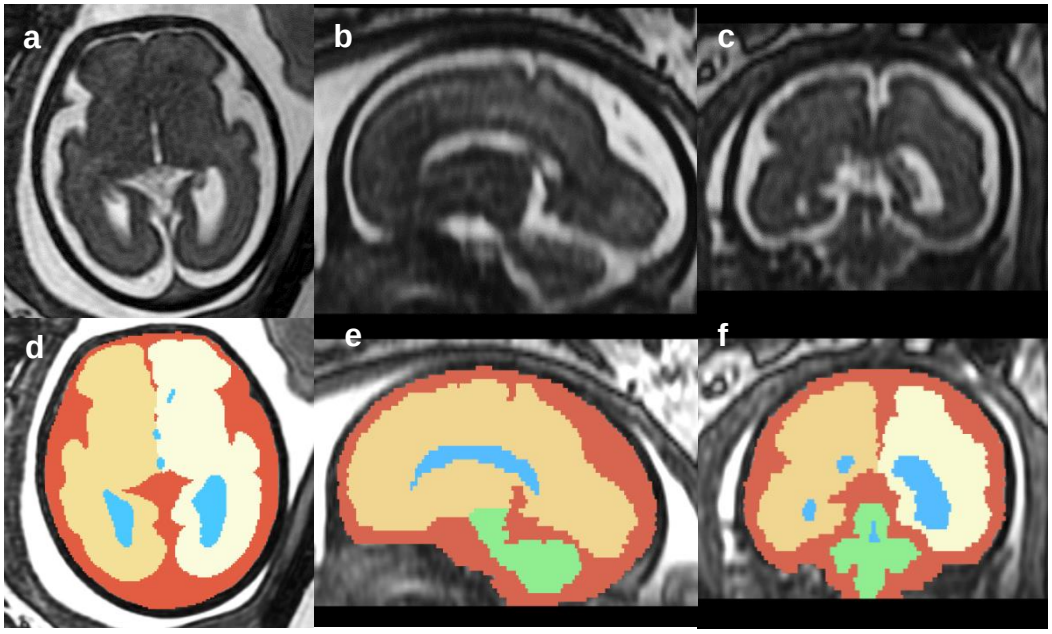


Figure 6.1 Axial image (a) and reconstructed coronal and sagittal images (b and c) as displayed by the 3D Slicer software. Figures d, e and f, the corresponding images with manual annotation completed and with the different regions represented by colours: blue for the ventricular system, yellow and cream for the cerebral hemispheres, green for the brain stem and cerebellum and red for the extra-axial CSF.

Image reproduced from 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.

Segmentation of the fetal brain in this way allowed initial analysis of subdivisions (brain parenchyma and ventricles), offered the potential for additional analysis of anatomical subdivisions in the future, for example right, and left cerebral hemispheres, or supratentorial and infratentorial brain. Using the model-making algorithm within 3D Slicer, the resulting annotated areas created a 3D representation of the volume that could be visualised and rotated. This was a requirement of the software to permit the volume data to be determined. Masks representing the segmented tissues were exported in Analyze format and custom software written in the C programming language to calculate the volumes of each structure. The software interrogates the tissue mask file that was created from the manual segmentations in 3D Slicer and sums the number of voxels belonging to each tissue class, outputting a volume for each by multiplying the number of voxels by the voxel size in each region of interest (ROI). The software outputs the volumes into a text file format that can then be loaded into a spreadsheet for further analysis.

6.3.4 Calculation and validation of brain volumes

For this work we calculated total brain volume (TBV) by adding the volumes of both cerebral hemispheres and the infratentorial structures. It should be noted that these values did not include the volume of the enclosed cerebral ventricles which were analysed separately. The resultant volumes were used to chart fetal brain growth in relation to gestational age after statistical analysis (see below). We also plotted total intracranial volume (TICV), i.e. TBV+ extra axial CSF+ ventricular volume against gestational age, and against TBV.

The manual segmentation of all cases was performed by DJ (Observer 1) and a subgroup of 30 randomly selected cases were re-analysed by the same observer, after a 2 month interval, blinded to the original measurements in order to investigate intra-observer reproducibility. A different group of 30 fetal brains were analysed by a second operator (observer 2, RA), who was less experienced in fetal brain segmentation than observer 1, in

order to study inter-observer reliability. We also imaged two 3D printed brain models of different stages of gestation (23 weeks and 30 weeks) in order to establish the level of error that our methods for estimating brain volume might introduce. Volumes for both the models were established by placing them separately into a measuring beaker of water and the volumes were defined by the amount of water displaced. The brain models, being made of a polymer, do not give an MR signal, therefore each was placed in a glass beaker and suspended in gelatin (Figures 6.2 a and b). All air bubbles were removed so that these would not interfere with the volume of the brain model, as these also do not give an MR signal. The gelatin surrounding the models enabled a 3D MR data set to be acquired, with the signal void being a true representation of the size and shape of the brain models (Figure 6.2 c and d). The MR scanner, coil, imaging parameters (apart from partition thickness) and technique used to acquire the 3D data of the brain models were identical to those used for the iuMR fetal brain acquisitions. Each brain model was scanned 3 times. The smaller model was scanned using partition thicknesses of 2.0, 2.2 and 2.4mm and the larger model using 2.2, 2.4 and 2.6mm partition thickness in order to replicate the adjustments made for the variation in sizes of the real fetal brains.

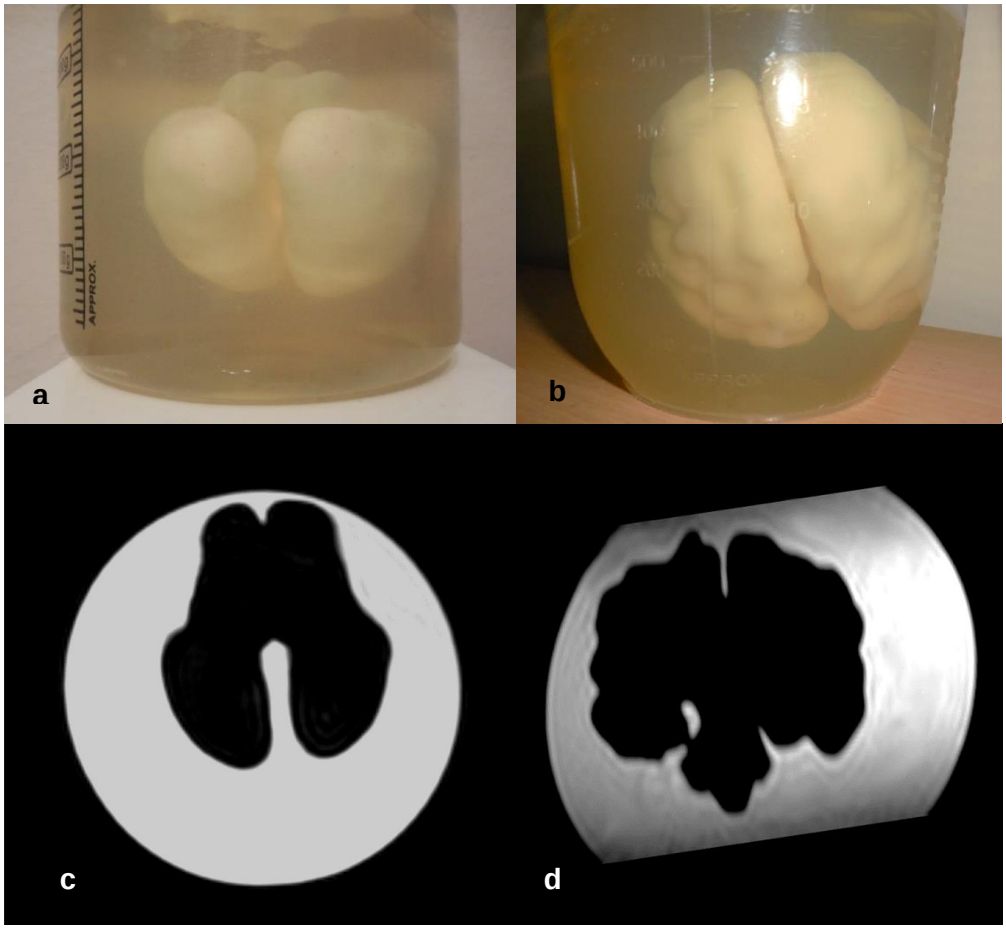


Figure 6.2 23 weeks gestation brain model suspended in gelatin (a) and resultant MR image (c) and equivalent images (b and d) for the 30 week brain model

The brain volume measurements were also compared to the published weights of fetal brains measured at post mortem examination (284). It is impossible to know the real weights of fetal brains *in utero*, and therefore their weight was estimated from the volume measurements using a density of 1.08g/cm^3, a calculation proposed by Breeze et al (285). We also included ventricular volume in the calculation of weight from brain volume in order to allow for retained CSF when the post mortem brains were weighed. The calculation for conversion of each brain volume to weight was therefore;-

(TBV [cm^3] x 1.08) + Ventricular volume [cm^3] = weight in g.

6.3.5 Statistical Analysis

All total brain volumes are quoted in cm^3 and rounded to one decimal place. Statistical analysis on the data was performed using SPSS software (IBM, version 20).
Intraclass correlation coefficient (ICC) was calculated to convey association within, and between, observers for fetal brain volumes, and independent *t*-tests were used to compare differences. Bland-Altman plots were drawn to assess inter and intra-observer agreement, variability and bias. Disagreement between measurements was considered clinically significant if differences in volume measurements both between and within raters were >10% and statistically significant if p= <0.05.
Regression Analysis of volumes versus gestational age was performed and regression fit chosen on the basis of highest adjusted R^2 value selected by successive analysis of polynomial fits (linear, quadratic and cubic). Analysis of the residuals was performed to check model fit and best regression fit used to determine 95% confidence intervals (CI) and prediction limits. 2 and 3 Standard deviations from the mean were calculated for TBV at each time point, based on the original raw data, and are presented in tabulated form. Ventricular system volumes were also measured and plotted against both gestational age and TBV.

6.4 Results

6.4.1 Brain volumes

132 normal fetal brains between 18 and 36 weeks' gestation were analysed.
The best regression fit was found to be a quadratic model with $R^2_{adj} = 0.974$ whose prediction equation is $y=0.53x^2 -13.33x+ 89.69$. The TBV of all cases are shown in Table 6.1 and presented graphically in Figure 6.3, which displays the regression fit line. Also displayed are the 95% confidence intervals for both the predicted limits of the means and the predicted individual y values for each gestational age in relation to the regression line.

The TBV ranged from 20.2cm^3 at 18 weeks to 289.8cm^3 at 36 weeks gestation, with a mean growth rate of 12.8% (range 1.0 - 21.4%) per week.

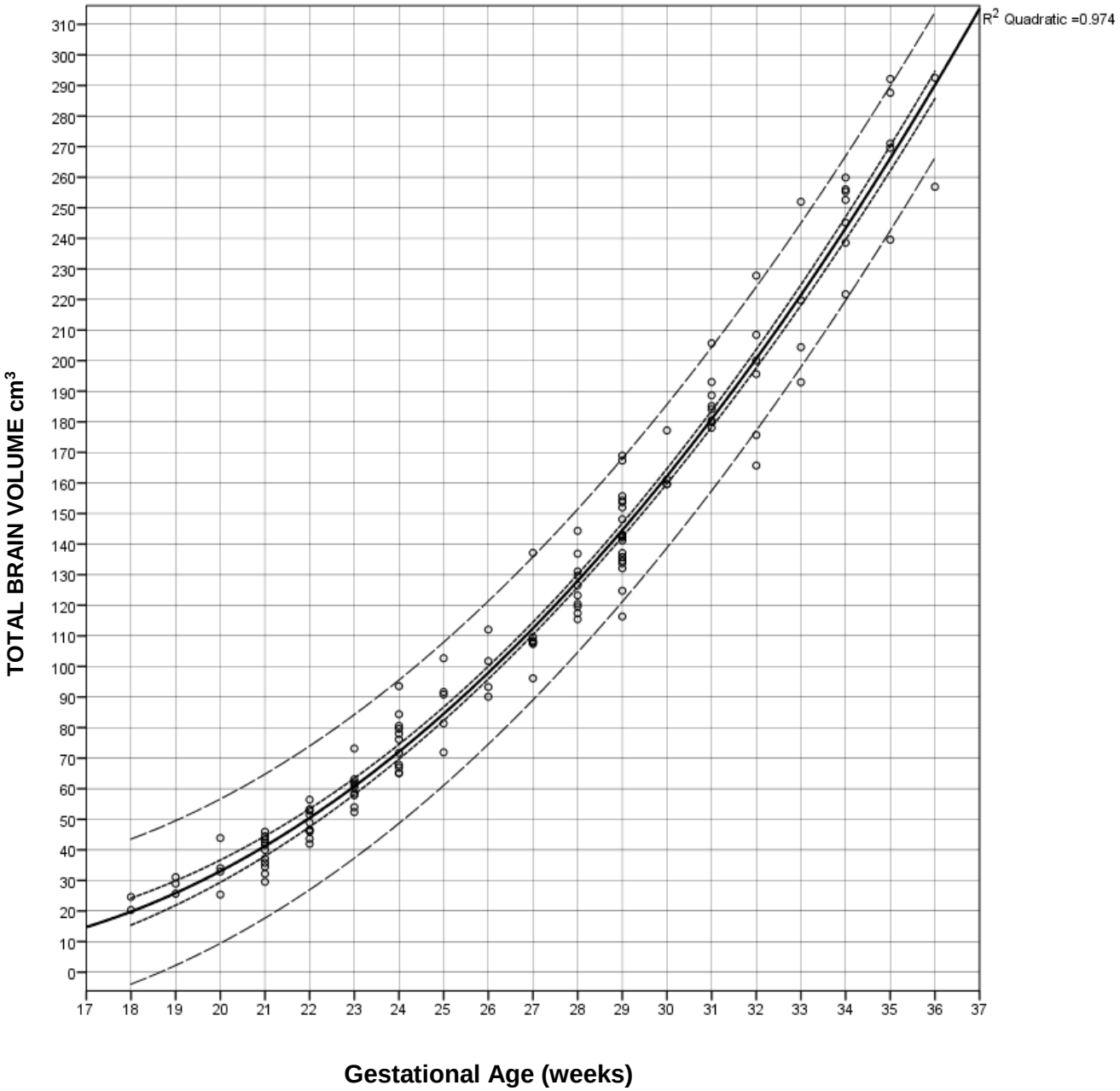


Figure 6.3 Graphical Representation of Total Brain Volume at each completed week. Dashed lines representing 95% confidence intervals (prediction limits) and the intervals based on the predicted mean (dotted lines) from the regression line for each gestational age.

Image reproduced from 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.

Table 6.1 Total Brain Volume Measurements														
Gestation (Completed Weeks)	Frequency (n=132)	RANGE cm^3		Values Based on Original Raw Data ($cm^{3)}$						PREDICTION LIMITS using Polynomial Regression (R^2= 0.974)				
		Minimum	Maximum	Mean	SD	3SD Below Mean	2SD Below Mean	2SD Above Mean	3SD Above Mean	Predicted Mean Value	Lower Predicted CI	Upper Predicted CI	Lower predicted Limit	Upper predicted Limit
18	2	20.3	24.6	22.5	2.1	16.1	18.2	26.7	28.8	19.8	12.6	27.0	-4.6	44.2
19	3	25.7	31.1	28.6	2.7	20.4	23.1	34.0	36.7	25.9	20.2	31.6	1.9	49.9
20	4	25.4	44.2	34.1	7.6	11.3	18.9	49.3	56.9	33.0	28.5	37.5	9.3	56.8
21	11	29.6	45.9	38.8	5.4	22.7	28.1	49.5	54.8	41.2	37.7	44.8	17.6	64.8
22	10	42.0	56.4	48.7	4.6	34.9	39.5	58.0	62.6	50.5	47.5	53.4	27.0	74.0
23	9	52.3	73.2	60.3	6.0	42.2	48.3	72.4	78.4	60.8	58.1	63.5	37.3	84.2
24	11	65.1	93.6	75.4	9.0	48.3	57.3	93.4	102.4	72.1	69.4	74.8	48.6	95.6
25	5	71.9	102.7	87.7	11.6	52.8	64.4	110.9	122.5	84.5	81.8	87.3	61.0	108.0
26	4	90.1	112.0	99.3	9.8	69.8	79.7	118.9	128.7	98.0	95.1	100.8	74.5	121.4
27	7	96.1	137.1	110.6	12.6	72.9	85.5	135.7	148.3	112.4	109.6	115.3	89.0	135.9
28	10	92.8	144.3	126.5	9.2	98.9	108.1	144.8	154.0	128.0	125.1	130.9	104.5	151.5
29	20	116.3	169.0	143.2	13.1	104.0	117.1	169.3	182.4	144.6	141.8	147.4	121.1	168.1
30	4	159.6	177.2	164.4	8.6	138.8	147.3	181.5	190.1	162.2	159.5	165.0	138.8	185.7
31	8	178.1	205.7	186.9	9.1	159.7	168.8	205.0	214.0	180.9	178.2	183.7	157.5	204.4
32	6	165.7	227.8	195.5	22.4	128.3	150.7	240.4	262.8	200.7	197.6	203.7	177.2	224.2
33	4	192.9	252.0	217.3	25.6	140.4	166.0	268.5	294.1	221.5	217.9	225.1	197.9	245.1
34	7	221.7	262.4	247.0	13.3	207.1	220.4	273.6	286.9	243.3	238.8	247.8	219.6	267.1
35	5	239.5	292.1	272.0	20.7	210.0	230.6	313.3	334.0	266.2	260.5	271.9	242.2	290.2
36	2	256.9	292.5	274.7	25.2	199.0	224.2	325.1	350.3	290.2	283.0	297.3	265.8	314.5

Total intracranial volumes (TICV) ranged from 39.6 cm^3 at 18 weeks gestation to 519.6 cm^3 at 35 weeks gestation which were also plotted against gestational age and presented graphically in Figure 6.4. Lines representing 95% confidence intervals and the intervals for the predicted means and the predicted y values for each gestational age from the regression line are also displayed. This was also found to be a quadratic model with $R^2_{adj} = 0.947$.

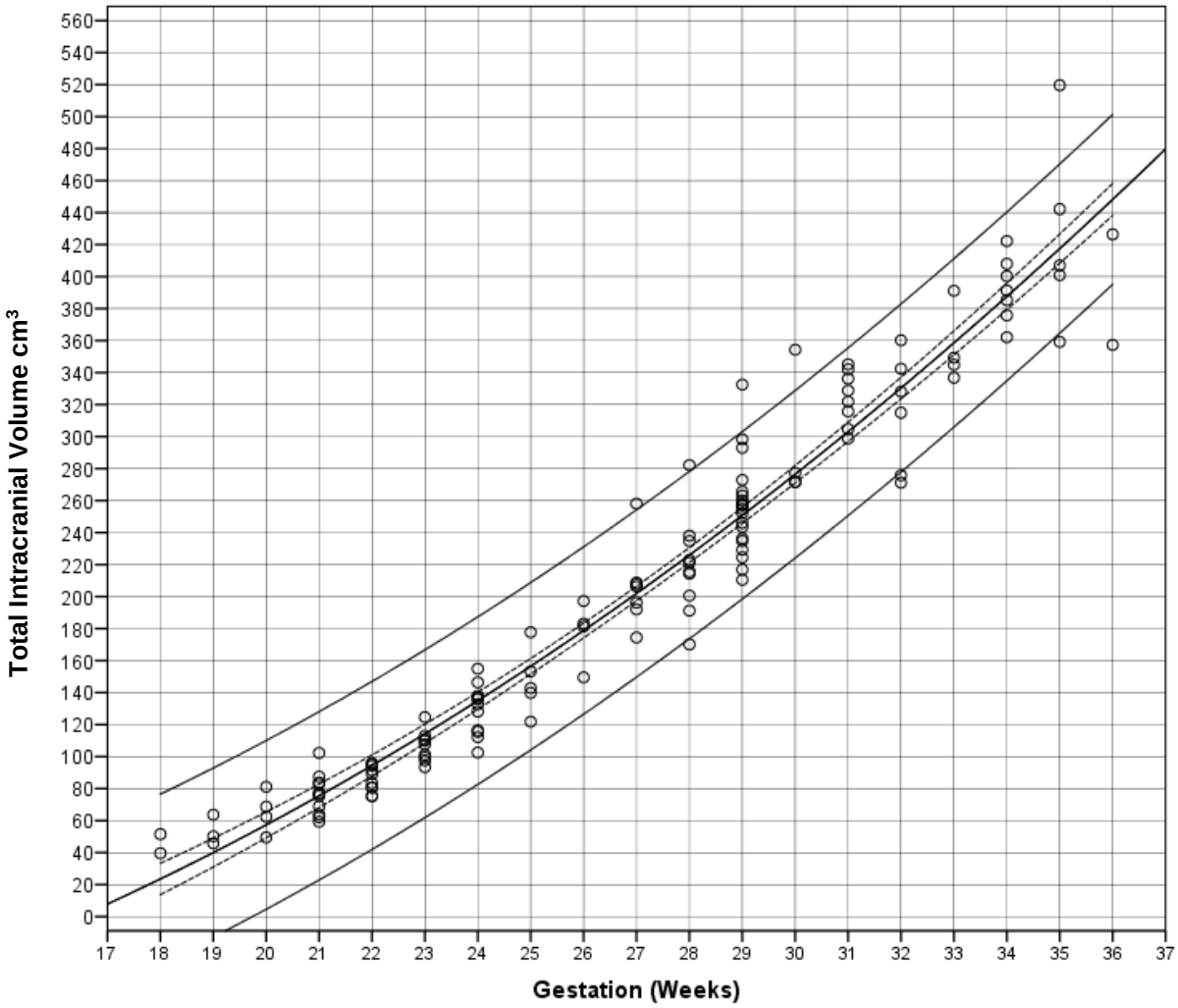


Figure 6.4 Graphical Representation of Total Intracranial Volume at each completed week. Dashed lines representing 95% confidence intervals (prediction limits) and the intervals based on the predicted mean (dotted lines) from the regression line for each gestational age.

There was a strong positive correlation between TBV and total intracranial volume (TICV) (*r* [98] = 0.983, p=<0.001, Figure 6.5). The ratio between TBV and TICV increased slightly with gestational age (Range 40.6-71.9 $cm^{3,}$ Mean 57.3cm^3, SD 5.3$cm^{3,}$ (95% CI 55.8 – 58.1) (Figure 6.6).

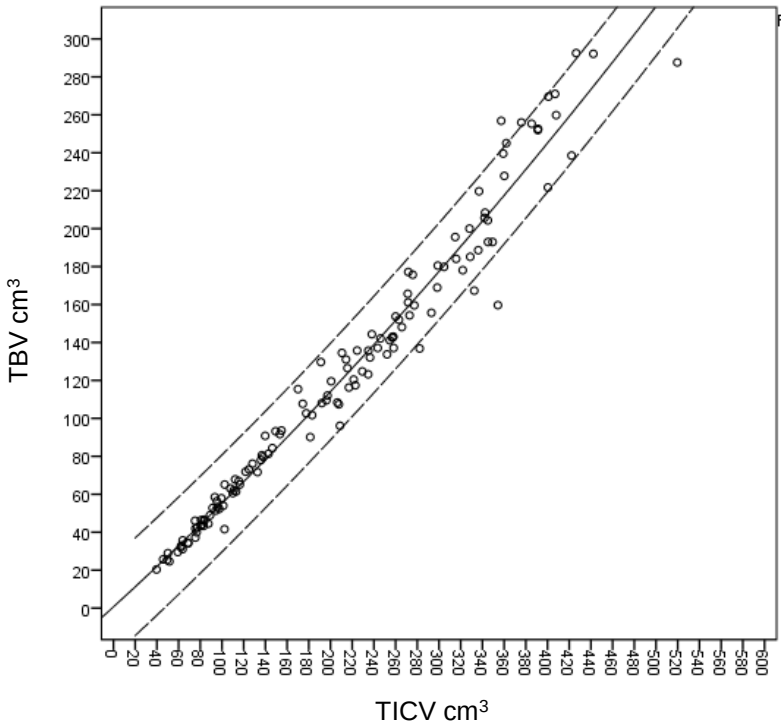


Figure 6.5 Graph Showing Relationship between Total Brain Volume and Total Intra-cranial Volume

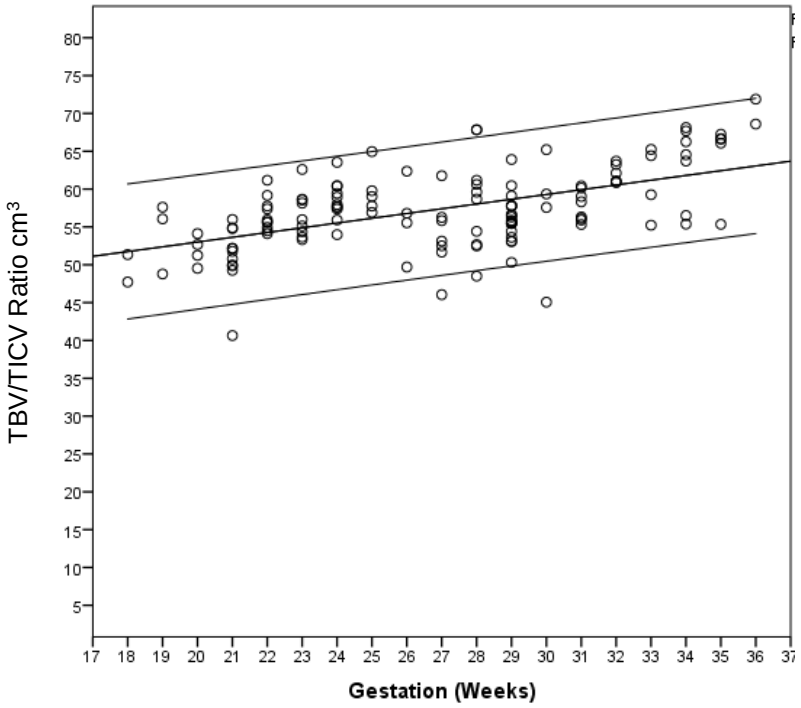


Figure 6.6 Graph Showing Relationship between the Ratio of Total Brain Volume to Intracranial Volume and Gestation

6.4.2. Ventricular System Volumes

Ventricular system volumes (VV) ranged from 1.3cm^3 to 11.6cm^3 (Mean 5cm^3, SD 2.3cm^3, 95% CI 4.6 - 5.4cm^3) and the best regression fit was found to be a quadratic model with R^2_{adj} = 0.45 (Figure 6.7). The ratio of TBV to ventriclular volume (VV) ranged from 2cm^3 to 11cm^3 (95% CI =4.7- 5.7). It showed a negative correlation to gestational age (*r* = -0.683), and the best regression fit was a cubic model R^2_{adj} = 0.633 (Figure 6.8).

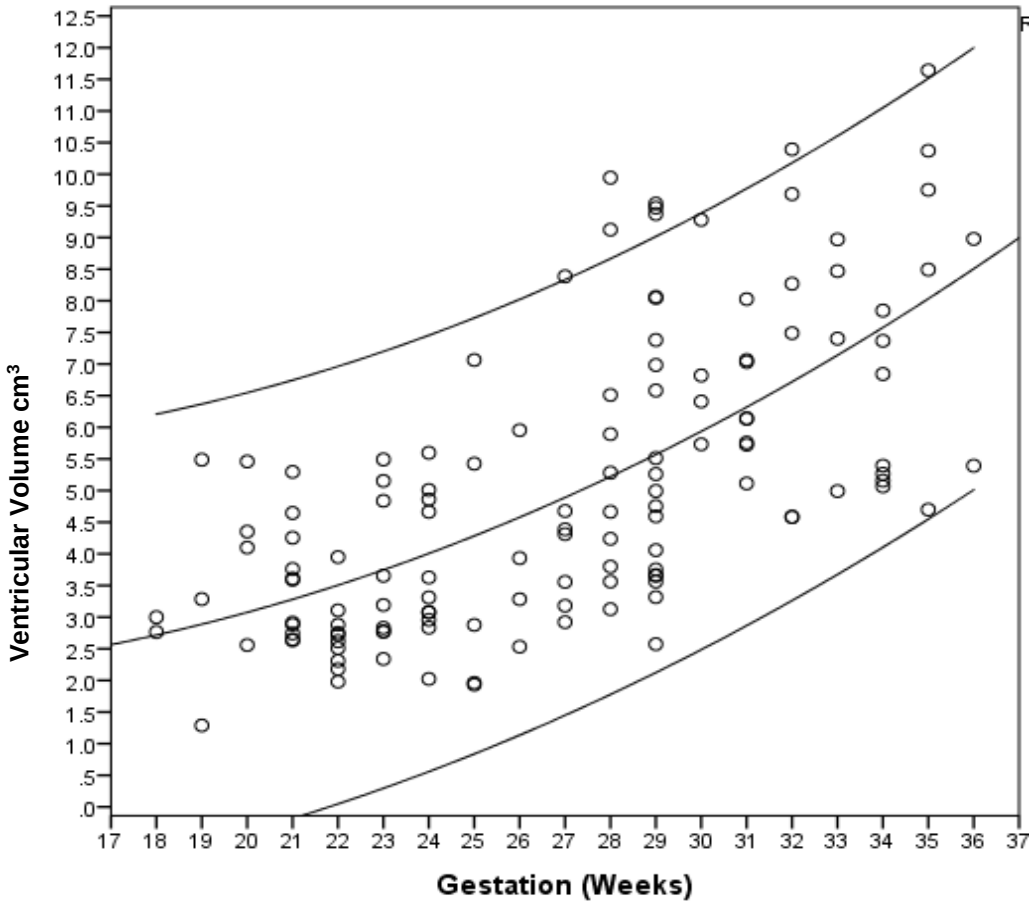


Figure 6.7 Graph showing Ventricular Volume in Relation to Gestational Age.

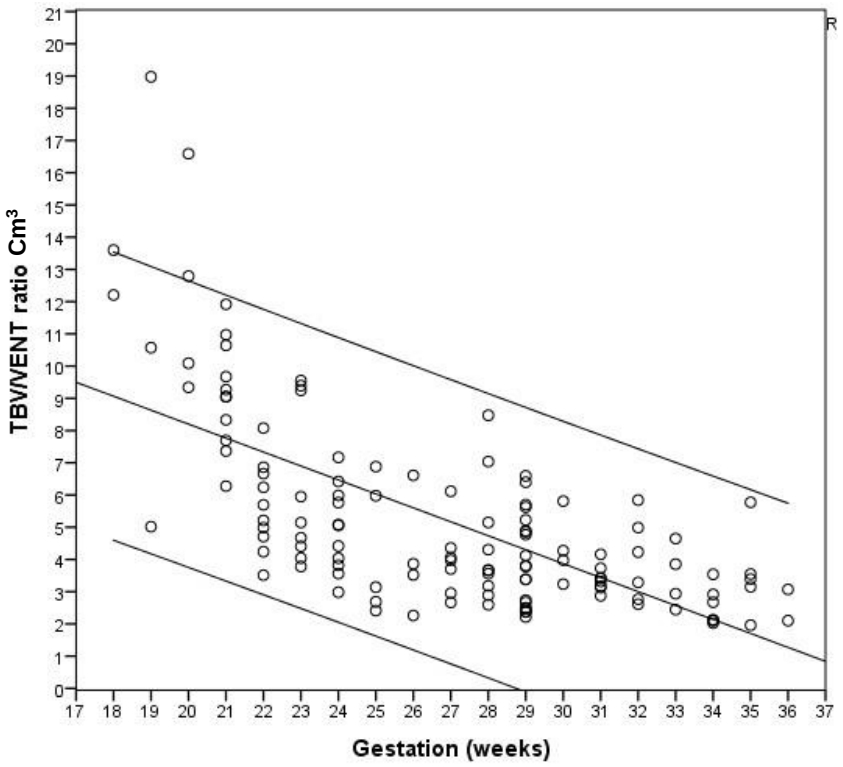


Figure 6.8 Graph showing TBV/Ventricle Ratio in Relation to Gestational Age.

6.4.3 Reliability and Reproducibility

The intra-rater analysis showed good repeatability of TBV measurements when observer 1 re-analysed a subgroup of 30 cases after a 2 month period (ICC=0.999, CI, 0.998-1.00, p<0.001). A one sample *t* test revealed that the brain volume differences between measurements were not statistically significant, *p*=0.427, (95% CI -0.68 to 1.57). The Bland-Altman plot of the differences between measurements are shown in Figure 6.9 with one value outside the 95% CI but no bias between measurements observed (B= -0.001, *p*=0.877). Table 6.2 shows the raw data TBV of first and second measurements and the percentage difference between the two measurements, which were between 0.31 and 7.10% (Mean 0.93%, SD 3.39%).

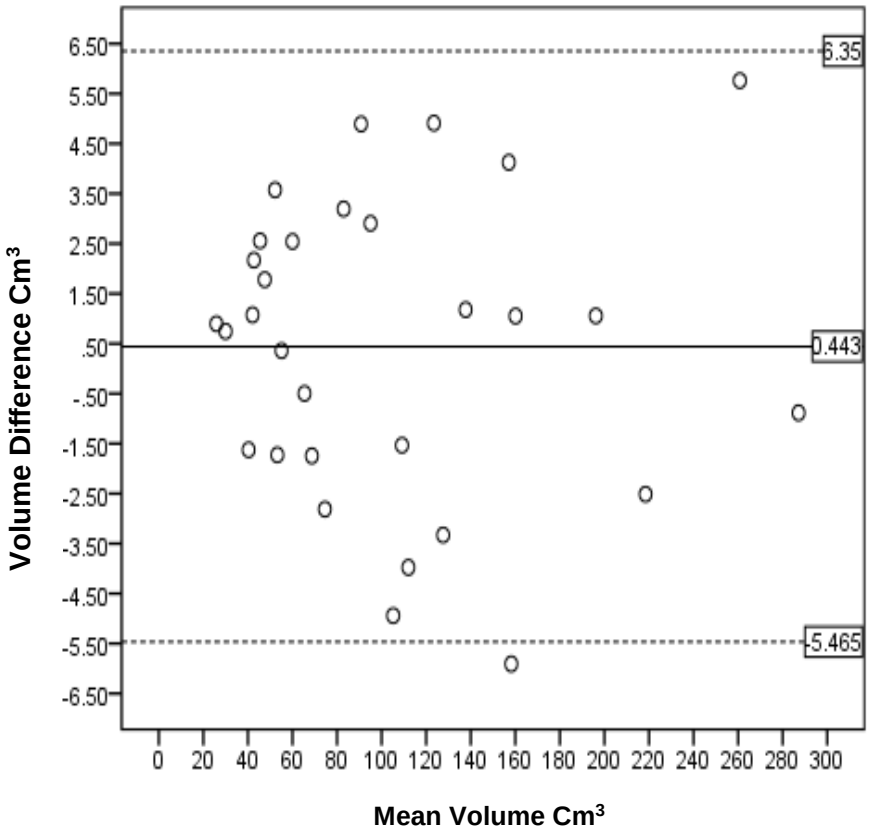


Figure 6.9 Bland Altman plot of the differences between the two measurements made by the experienced operator (observer 1, DJ) Solid black line=mean. Dashed lines=95% limits of agreement.

Inter-rater analysis demonstrated good reliability with no statistically significant difference found between measurements: p=0.476 (95% CI, -1.799 to 3.761). The average measure ICC was 0.977, p<0.001 (95% CI, 0.952 to 0.989). The corresponding Bland-Altman plot for inter-rater agreement (Figure 6.10) demonstrates the limits of agreement with one value outside the 95% CI, and a bias toward higher values by the more experienced operator 1 (DJ) (B= -0.123, p= 0.001). The changes in measurement between observers as percentage difference, range between 0.05 and 9.31% (Mean 1.27%, SD 4.8%) as shown in Table 6.3

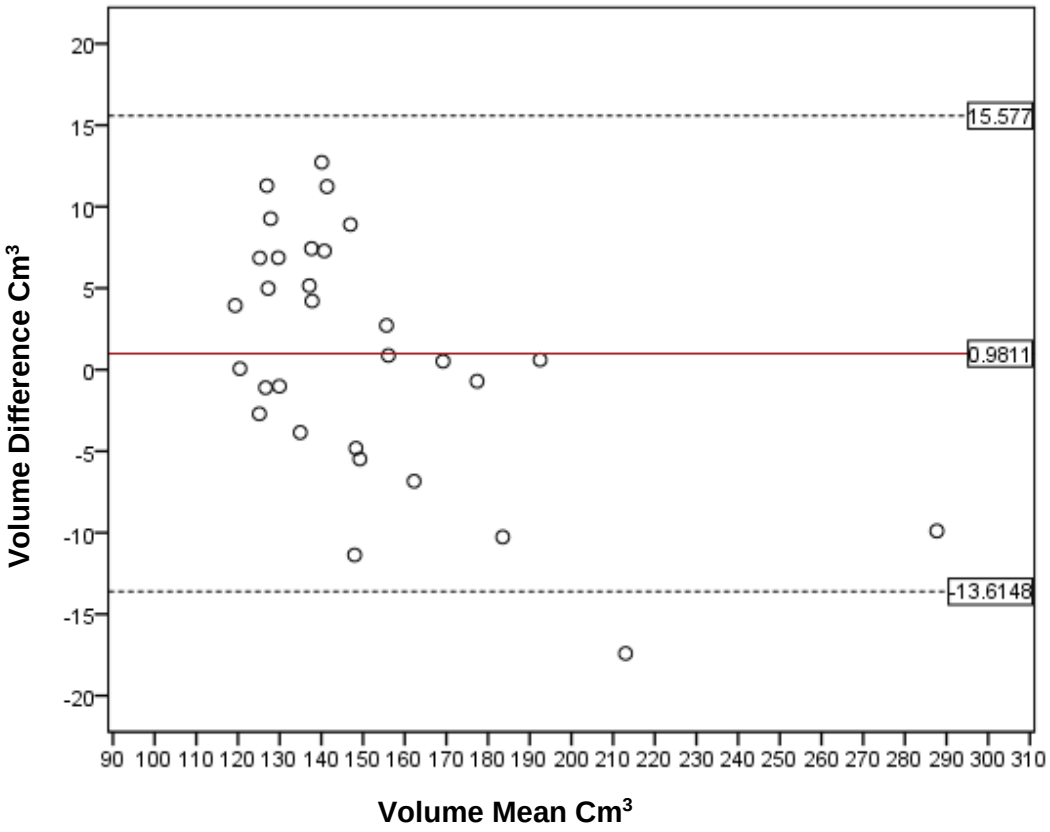


Figure 6.10 Bland-Altman plot of differences between operator 1 (DJ, experienced) and 2 (RA, newly trained). Solid black line=mean. Dashed lines=95% limits of agreement.

Table 6.2 Intra Rater Reproducibility TBV Measurements (cm^3)			
Case Number	Observer 1 First Measurement	Observer 1 Second Measurement	% Change
1	69.6	67.8	-2.5
2	121.0	125.9	4.1
3	109.9	108.4	-1.4
4	25.4	26.3	3.5
5	44.1	46.7	5.8
6	88.3	93.2	5.5
7	107.7	102.7	-4.6
8	29.6	30.3	2.5
9	287.6	286.7	-0.3
10	50.4	54.0	7.1
11	159.6	160.7	0.7
12	41.6	43.8	5.2
13	76.0	73.2	-3.7
14	114.0	110.0	-3.5
15	54.0	52.3	-3.2
16	195.6	196.7	0.5
17	58.7	61.3	4.3
18	219.7	217.2	-1.1
19	81.3	84.5	3.9
20	41.5	42.6	2.6
21	257.9	263.7	2.2
22	155.0	159.2	2.7
23	65.6	65.1	-0.8
24	161.2	155.2	-3.7
25	46.6	48.4	3.8
26	54.9	55.3	0.7
27	41.1	39.5	-4.0
28	129.3	125.9	-2.6
29	93.6	96.5	3.1
30	137.1	138.3	0.9
Mean	103.9	104.4	-0.5
STDev	68.2	68.1	0.2

Table 6.3 Inter Rater Reproducibility TBV Measurements (cm^3)			
Case Number	Measured TBV Observer 1	Measured TBV Observer 2	% change
31	134.5	139.7	3.8
32	120.4	120.5	0.1
33	153.7	142.3	-7.4
34	117.4	121.3	3.4
35	135.7	139.9	3.1
36	123.2	132.5	7.5
37	133.7	146.5	9.5
38	137.1	144.4	5.3
39	152.0	146.5	-3.6
40	188.7	178.4	-5.4
41	192.2	192.8	0.3
42	121.3	132.6	9.3
43	168.9	169.5	0.3
44	142.5	151.4	6.2
45	155.7	156.5	0.6
46	135.7	147.0	8.3
47	136.9	133.0	-2.8
48	177.7	177.0	-0.4
49	154.3	157.0	1.8
50	124.8	129.7	4.0
51	165.7	158.9	-4.1
52	221.7	204.3	-7.9
53	292.6	282.7	-3.4
54	127.2	126.1	-0.9
55	130.4	129.4	-0.8
56	133.9	141.4	5.5
57	121.8	128.7	5.6
58	126.5	123.8	-2.1
59	126.2	133.1	5.4
60	150.7	145.9	-3.2
Mean	150.1	151.1	-0.7
STDev	36.5	32.3	13

The volumes of the brain models used to test the accuracy of our method, when measured by water displacement, were 68.0cm^3 (23 weeks gestation brain model) and 158.5cm^3 (30 weeks gestation brain model). The results of the manual segmentations showed the experiment had recorded between 101.5 and 99.5% of their actual volume (Table 6.4).

Table 6.4 Accuracy of manually segmented 3D volume data compared to ground truth volume measurements in two brain models

Partition Thickness of MR Acquisition for the Brain Model	Manually Segmented Volume Measured (cm^3)	Relative Accuracy
Small, 2.0mm	69.0	1.5%
Small, 2.2mm	68.6	0.9%
Small, 2.4mm	68.3	0.4%
Large, 2.2mm	158.4	0.1%
Large, 2.4mm	157.9	0.4%
Large, 2.6mm	157.7	0.5%

The mean weights of the fetal brains measured at post mortem examination ranged from 32.7g at 18 weeks gestation to 319.3g at 36 weeks gestation (mean 153.6g, SD 90.4). The mean estimated weights from the iuMR volume measurements were 27.0g at 18 weeks to 285.8g at 36 weeks gestation (mean 141.4g, SD 90.5). The weights from the measured iuMR brain volumes were marginally lower than the post mortem weights (Figures 6.11 and 6.12). but a one sample t-test revealed no statistically significant differences between the two measurements, (p=0.68).

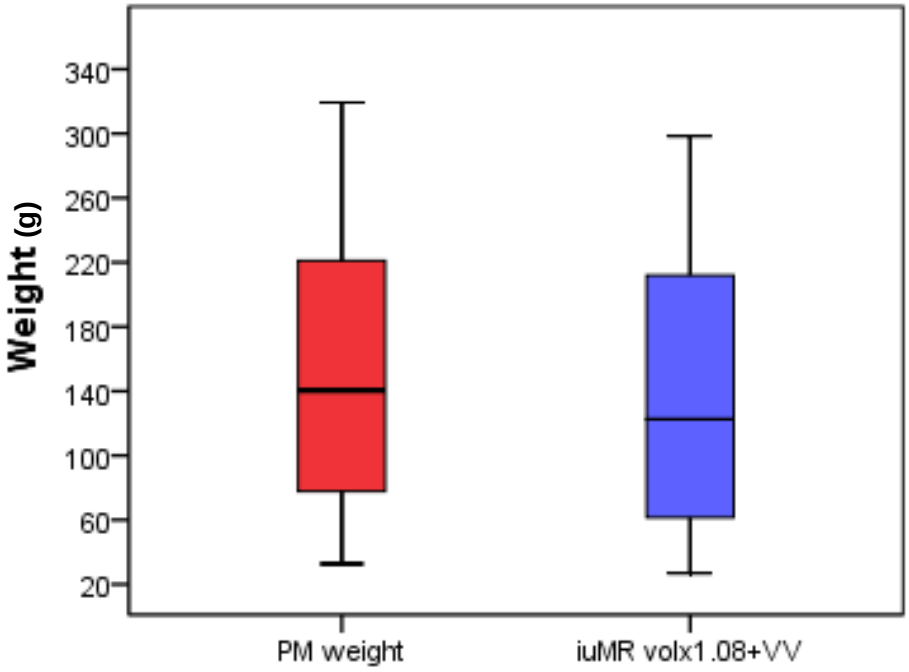


Figure 6.11 Box plot comparing the fetal brain weights at post mortem with the estimated weights using iuMR volume measurements.

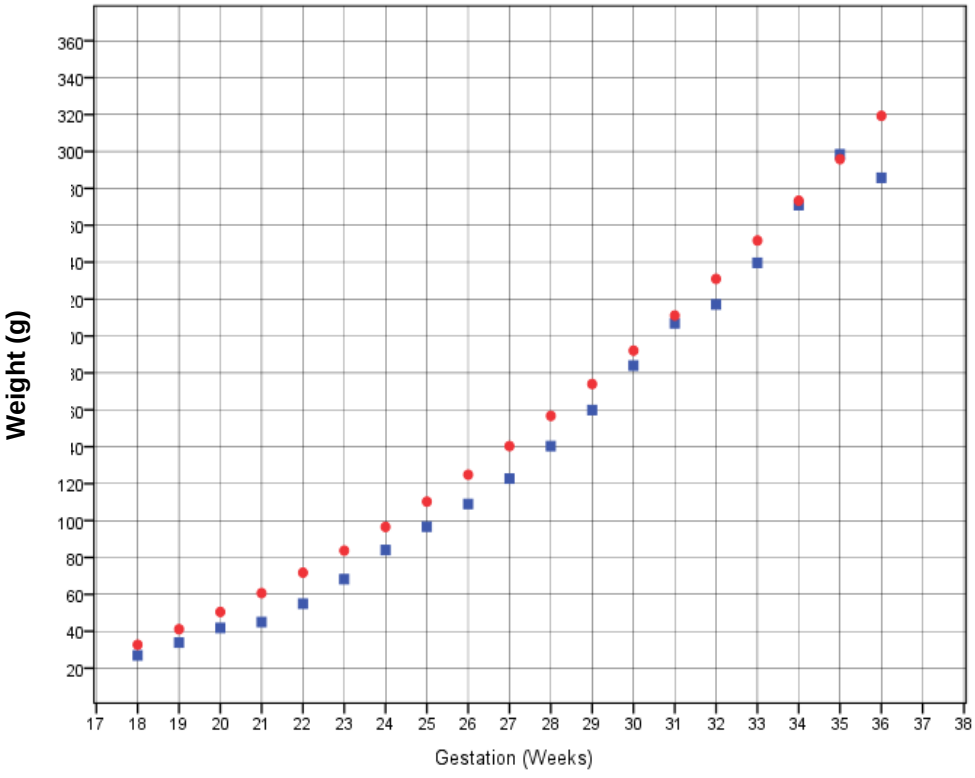


Figure 6.12 Graph plotting the mean weight of fetal brains at each gestational age measured at post mortem (red marker) and the mean weight as a result of recalculating the iuMR data (blue markers)

6.5 Discussion

We have demonstrated that quantification of fetal TBV using 3D steady state sequences is possible in second and third trimester fetuses. The time required for manual segmentation ranged between 1 and 3 hours depending on the complexity of the surfaces (more mature fetuses have more complex surfaces because of progressing sulcation/gyration). Despite this time requirement, our method appears to be accessible, easily replicated and reproducible, even when undertaken by a relatively inexperienced operator. A significant advantage to having manually segmented such a large number of fetal brains is the potential to use the resultant label maps as templates to form an Atlas of normative brain development to guide automated methods. To date this data has not been previously available. The results of 132 normal fetal brains are presented in this Chapter, but recognise that we require more cases to consolidate the data, particularly at the upper and lower ends of our range of gestational ages. For example, there were only 2 data points at 18 gestational weeks and 3 at 19 gestational weeks. This has resulted in unrealistic lower 95% CI for predicted brain volumes at these early gestations (i.e. below zero at 18 weeks) so should be regarded with caution. It is therefore possible that the standard deviations calculated from the original TBV data may provide more reliable volume estimations for these gestations.

It is not feasible to know the true volumes of the fetal brains but our tests, as judged by the segmentation results of the brain models of known volume, suggest our method is accurate with only a small margin of error (<2%). The accuracy, reliability and reproducibility of our methods, specifically comparing the results of different observers and the results of the same observer at different times is important in order to ensure that any deviation from values observed in the normal population can be assigned to abnormal development rather than to inconsistencies in the methods used to extract the data. Our analysis by ICC and Bland-Altman plot have shown that the discrepancies both within the same rater and

between raters, were not statistically significant, so it is encouraging that there are not likely to be any major systematic methodological flaws. Inter-observer agreement was not as closely matched when compared with intra-observer assessments (shown by the wider limits of agreement and the bias toward higher volumes by the more experienced observer). However, these differences are still small and thus unlikely to cause clinically relevant errors. The discrepancies could be due in part to earlier, more inexperienced measurements by observer 2 in the training period or due to variation in the practical aspects of segmentation such as image windowing. Although 3D Slicer has previously been used for fetal brain segmentation and 3D reconstruction (286) (287, 288), the initial information was acquired from 2D ssFSE acquisitions which then required post processing algorithms to create 3D data sets (266, 289). Our method has the advantage of acquiring a 3D data set which is possible on most clinical scanners. As it does not require and advanced post-processing to create the further 3D information required, it could easily be implemented in practice.

One possible solution to reduce the required time for manual segmentation would be to automate the process to extract the volume data Although several publications have described the development of automated segmentation techniques, they have not reported any brain volumes measured using these techniques (273, 281). Those that have published values have focused on different anatomical subdivisions of the brain to our own study, making it difficult to correlate our TBV findings with the published work. Indeed most previous studies report volume data from the supratentorial brain only (281, 290, 291). Other studies have reported brainstem and cerebellar volumes but without the paired supratentorial data (276, 292, 293). We chose to quantify the fetal TBV as the borders of the whole brain can be easily identified due to the contrast between the brain parenchyma and CSF. In earlier studies smaller areas within the brain were less consistently identified due to poor resolution (281). Clouchoux *et al* (294) published brain volumes, measured using motion correction and automated methods, from 64 healthy second and trimester fetuses. Unlike our data which described the relationship between gestational age and brain growth

as quadratic, they found a linear relationship. This may be explained by the fact that whilst TBV matched at an earlier gestation (25 weeks in both studies) at later gestation (36 weeks) the volumes Clouchoux *et al* measured were greater than the volumes measured by our method. The reason for this difference is unclear but a possible explanation is the limited number of fetuses measured at this gestation.

We also compared our volume measurements to the weights of total fetal brains recorded at post mortem examination (284). The results showed that although there was a good match between the two measurements, the post-mortem weights were consistently marginally larger than the weight taken from volume measurements. This may have been due to post mortem brain oedema. An alternative explanation may be that the method of estimation of brain weight from brain volumes was limited by the use of estimated fetal brain density and assumption of retained CSF. As far as we were aware there was no published data regarding density of the fetal brain. We therefore relied on the density postulated by Breeze *et al* (285). They estimated average tissue density for the fetal brain based on their findings and published paediatric brain densities, but acknowledge that the resultant value should be used with caution.

Egana-Ugrinovic *et al* (295) calculated TBV (consisting of the supra and infratentorial compartments) for 50 fetuses at 37 weeks gestation, and reported mean values of 312.07 cm^3 (SD 40.85cm^3). These values included the intraventricular CSF spaces, unlike our data which measured brain parenchymal volume only. We were unable to compare our data with that of Egana-Ugrinovic *et al*. directly, because we did not obtain any data for fetuses of 37 weeks gestation (the maximum age of our fetuses being only 36 weeks), although extrapolation of our curves suggests a close match, the mean value being 320cm^3.

Anatomical areas measured by previous studies report a growth rate of 15% per week (260, 276). Our work demonstrated that a quadratic model provided best fit to describe the changes of fetal brain growth relative to gestational age, with a mean growth rate of 12.8% (range 1.0 - 21.4%) per week.

6.6 Conclusions

This study evaluated a manual method to post-process 3D iuMR data to determine quantitative measurements of the fetal brain with a high degree of reproducibility. The resultant graph of normal brain volumes across a broad range of gestations, with associated prediction limits, could potentially be used as a reference tool in the clinical setting. The normative data generated will form the basis of continuing work allowing comparisons to be made with the brain volumes of fetuses in whom there is suspected abnormal development, for example in fetuses affected by microcephaly. This could potentially provide additional and confirmatory evidence beyond routine imaging and biometry, and improve the diagnostic capability of iuMR imaging. Part of the ongoing work will also be to increase the reference data by studying a larger number of normal fetuses, particularly at the extremes of the gestational age range

Chapter 7

Clinical Applications of 3D fetal brain MR imaging and post processing.

7.1 Chapter Summary

Part of the second aim of this thesis was to investigate the clinical application of the 3D volume acquisition. Chapter 5 demonstrated that the 3D volume acquisitions are a reliable addition or alternative to 2D sequences in our routine fetal imaging protocol and in Chapter 6 it was shown that the ability to determine brain volume measurements had additional potential for the diagnosis of brain abnormalities. This chapter revisits the key brain abnormalities that were first described in Chapter 1 and demonstrates how the additional information provided by the 3D acquisition and post-processing methods can be used in novel ways to potentially improve diagnosis. This is achieved using images and quantitative data to demonstrate how the abnormalities affects the external appearance of the brain and its growth relative to gestational age. Case studies of each abnormality are also included to show how the additional information could potentially be applied in clinical practice.

The images and cases presented with abnormalities are from the primary MERIDIAN study and normal fetal brains are from the MERIDIAN Add-on study. Approval was also obtained from the Institutional Clinical Effectiveness Unit and Research Department to review and include two clinical cases. This work resulted in three peer reviewed publications (253, 296, 297)

This work in this chapter was undertaken solely by DJ and includes;

- The manual segmentation of 150 fetal brains affected by abnormalities (700 hours work)
- The preparation of the data files for 3D printing
- Analysis of VM cases.
- Writing or contributing to the manuscripts that were published in peer reviewed journals as a result of this work. These include;

- Jarvis D, Armitage P, Dean A, Griffiths PD. Surface reconstructions of foetal brain abnormalities using ultrafast steady state 3D acquisitions. Clinical radiology. 2014;69(10):1084-91.

- Griffiths PD, Jarvis D. In Utero MR Imaging of Fetal Holoprosencephaly: A Structured Approach to Diagnosis and Classification. AJNR American journal of neuroradiology. 2016;37(3):536-43.

- Jarvis D, Griffiths P, Majewski C. Demonstration of Normal and Abnormal Fetal Brains Using 3D Printing from In Utero MR Imaging Data. American Journal of Neuroradiology. 2016;37(9):1757-61.

- Jarvis D, Griffiths PD. Clinical applications of 3D volume MR imaging of the fetal brain in utero. Prenatal Diagnosis. 2017, 37, 556–565

The 3D printed models shown in this chapter were produced by Dr C Majewski at the Centre for Advanced Additive Manufacturing (AdAM) at the University of Sheffield, using imaging data and segmentations created by DJ.

7.2 Introduction

Manual segmentation of the fetal brain from the surrounding anatomy using the 3D Slicer software creates label maps, which can be used for several different applications. This includes generation of the quantitative data previously described, as well as the creation of electronic 3D models of the fetal brain. The data obtained can also be saved in the stereolithography (.stl) format. As this is compatible with 3D printing technology, we were able to utilise this to have several fetal brain models manufactured. 3D printing is being used

increasingly in healthcare for anatomical parts either for bespoke implants or to increase patient understanding, but the manufacture of the fetal brain models shown in this chapter, is a novel application.

It is important to consider how the additional quantitative information and visualisation techniques can contribute to the diagnosis of fetal brain abnormalities. This chapter therefore, uses these unique ways of visualising the external surfaces to show both normal anatomy and the manifestation of developmental brain abnormalities that were described in chapter 1 to show the additional value of 3D imaging.

7.3 3D Printing

3D Printing (also known as Additive Manufacturing) creates parts in a layer-by-layer manner by digitally transforming the electronic 3D data into a series of 2D slices. Our fetal brain models were created using laser sintering, a powder bed fusion process, whereby polymer material (Nylon-12 powder) is melted by a CO_2 laser and deposited one layer at a time. Each new layer is sintered to the one below and the re-solidified layers of melted powder eventually make up the brain model. Once cooled, unmelted powder is removed using compressed air to reveal the finished model.

The main advantages of 3D Printing are the ability to produce one-off models efficiently and cost-effectively. The relatively high mechanical strength that results from the Laser Sintering process compared with other 3D Printing processes made this a suitable method for manufacturing the brain models that may have to be handled by a large number of people.

As described previously in Chapter 6, the fetal brains were segmented manually and assigned different colours to identify the different anatomical areas on each imaging slice within the acquired volume. Each of these anatomical areas is also assigned a numerical value in the label map. Each label within the map representing individual parts of the anatomy is stored in a separate data file, which was used to create the electronic 3D models and subsequently saved as .stl files for 3D printing. The .stl files cannot be edited and the resultant 3D printed model is an exact representation of the generated electronic 3D surface

model. The electronic model was therefore examined for any extraneous parts to ensure that the contours were in keeping with the relevant anatomical detail. Laplacian smoothing within 3D Slicer was applied at the model building stage in order to smooth contours when necessary. In order for the brain model to be 3D printed as a complete, single part, only a single label can be identified at the segmentation stage (Figure 7.1) as the .stl data files of separate colour label maps would ultimately result in a brain model being printed as separate parts. Thus tissues assigned distinct labels in the map may need to be merged before 3D printing.

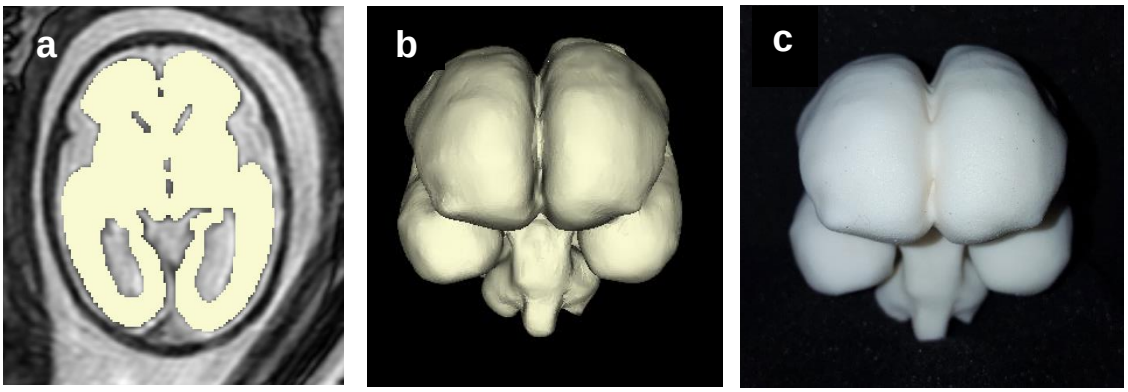


Figure 7.1 (a) Single colour label map, (b) resultant electronic 3D surface representation which is saved as an .stl file, (c) Resultant 3D printed model

However, there are scenarios where the ability to segment and print the brain models as multiple parts can be used to advantage. Firstly, by segmenting the brain into 3 separate cross sections, (Figure 7.2 a-c), the 2D images acquired using T2 FSE imaging were transposed onto cross sections of the 3D model. By acquiring the 2D data in the same orientation and slice positions as the 3D volume acquisition, the resultant 2D images were matched to the relevant cross sections of the 3D printed model as shown in Figure 7.2d and 7.2e. This could help improve the understanding of fetal brain anatomy and how it relates to imaging data. Secondly, the majority of 3D Printing processes produce parts using a single colour, but it is possible to use the separate data files to produce a single model of multiple

colours and/or materials. The use of two colours and materials within the same model were used to distinguish between the brain parenchyma and ventricular system within a brain model (Figure 7.3).

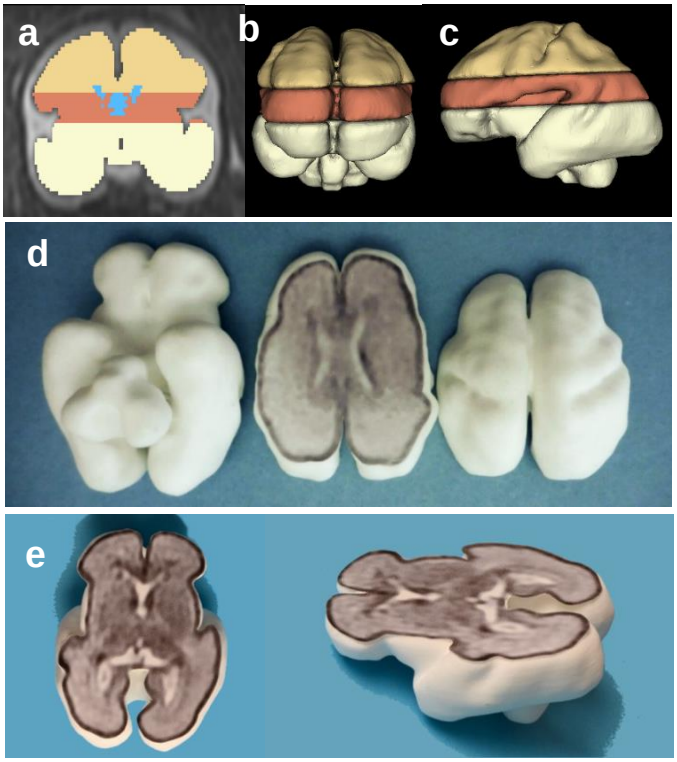


Figure 7.2 (a) Fetal brain segmented with 3 labels defined in the label map, (b) and (c) 3D surface representations which are saved as three separate .stl files, (d) resultant 3 part 3D printed brain model and (e) cross sections with the relevant 2D images transposed onto the printed model.

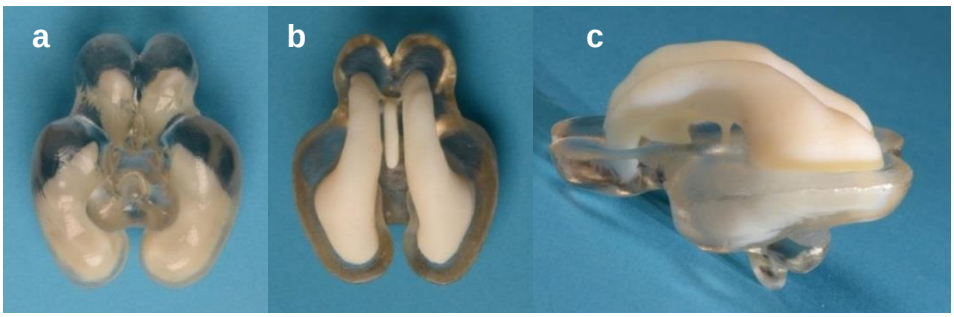


Figure 7.3 A two-colour part produced on a Connex multi-material system, produced by Loughborough University. The model is of a 21 weeks gestation fetus with ventriculomegaly. The use of two materials of different colours allows clear differentiation of the ventricles (white material) compared to the remainder of the brain (clear Perspex). (a) inferior view, (b) superior view and (c) lateral view.

A potential application for the fetal brain models is to improve anatomical understanding for radiologists who are keen to develop their skills in fetal neuroimaging. We have created a teaching file that contains several normal fetal brain models at different gestation and a number of abnormal cases with accompanying information to the condition demonstrated and selected images from both the 2D studies and 3D printed models. The 3D models could also be used as a novel visual aid for improving parental understanding regarding the impact of brain abnormalities on their fetus and assist in counselling, but further work is required to determine this.

7.4 Visual and Quantitative Applications of 3D post-processing

The remainder of this chapter revisits some of the brain abnormalities described in Chapter 1. The images of surface reconstructions and 3D printed brain models, as well as tables of quantitative analysis based on the methods described in Chapter 6 are shown to provide an insight into how those abnormalities affect brain development. Several case examples are also included, some of which are from the teaching file. Firstly, 3D surface reconstructions and printed brain models of normal brains are shown to allow comparisons to be made with the brains affected by developmental abnormalities.

7.4.1 Normal Brain Development

The fetal brain grows and develops following a predetermined trajectory that results in both consistent and predictable sulcation and gyration formation. There may be some discrepancy due to natural biological occurrences which may lead to a small delay or advancement of cortical folding. The ability to identify early folding in some parts of the brain can also be limited due to inherent image resolution restrictions of iuMR imaging (298, 299). An understanding and knowledge of the process of cortical development is required to

ensure that pathological processes which disrupt or alter the normal trajectories of growth can be identified. Included in this section are images of electronic 3D surface reconstructions and 3D printed models of fetal brains at 6 different gestational ages (Figures 7.4 – 7.9), and images of the ventricular system which are representative of the anatomy regardless of gestational age (Figure 7.10). It should be noted that the 3D surface and brain models may not be of the same fetal brain.

Figure 7.4 20 weeks gestation TBV 43.9cm^3

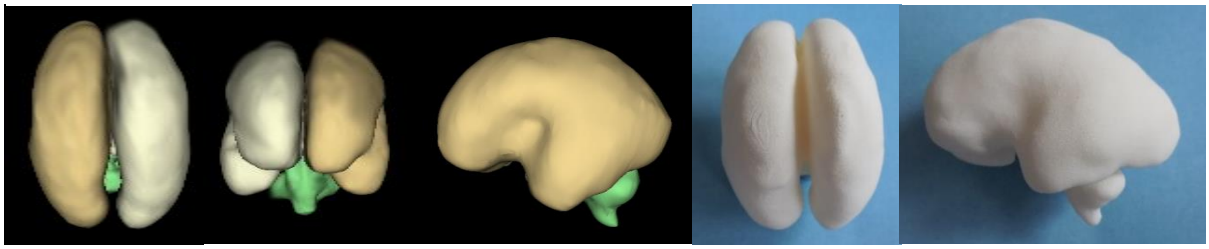


Figure 7.5 23 weeks gestation TBV 61.4cm^3

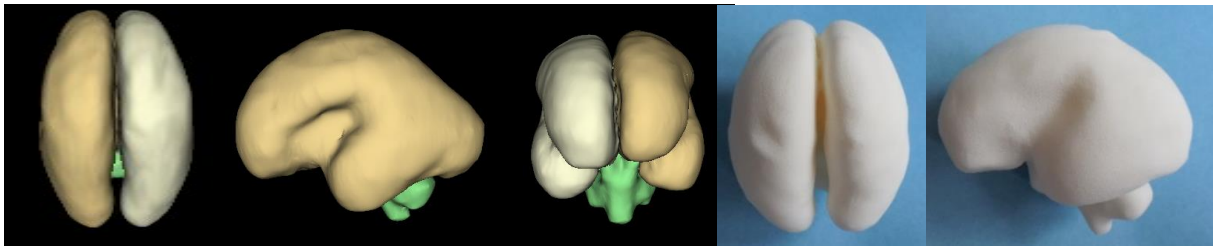


Figure 7.6 26 weeks gestation TBV 112.0 cm^3

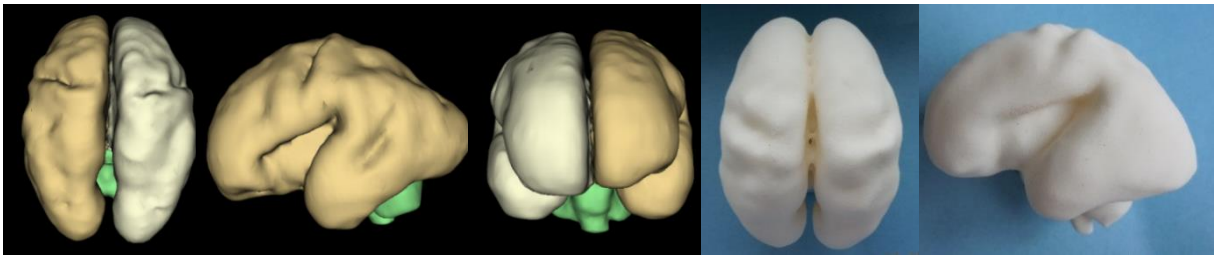


Figure 7.7 29 weeks gestation TBV 135.7cm^3

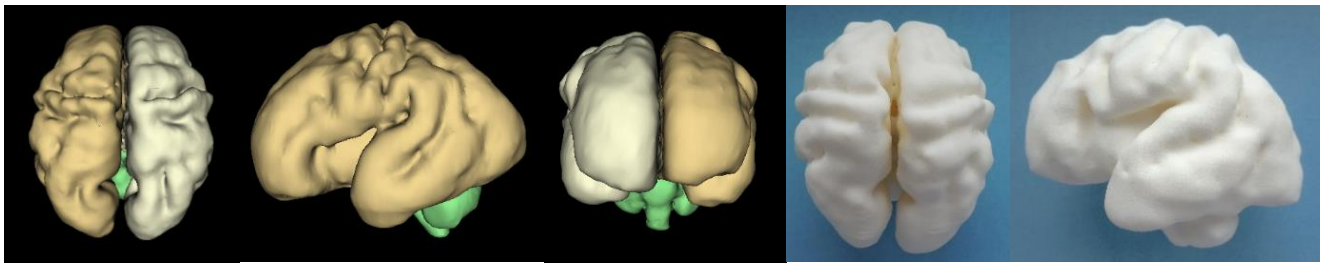


Figure 7.8 31 weeks gestation TBV 188.7cm^3

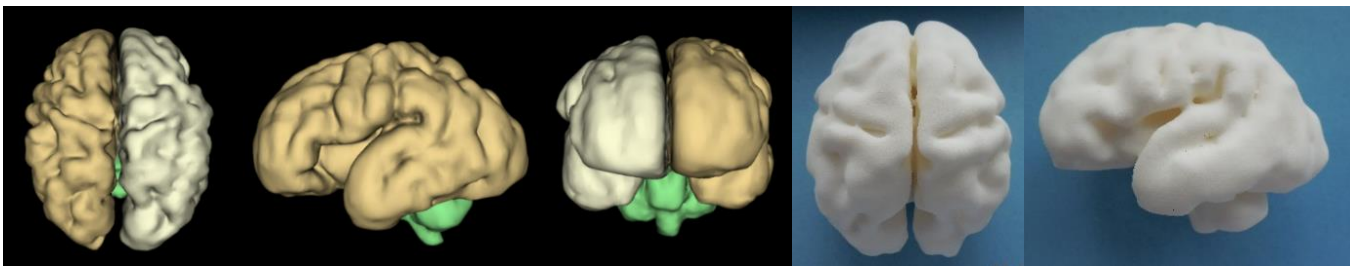
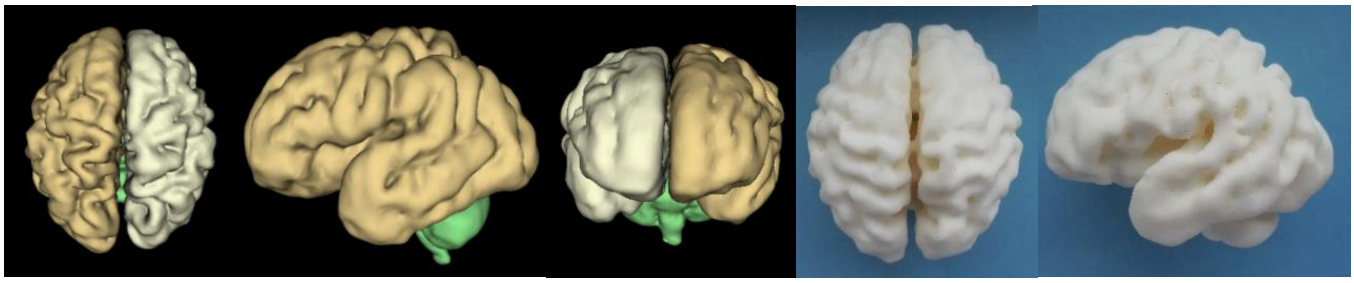


Figure 7.9 33 weeks gestation TBV 192.9cm^3



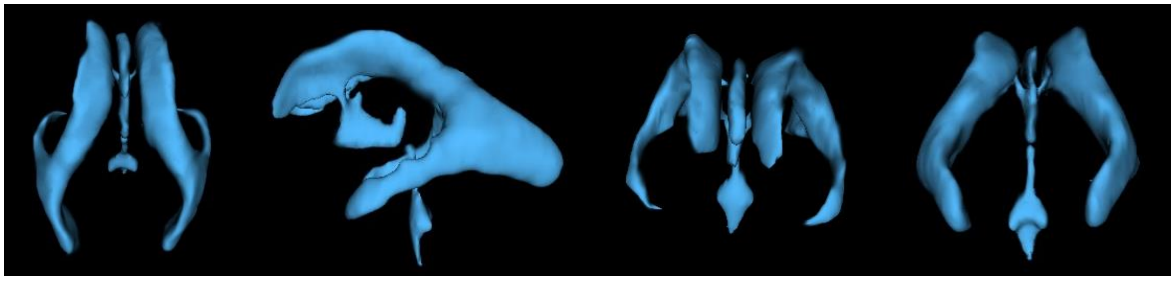


Figure 7.10 Images of the ventricular system of a 28 weeks gestation fetus. Left to right - superior, lateral, frontal and posterior views. Ventricular system volume 6.5cm^3

Figure 7.11a shows a photograph of a fetal brain of 28 weeks gestation taken at post mortem examination, contrasted with the equivalent 3D surface reconstruction (Figure 7.11b), from a different fetus, generated using the MR imaging data acquired at an equivalent gestational age. Figure 7.12 demonstrates in two orientations the electronic surface reconstructions, compared with the resultant 3D printed models and pathology slides from the same fetus with a cortical formation abnormality at 26 weeks gestation. The images from these two cases demonstrate that the electronic surfaces generated by our post-processing methods replicate with a high degree of precision the fetal brain from which the data was taken.

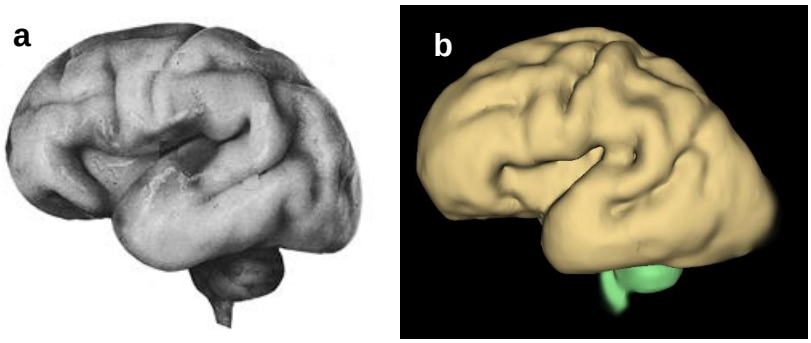


Figure 7.11 (a) image of a pathology slide of a fetal brain of 28 weeks gestation (b) an equivalent surface reconstruction from a different fetus at the same gestation

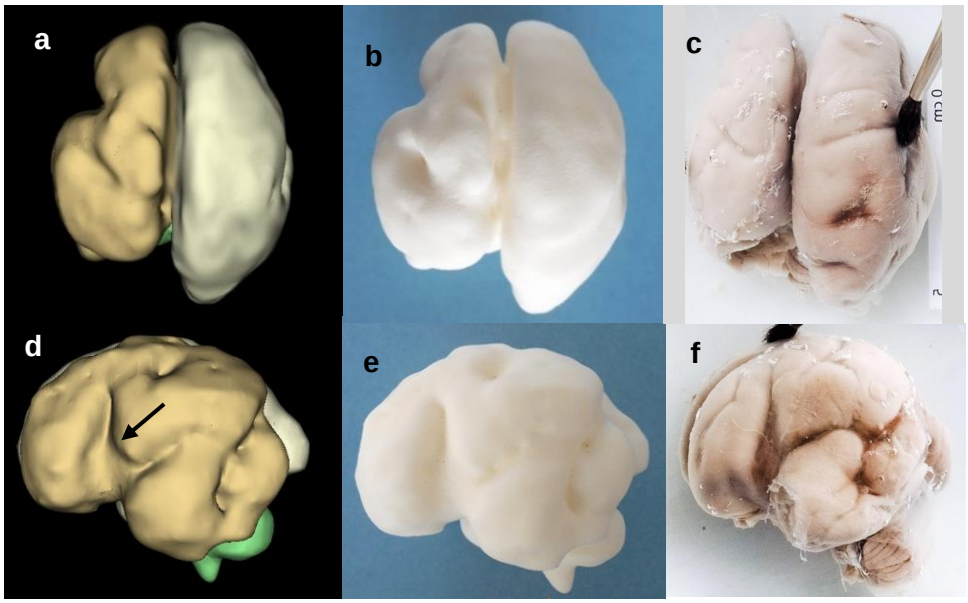


Figure 7.12 Images of a 26 week old fetus with focal megalencephaly. (a) 3D surface reconstructions superior view, (b) equivalent 3D printed model, (c) equivalent pathology slide. (d) 3D surface reconstruction lateral view, (e) equivalent printed model, (f) equivalent pathology slide.

7.5 A Review of Fetal Brain Abnormalities

7.5.1 Holoprosencephaly

Although there are no widely accepted classifications to distinguish between the two lesser forms of HPE (lobar and semilobar), when additional abnormalities or complex features manifest the latter classification is usually assigned. HPE is often missed altogether or misdiagnosed by USS. This is demonstrated in case H1, (the 3D printed model and surface reconstructions from which are shown in Figure 7.13) which was referred for iuMR at 21 weeks gestational age following USS. This showed VM and possible ACC. iuMR confirmed enlargement of the cerebral ventricles but also noted that they were contiguous over the mid line superiorly, and that the cavum septum pellucidum was absent. The diencephalon and the anterior portions of the cerebral hemispheres were incompletely separated and there was a deep abnormal sulcus extending superiorly from the expected position of the sylvian fissures towards the vertex. The frontal lobes anterior to those fissures were significantly hypoplastic as well as being incompletely separated. The cerebellum and brain stem were also smaller than expected for gestational age. These findings led to a diagnosis of lobar holoprosencephaly.

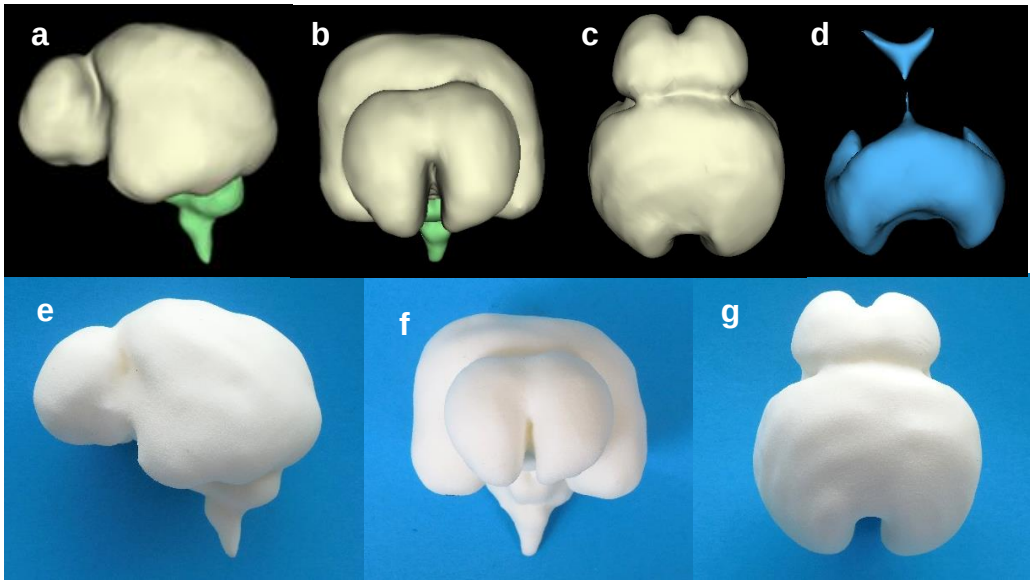
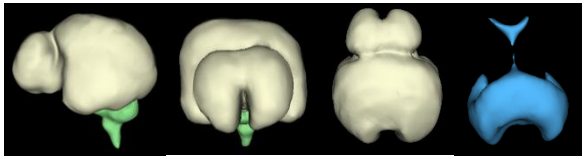
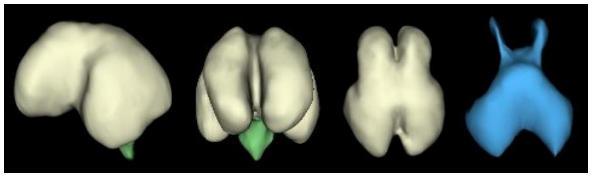
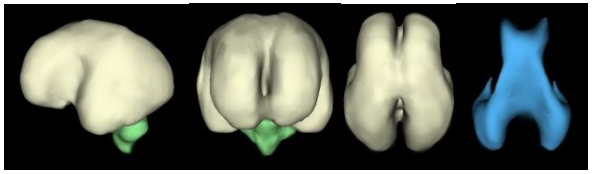
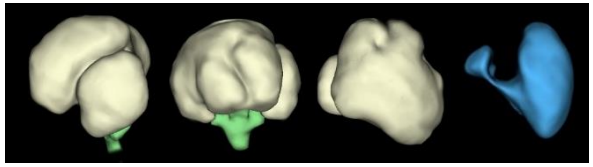
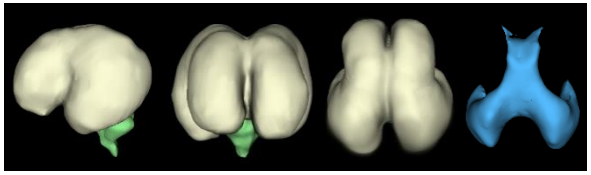
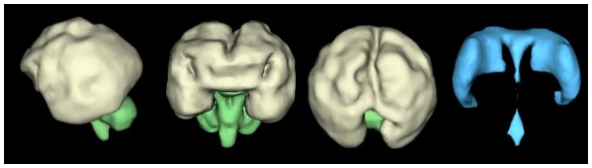


Figure 7.13 Case H1. Surface reconstructions and 3D Printed model of a 21 week old fetus with semi-lobar holoprosencephaly. Abnormal appearances are shown on lateral (a and e), anterior (b and f) and superior (c and g) views showing the abnormal appearances. The ventricles (d) are contiguous over the midline, both at the frontal horns and lateral ventricles.

Table 7.1 shows the surface reconstructions of six cases (H2-6) with differing severity of HPE from the MERIDIAN cohort, in whom post-mortem examination or postnatal imaging confirmed the diagnosis. The images demonstrate the differing extent of cortical and ventricular involvement in each case. A single label was used for the manual segmentation of both cerebral hemispheres as the manifestation of HPE prevented the distinction between right and left anatomical parts.

The results of the quantitative analysis of the brain volumes for each case are also shown in Table 7.1. The values for each case (identified by a different colour marker) are plotted against the graph of the mean and upper and lower prediction limits of the normative data reported in Chapter 6 (Figure 7.14).

Table 7.1 Details of six cases with confirmed HPE

Case	Gestation (weeks)	Additional abnormalities	TBV cm^3	Ventricular System cm^3	Head Size (BPD and Circumference)	Images of the surfaces of each case. Left to right: lateral, anterior, superior view of brain surface and superior view of ventricular system.
H1	21	Bilateral abnormal sulcation	33.6	6.1	Normal	
H2	19	No	26.8	5.5	Normal	
H3	20	No	29.5	4.4	Lower end of normal	
H4	20	Dandy Walker Malformation, abnormal sulcus left side	23.6	11.7	Normal	
H5	22	VM	30.0	3.8	Below 3rd Centile	
H6	26	Abnormal skull shape (trigonacephaly). Hypotelorism	57.5	3.3	Below 3rd Centile	

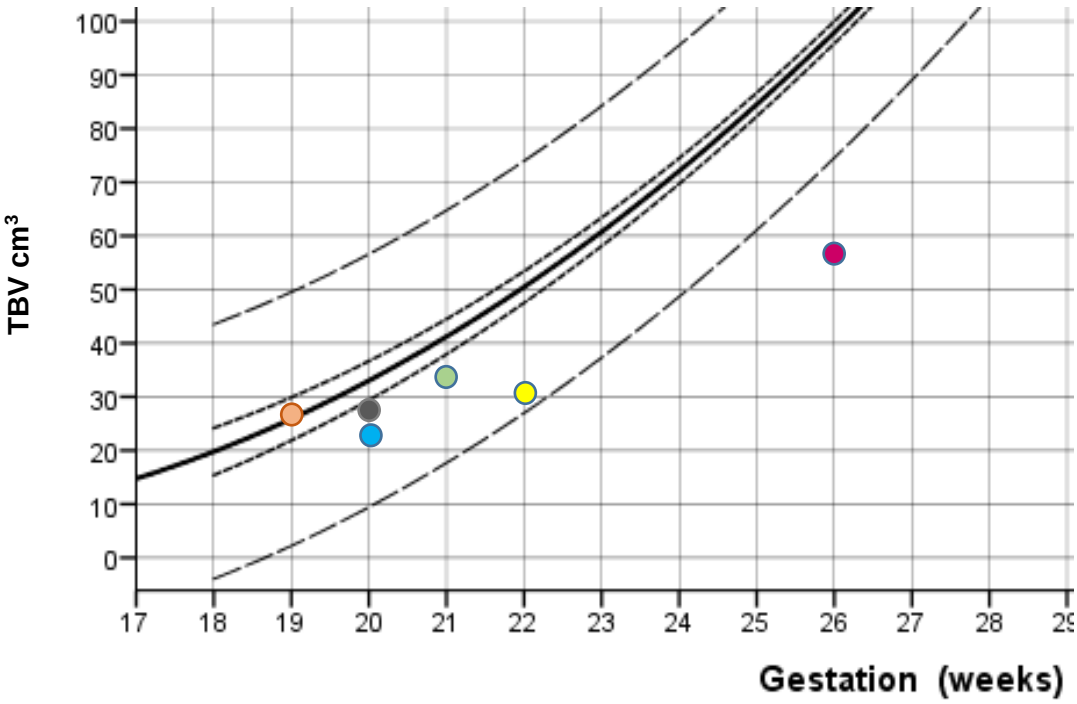


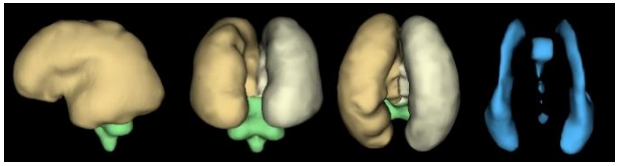
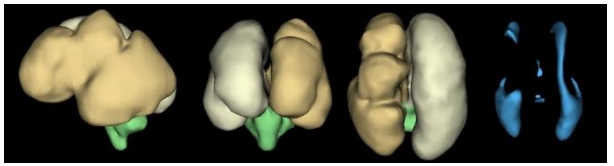
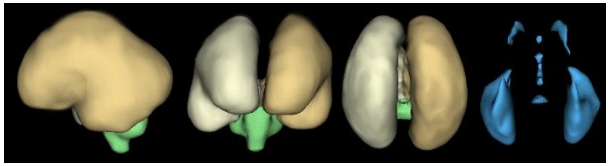
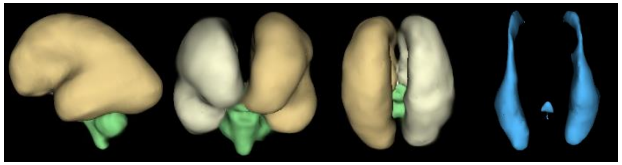
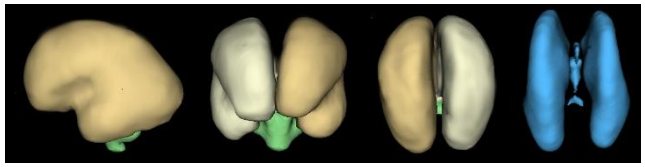
Figure 7.14 An abridged graph of HPE Cases plotted against the mean (solid line) and predictive values (outer dashed lines) derived from the cohort of normal fetal brain

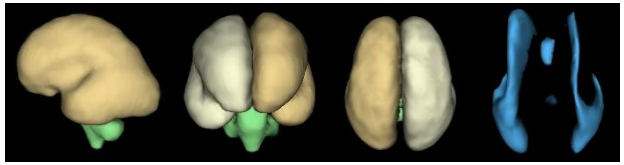
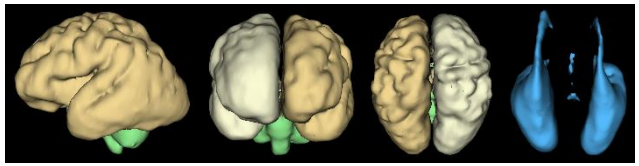
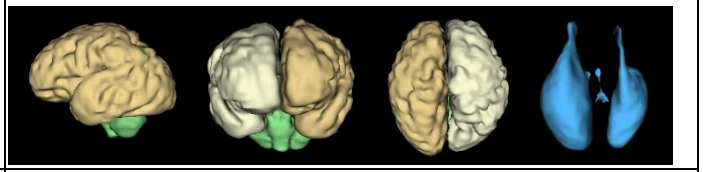
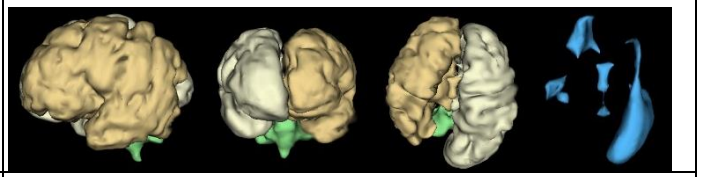
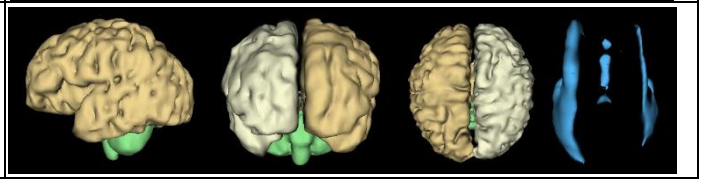
7.5.2 Agenesis of the Corpus Callosum (ACC)

Failed commissuration (either agenesis or hypogenesis of the corpus callosum) was a confirmed diagnosis in 79/570 (14%) of the fetuses within the MERIDIAN study, making it the third highest structural anomaly in the cohort. iuMR accurately diagnosed 94.9% of those cases, a significant improvement over USS which accurately diagnosed 34.2% of the cases (300). Table 7.2 shows the details and images of 9 cases of ACC from the MERIDIAN group. It includes the brain volumes of each fetus, which are also plotted against the mean and predictive values of brain volumes from the normal data (Figure 7.15).

The 2D images, 3D surface reconstructions and 3D printed model of Case A9 are also given along with descriptions of the USS and iuMR findings.

Table 7.2 Details of 10 cases, all with ACC scanned as part of the MERIDIAN study.

Case	Gestation (Completed Weeks)	Additional abnormalities	TBV Cm^3	Ventricular Volume Cm^3	Head Size	Images of the surfaces of each case. Left to right- lateral, anterior (case A1 posterior), superior view of brain surface and superior view of ventricular system.
A1 ●	20	Cortical Formation Abnormality (well visualised on the superior view of the surface image)	35.2	2.9	Normal	
A2 ●	20	Cortical Formation Abnormality (well visualised on the lateral and superior view of the surface images)	35.9	6.8	Normal	
A3 ●	21	No	34.6	2.8	Normal	
A4 ●	21	Interhemispheric cyst	45.4	4.1	Normal	
A5 ●	21	Dandy Walker Malformation	48.7	14.9	>95th centile	

A6 ○	21	Abnormal face	37.3	2.5	3rd centile	
A7 ○	29	No	150.7	22.9	90th-97th centile	
A8 ○	30	Interhemispheric cyst	148.2	9.7	Normal	
A9 ○	31	Interhemispheric cyst	224.0	6.3	90th centile	
A10 ○	32	Dilated cisterna magna	235.1	6.1	Normal	

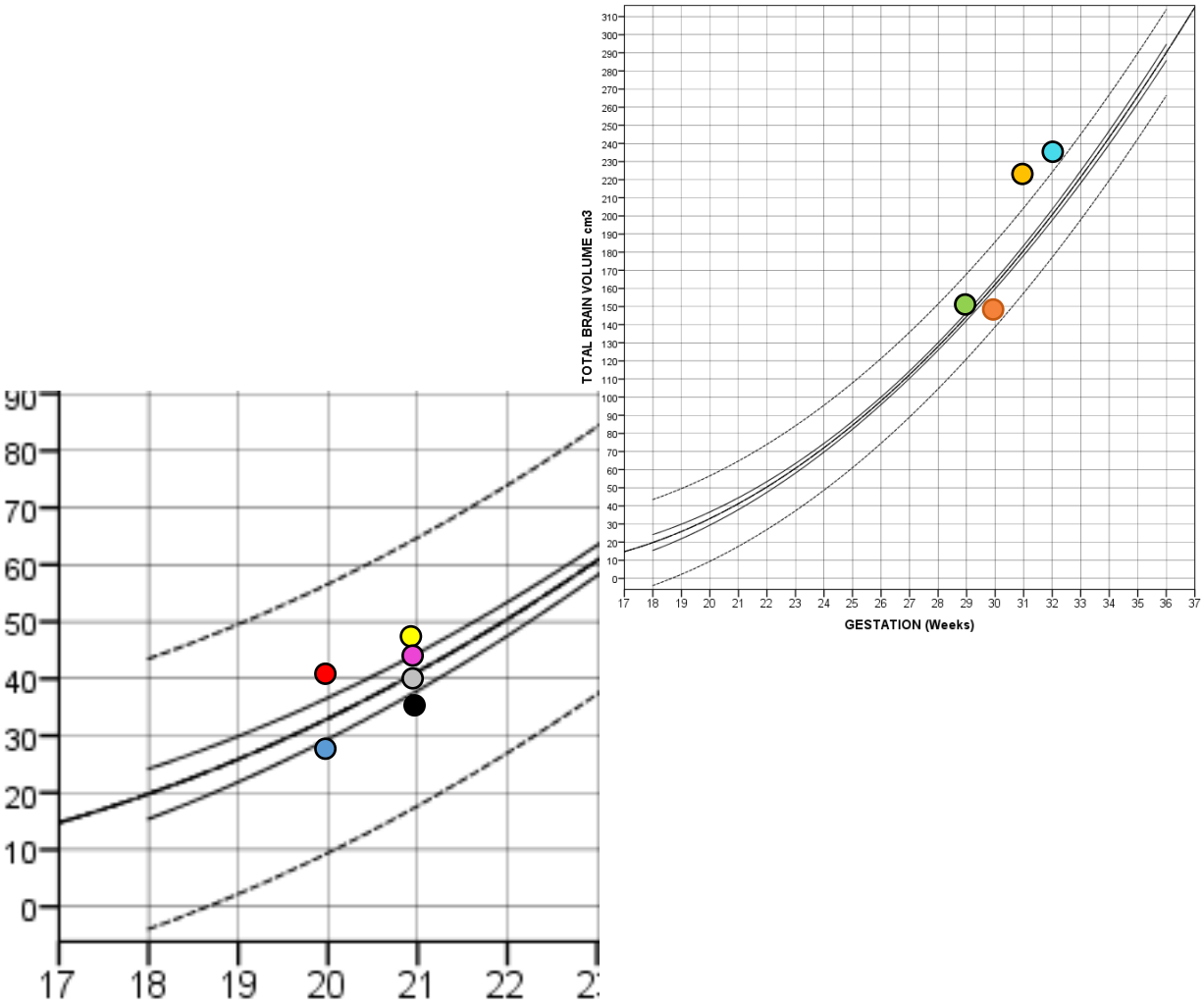


Figure 7.15 Graph showing TBV of fetuses with ACC listed in Table 7. 2, marked against the graph of normal fetal TBV data. (lower left section enlarged for clear visualisation of markers)

Case Study A9 (Figure 7.16)

A 32 year old with singleton pregnancy was referred for iuMR due to unilateral VM and arachnoid cyst in the fetus on USS. iuMR imaging was performed at 31 weeks gestation. This confirmed the unilateral VM but excluded the arachnoid cyst. An alternative diagnosis of multiple interhemispheric cysts to the right side of the falx associated with ACC was made. A hypoplastic cerebellar vermis was also noted on iuMR imaging as well as extensive cortical formation abnormality (heterotopia) of one hemisphere. Head size was measured at the 90th

centile on iuMR and further analysis revealed a TBV of 224cm^3, nearly 7SD above the mean. All iuMR findings were confirmed at post-mortem autopsy.

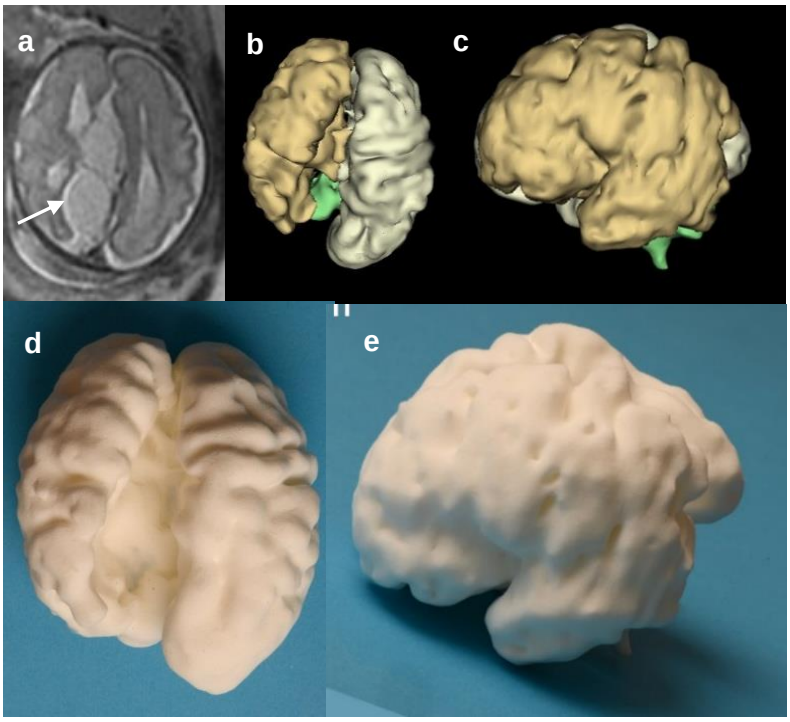
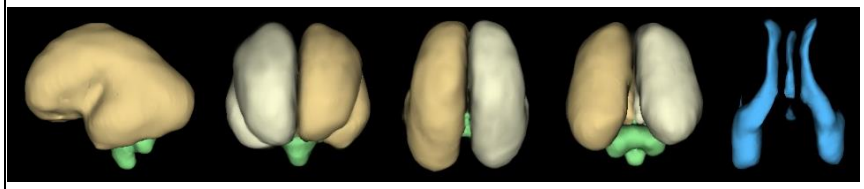
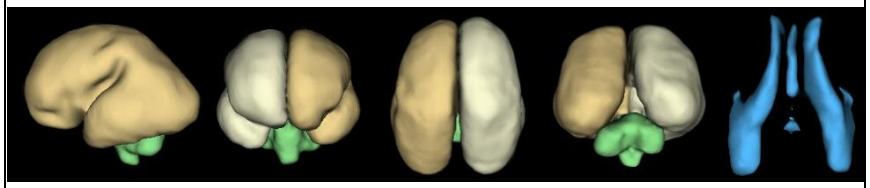
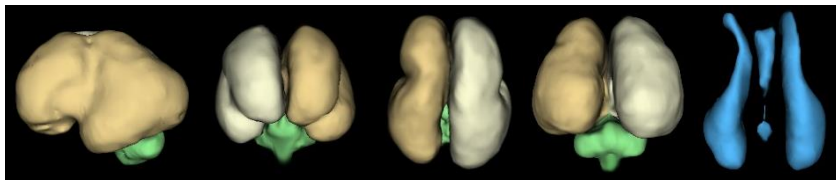
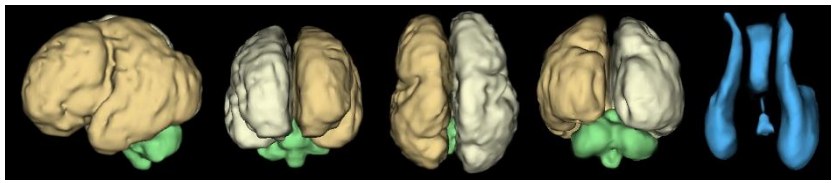
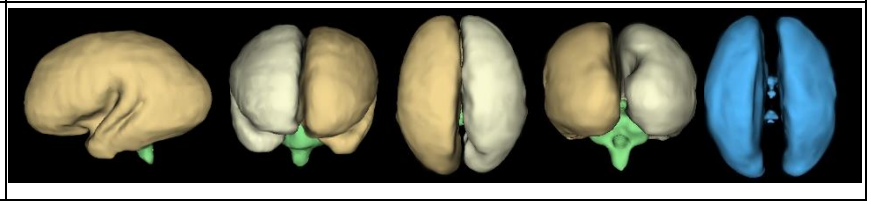


Figure 7.16 Images of a 30 weeks gestation fetus with ventriculomegaly, inter-hemispheric cyst (arrow) and ACC shown on the axial 2D ssFSE image (a) and on the superior view on the 3D surface (b) and 3D printed model (d). Left lateral views (c) and (e) show the widespread heterotopia, a feature that was confirmed at autopsy.

7.5.3 Lissencephaly

Lissencephaly is a rare disorder that is difficult to diagnose at early gestation as mild sulcation delay can cause false positives on iuMR. Diagnosis is therefore more reliable after 27 weeks gestation (301). Table 7.3 outlines the details of three cases diagnosed with lissencephaly and includes the surface reconstructions generated using the iuMR imaging data acquired at 2 gestational ages for cases L1 and L2 and for case L3 at a single gestation, with volumes plotted on the graph shown in Figure 7.17. Further details and images of cases L2 and L3 are given below.

Table 7.3 Details of three fetuses with lissencephaly. The first two cases have two MR studies and the third case a single MR study.

	Gestational Age (weeks)	Additional Abnormalities	TBV cm^3	Ventricular Volume cm^3	Head Size	Surfaces from each case, left to right, Lateral, Frontal, superior, posterior and superior ventricle views
L1. Visit1 	23	Germinal matrix cyst	48.8	2.7	Normal	
L1. Visit 2 	27	Germinal matrix cyst Small cerebellum	95.2	5.0	Normal	
L2. Visit 1 	22		50.1	6.4	Normal	
L2. Visit 2 	30		167.3	16.7	Normal	
L3 	29	Severe VM, Dandy Walker malformation	86.8	88.2	Normal	

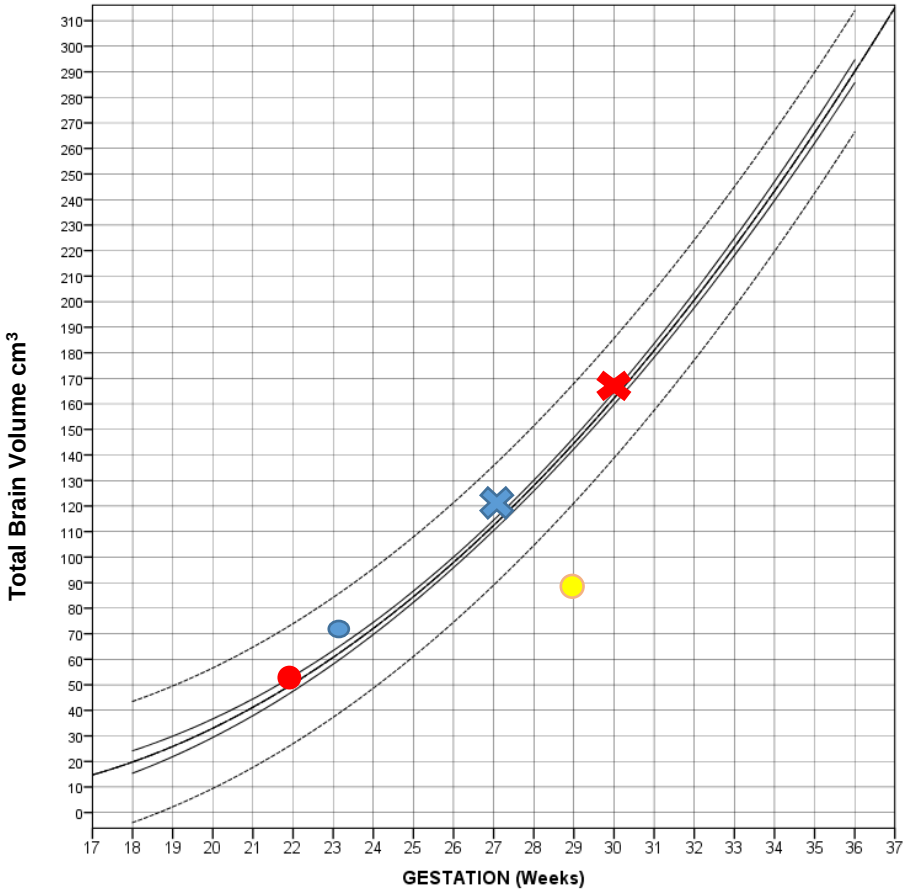


Figure 7.17 Graph of Lissencephaly cases plotted against chart of normal volumes:
Case L1- Blue dot visit 1 and blue cross visit 2
Case L2 Red dot visit 1 and red cross visit 2
Case L3 Yellow marker

Case Study L2 (Figure 7.18)

Figure 7.18 shows the images of case L2, a fetus of 22 weeks gestation referred for iuMR imaging due to VM and possible ACC on USS. iuMR excluded the possibility of ACC but confirmed VM and also demonstrated a possible bilateral cortical abnormality. A repeat MR was advised which was carried out when the fetus was 30 weeks gestation. This confirmed the VM, and the diagnosis of lissencephaly was made. Both head size and brain volume measurements were unaffected and within normal limits.

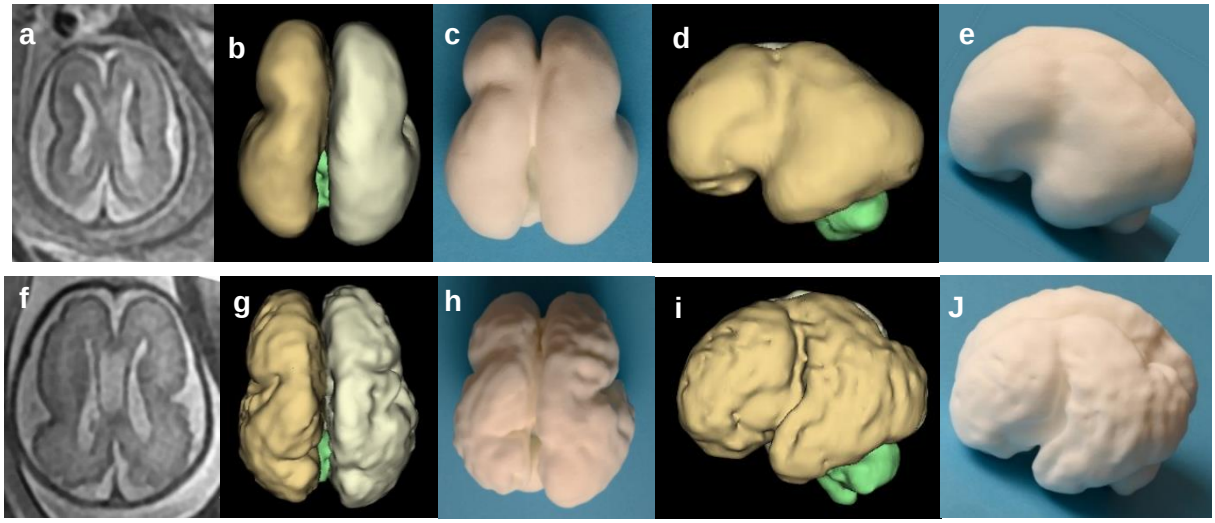


Figure 7.18 Images of case L2 from two MR studies. a-e: from the first visit at 22 weeks gestation and from left to right (a) axial 2D ssFSE, (b) axial surface reconstruction, (c) axial 3D printed model, (d) lateral 3D surface reconstruction and (e) lateral view of the 3D printed model. The same format is shown for the second MR study at 30 weeks gestation in the lower row (f - j)

Case Study L3 (figure 7.19)

A 24 year old with a singleton fetus at 29 weeks gestational age was found to have severe VM and a small cerebellum on USS. These were confirmed by iuMR imaging performed at 29 weeks, with the cerebellar abnormality classified as Dandy-Walker spectrum. A structural diagnosis of lissencephaly was easily made on routine 2D iuMR imaging although the surface reconstructions allowed the extent of the cortical abnormality to be understood more clearly (Figure 7.19). This case highlights the need to segment out the ventricular system as well as the external brain surface. The head size of this fetus (judged by bi-parietal diameter on iuMR) was on the 50th centile, but the brain volume, including the ventricles, was large. The mean value at this gestational age is approximately 150 cm^3, whereas in this case the brain volume was 175 cm^3. If, however, the ventricular volume and TBV are considered separately, the brain volume *per se* was exceptionally small at 86.8 cm^3 - 4 standard deviations below the mean, (Figure 7.17 Yellow dot). This discrepancy arose because of the severe ventriculomegaly (ventricular volume in this fetus - 88.2 cm^3 compared with the age-

matched mean in normal fetuses – 5.8 cm^3). All the primary structural abnormalities were confirmed on post-natal imaging, but there was an early neonatal death and autopsy was not performed.

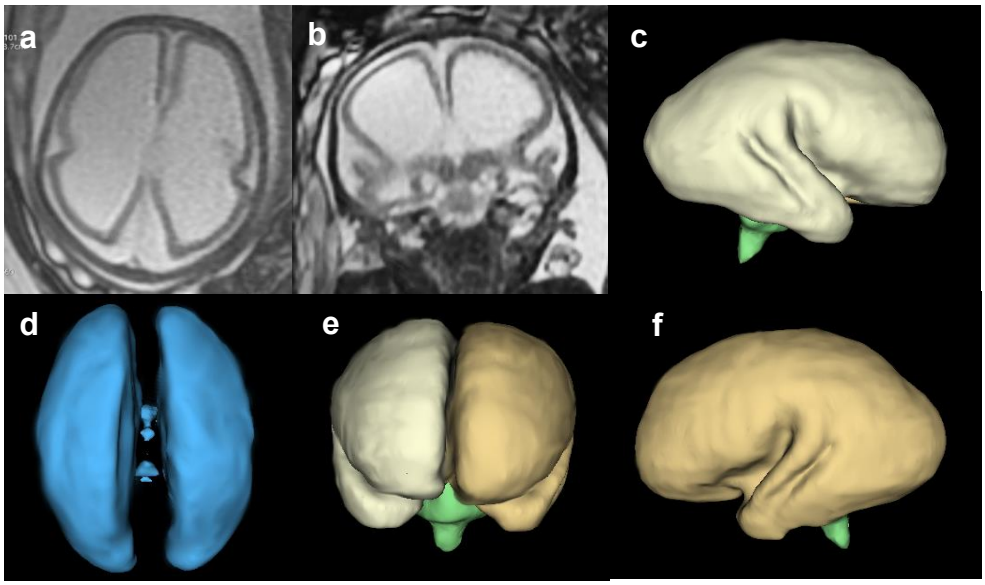
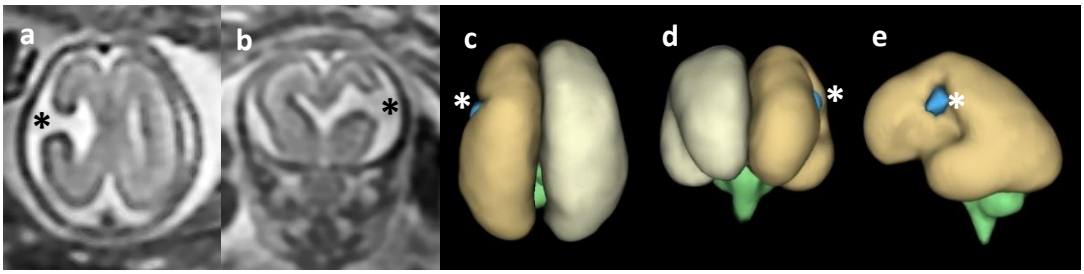


Figure 7.19 Case L3. Images of a fetus of 29 weeks gestation with severe VM and resultant lissencephaly: Axial and Coronal 2D ssFSE images (a and b), Lateral (c and f) and coronal (e) and (d) ventricle surfaces.

7.5.4 Schizencephaly

Schizencephaly is visualised on routine 2D imaging as a defect in the cerebral hemisphere with an abnormal connection between the CSF in the ventricular system and the external CSF. Abnormal grey matter lining the cleft distinguishes schizencephaly from destructive causes that can have similar appearances. It is often associated with other cerebral abnormalities. These include heterotopia, absent CSP with or without septo-optic dysplasia (as shown in case S1). Table 7.4 gives the details of two fetuses with schizencephaly and Figure 7.20 plots the brain volumes from those cases against the normative data.

Table 7.4 Details of two fetuses with schizencephaly.					
Case	Gestational Age (weeks)	Additional Abnormalities	TBV cm3	Ventricular Volume cm3	Head Size
S1 ●	21	Absent CSP, septo-optic dysplasia	24.8	4.3	Normal
Axial (a) and coronal (b) 2D ssFSE MR images and superior, frontal and lateral views of 3D surfaces of case S1 (c-e). In all images the open cleft schizencephaly can be clearly seen (asterix). 					
S2 ●	33	VM, microcephaly	99.7	21.8	< 3rd Centile
Images of S2 shown in the case study.					

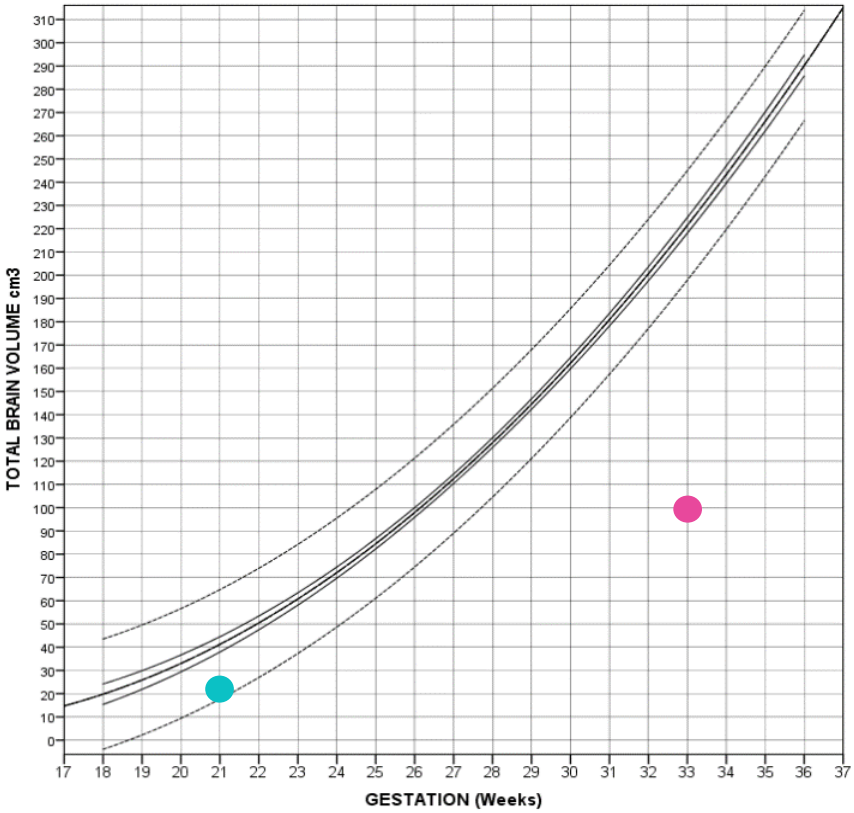


Figure 7.20 Brain volumes of schizencephaly cases S1 (blue marker) and S2 (pink marker) plotted against the graph of mean and prediction limits from the normative data

Case Study S2 (Figure 7.21)

A fetal MR was performed on a fetus at 33 weeks gestation following a diagnosis of VM and microcephaly on USS. VM was confirmed with trigone measurements of 16mm and 14mm. The other parts of the lateral ventricles were also enlarged and somewhat dysmorphic, but the third ventricle, aqueduct and fourth ventricle were within normal limits. The corpus callosum was present but only one thickened leaf of the septum pellucidum was identified. The optic nerves were seen but thought to be slightly small. The posterior fossa structure was within normal limits. On iuMR the head size, as assessed by bi-parietal diameter, measured below the third centile, confirming microcephaly. This was also matched by small brain size, 99.7cm^3 (>4 SD below the mean). Focal defects were seen within the cortical mantle at three sites: (1) left paracentral region (the site of the largest defect, with the lining portions of the hemisphere not in direct contact) (2) mid portion of the right frontal lobe on the convexity, (3) medial portion of the right frontal lobe (Figure 21). There were also abnormal neural elements lining the clefts at each site, suggestive of open lipped schizencephaly, and polymicrogyria.

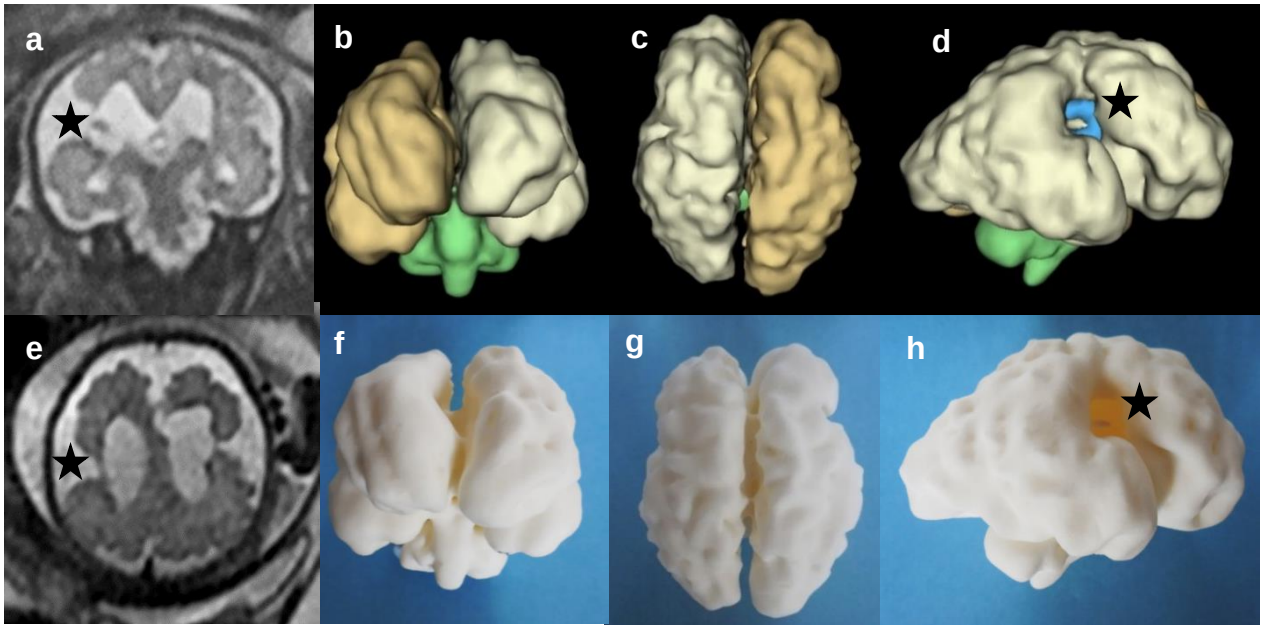


Figure 7.21 Images from Case S2 a 33 weeks gestation fetus with schizencephaly defects (stars). Images (a) coronal and (e) axial are 2D ssFSE images from the MR study. The other images show the 3D surfaces (b, c and d) created from manual segmentation and processing along with the equivalent orientations of the 3D printed brain model (f, g and h)

7.5.5 Polymicrogyria.

Polymicrogyria manifests as multiple small abnormal folds of the cortex and is difficult to depict by surface reconstructions due to the nature of the segmentation process and electronic model building. Despite the 3D volume acquisition being of higher resolution than our 2D imaging sequences, it is still limited and partial voluming can cause problems. In addition, the 3D Slicer software is bound by the voxel size and shape. As this is cuboid it cannot always represent the edges of the anatomy, which are often curved. Although smoothing is applied at the model building stage to counteract this, it can ultimately add to the problem as it may result in the small folds being 'smoothed' out and therefore less apparent. The following case (PLM 1), however, does allow visualisation of the abnormal surfaces of the brain due to polymicrogyria.

Case Study PLM 1 (Figure 7.22)

A 28 year old with a singleton fetus was referred for iuMR imaging due to appearances of extra axial CSF overlying the brain on USS at 23 weeks gestation. iuMR imaging at 25 weeks gestation confirmed the extra-axial CSF but also showed VM and a bilateral cortical formation abnormality. This manifested as shallow lateral fissures, generalised reduction in sulcation, and reduced volume of the superior portions of the frontal lobes (Figure 7.22 a-f). Head size as judged by bi-parietal diameter was normal, measuring between the 3rd and 10th centile on the MR study but the TBV was 55.2 cm^3 i.e. > 2 standard deviations below the mean (Figure 7.23). A cortical formation abnormality, probably bilateral polymicrogyria, was suggested. At repeat iuMR at 28 weeks gestation all the abnormalities seen at 25 weeks gestation were more pronounced (Figure 7.22 g-l) and with very little progression of sulcation since the first iuMR. The bi-parietal diameter on iuMR was just under the third centile but brain growth had slowed considerably. TBV was 4 standard deviations below the mean at 85.1 cm^3 (Figure 7.23). Post-mortem studies confirmed extensive polymicrogyria and a diagnosis of congenital infection (reactivation of CMV) was made on the basis of virology and the demonstration of CMV inclusion bodies in the placenta.

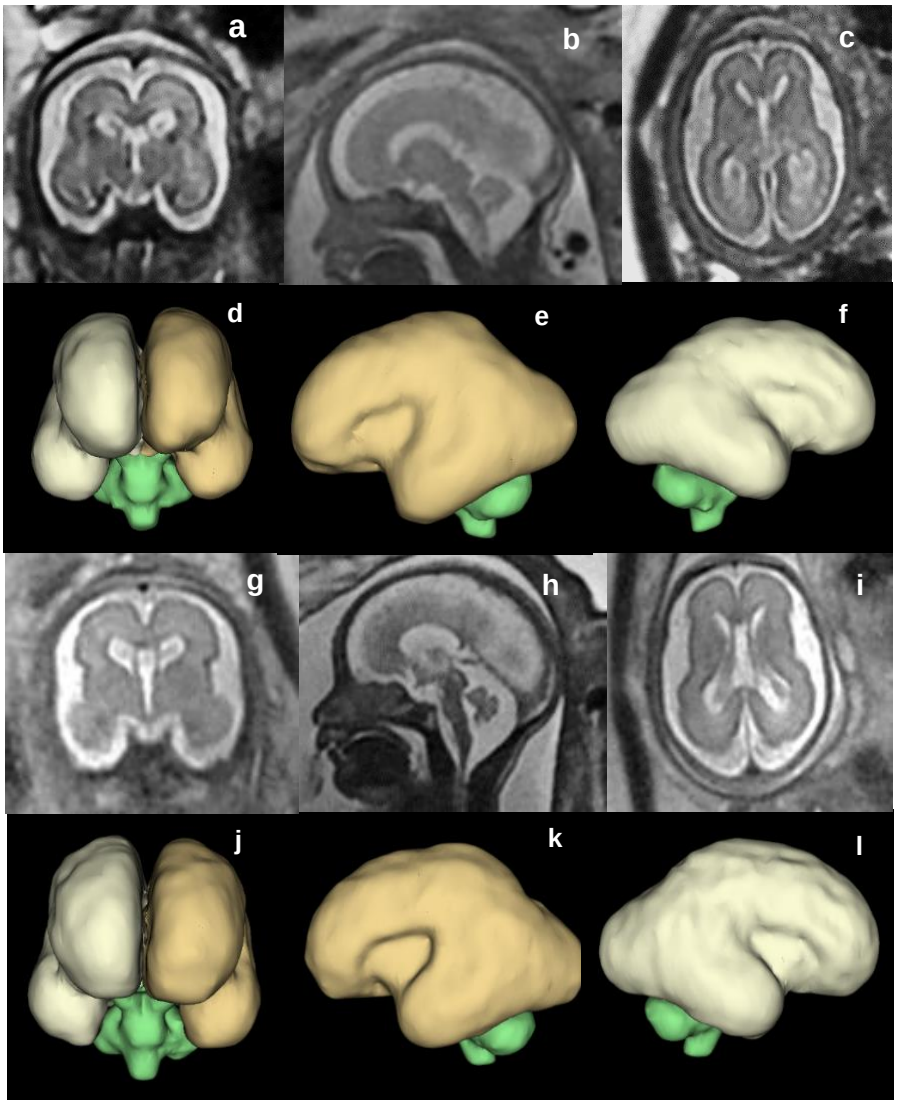


Figure 7.22 Images associated with case PLM1, a fetus with bilateral polymicrogyria. (a) Coronal, (b) sagittal, (c) axial 2D ssFSE images. (d) frontal, (e and f) both lateral projections of the cortical surfaces 25 weeks gestation. Images g to l are the equivalent images at follow-up iuMR imaging at 28 weeks.

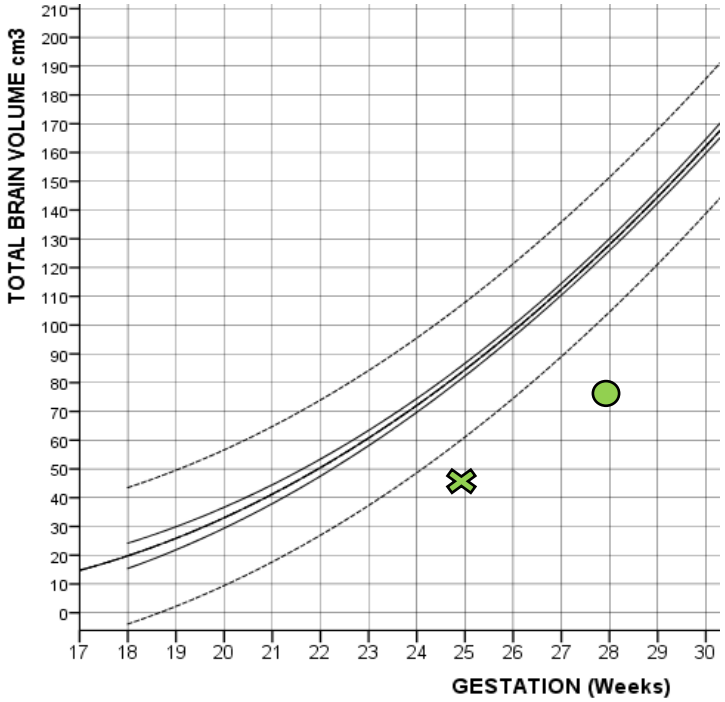
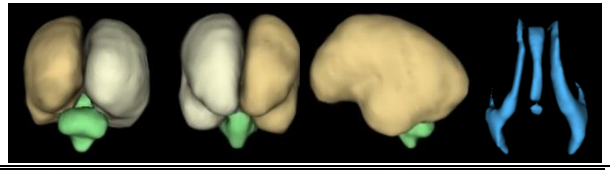
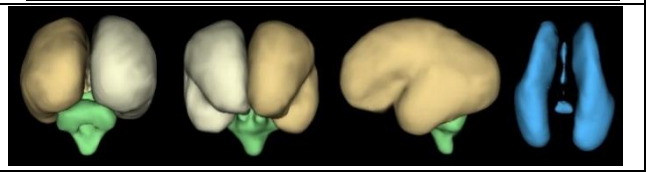
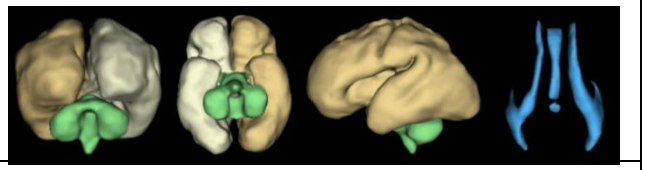
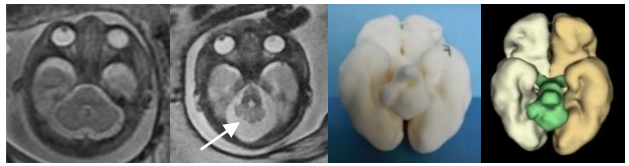
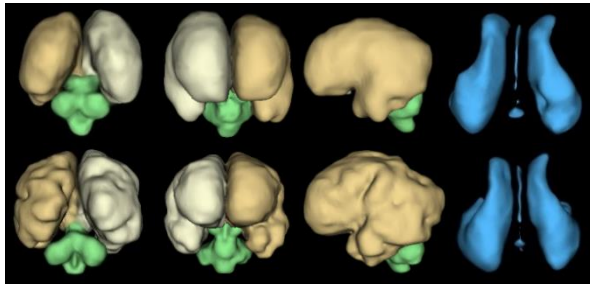


Figure 7.23 Chart of brain volumes associated with a fetus diagnosed with polymicrogyria on iuMR (case PLM1) plotted against an abridged chart from the normal data. Green cross marks visit 1 at 25 weeks gestation and green dot marks visit 2 at 28 weeks gestation.

7.5.6 Posterior Fossa Abnormalities

There are many developmental abnormalities that affect the formation and structure of the anatomy within the posterior fossa (cerebellum, vermis and brain stem), and the size of the posterior fossa or the cisterna magna. Subgroup analysis of the MERIDIAN study data revealed that anomalies of the posterior fossa were the second most frequently occurring abnormalities (302). iuMR imaging gave an accurate diagnosis of 87.7%, providing an improvement in diagnostic accuracy of 22.3% over USS. The errors made on iuMR in relation to the posterior fossa consisted of eight cases. This included cases in which iuMR reported abnormalities that were not to be present on ORD and two cases in which iuMR imaging failed to detect an abnormality subsequently shown on ORD. Table 7.5 gives the details of and images from five cases in which the fetus had a posterior fossa abnormality. The brain volumes of those cases are also plotted against the graph of normal volumes in Figure 7.24

Table 7.5 Details and images of six fetuses with different posterior fossa abnormalities

Case	Gestational Age (weeks)	Posterior Fossa Abnormality	Additional Abnormalities	TBV cm^3	Head size	Images left to right- Cases PF1, 2 and 5- views left to right: posterior, anterior, lateral and ventricle surfaces. Case 3- posterior, inferior, lateral and ventricles..Case PF4- age matched normal axial ssFSE, ssFSE axial from the case, inferior view of the 3D printed model and the inferior view of the electronic surfaces.
PF1 ●	21	Rhombencephalosynapsis	Hydrocephalus	70.9	Normal	
PF2 ●	21	Dandy Walker variant	Hypogenesis of the corpus callosum, VM	41.4	Normal	
PF3 ●	28	Dandy Walker Malformation	-	122.0	Normal	
PF4 ●	30	Rhombencephalosynapsis Pontocerebellar hypoplasia (arrow)	Unliateral VM	150.9	Normal	
PF5 ✖	23	Brain stem malformation	Walker-Warburg syndrome	28.0	Normal	
PF5 ●	27			77.3	Normal	

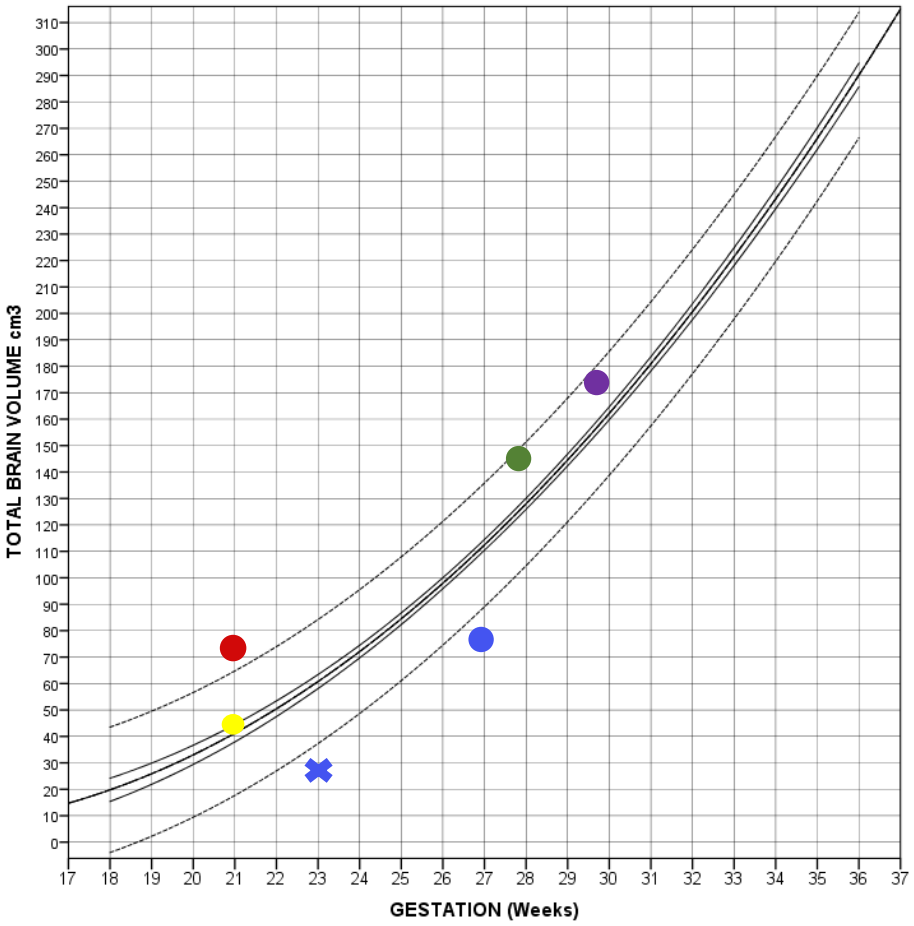


Figure 7.24 Graph of the brain volumes from the cases with posterior fossa abnormalities (Table 7.7) plotted against the mean and prediction limits of normal brain volumes.

Case PF1 (Figure 7.25)

A 25 year old with a singleton fetus at 22 weeks gestational age was referred for iuMR imaging because of mild ventriculomegaly and an enlarged cisterna magna identified on USS. These appearances were confirmed at iuMR imaging performed at 23 weeks gestation, but vermian hypoplasia and an abnormal brainstem (Figure 7.25a-d) were also demonstrated. The head size was normal on iuMR (biparietal diameter on the 10th centile). Sulcation/gyration around the lateral fissures was less than expected for a normal 23 week fetus, a feature shown clearly on the surface reconstructions, as was focal reduction of volume in the temporal lobes and posterior parts of the cerebral hemispheres. The TBV was

28.0 cm^3 (>3 standard deviations below the mean). The combination of a supratentorial sulcation abnormality and a brain stem malformation led to Walker-Warburg syndrome being considered. A follow-up iuMR study was recommended for clarification and repeated at 27 weeks gestation.The head size remained within normal limits with a bi-parietal diameter close to the 10^{th} centile, but the TBV was 77.3cm^3 (2.5 standard deviations below the mean). The diameter of the trigones of the lateral ventricles had increased to 15mm bilaterally and the abnormalities in the posterior fossa were again demonstrated, and were more pronounced. The cortical gyration/sulcation abnormalities on the surface reconstructions were more obvious, allowing a more confident diagnosis of lissencephaly to be made (Figure 7.25 e-h). The findings were consistent with Walker-Warburg syndrome but the fetus was stillborn at 29 weeks gestational age and no post-mortem investigations were performed. Figure 7.24 shows the TBV of the index fetus at 23 and 27 weeks plotted on the graph of normative values (blue dot and cross).

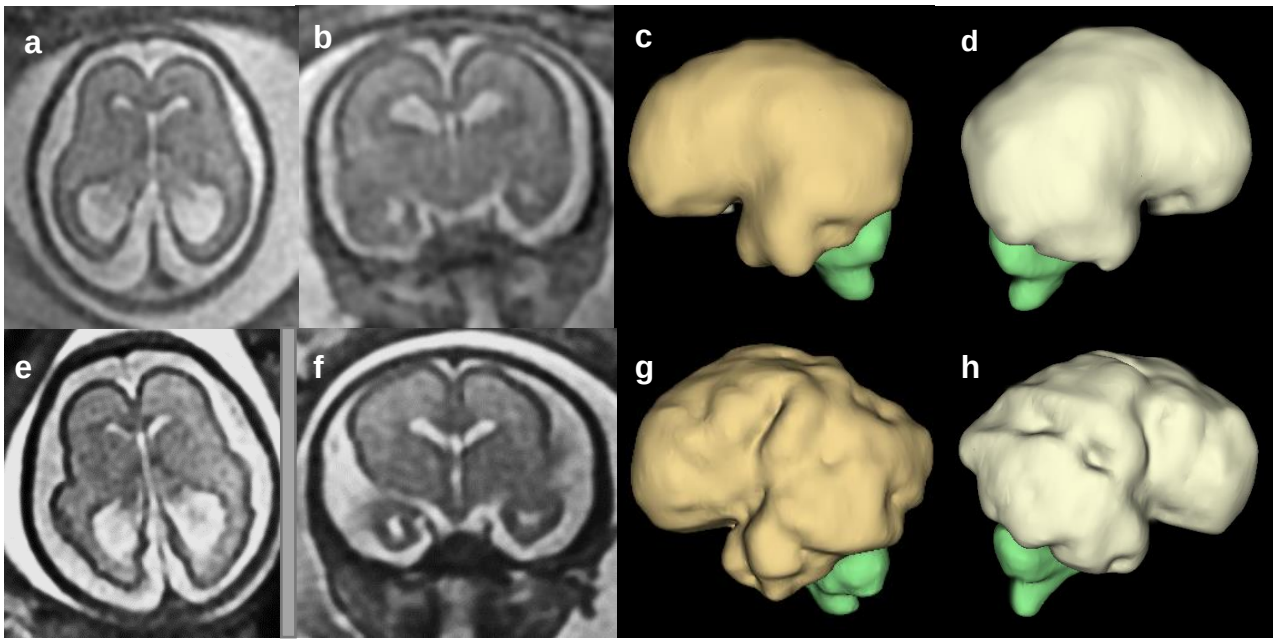


Figure 7.25 Images associated with case PF1, a fetus with presumed Walker-Warburg syndrome. (a) axial, (b) Coronal 2D ssFSE images and (c) left, (d) right lateral projections of the cortical surface at 23weeks gestation. Equivalent images at 27 weeks (e-h).

7.5.7 Abnormalities of the Ventricular System

Ventriculomegaly was the commonest abnormality within the MERIDIAN cohort at 73.9% (421) of the 570 fetuses with an ORD. This was an isolated finding in 306/421 (53.7%) fetuses, either as mild VM (10-12mm, 80%), moderate VM (13-15mm, 12%) or severe VM (>15mm, 8%). These categories were based on the USS measurements of the largest trigone. Image postprocessing and segmentation was completed for 50 mild VM cases. The comparison between these and normal and ventricular volumes are summarised in Table 7.6 and plotted on a graph for comparison (Figure 7.26). An independent samples Mann-Whitney U test found there was a statistically significant difference between the ventricular volumes of fetuses with and without VM ($p = <0.001$), and between the ratio of TBV to ventricular volume of the two groups ($p = <0.001$).

A case example, V1, is also reported which demonstrates how enlargement of the ventricular system has impact on brain growth and development.

Table 7.6 Comparison of ventricular volume between normal fetuses and fetuses with mild VM

Category	Number of Cases	Gestational Age Range (weeks)	Ratio of ventricular volume to TBV cm^3 Range Mean (standard deviation)	Ventricular system Volume Range cm^3 Mean (Standard deviation)
Normal (Add on Study)	132	18-36	2.0-18.9 5.2(2.9)	1.3 to 11.6 5.0 (2.3)
Mild VM	50	20-34	4.6-22.6 13.0 (4.5)	3.7- 40.8 8.2 (5.5)

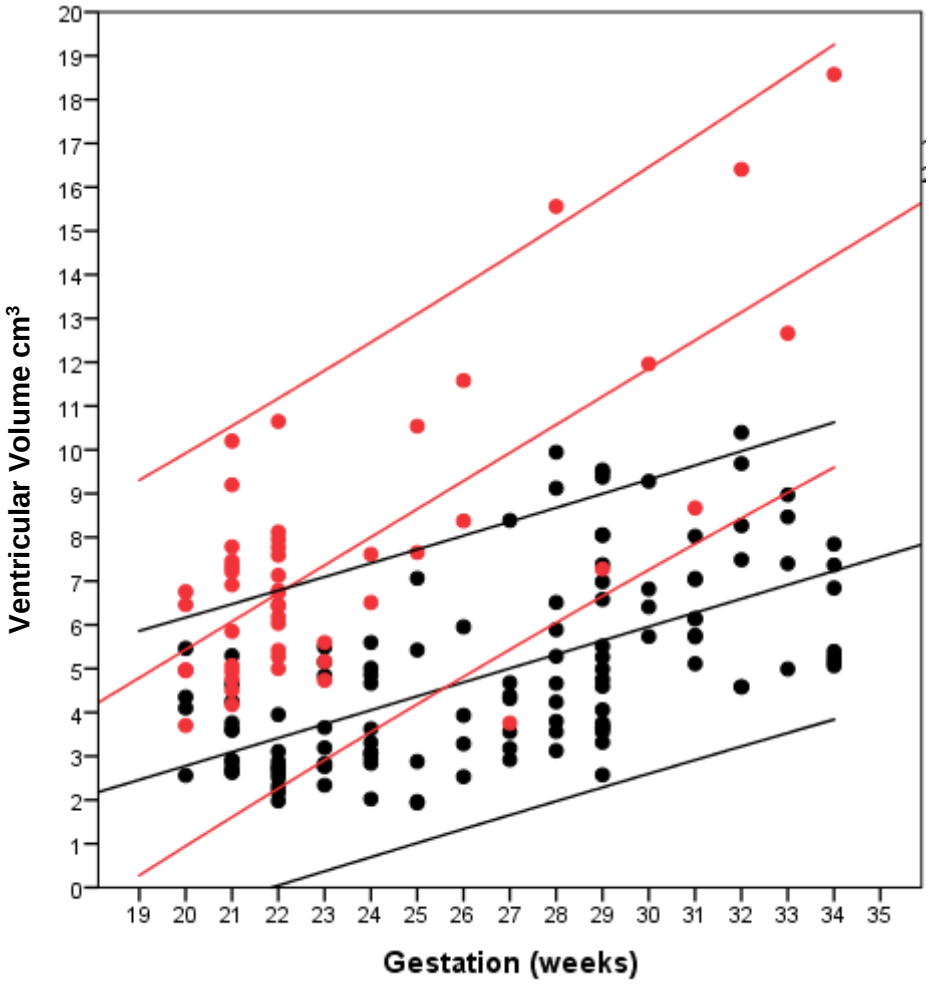


Figure 7.26 Graph comparing ventricle volumes, with lines for mean and 95% confidence limits, from normal fetuses (black) and fetuses with ventriculomegaly (red)

Case Study V1 (Figure 7.27)

Severe VM was detected at USS on a singleton fetus of 20 weeks gestational age which was subsequently referred for iuMR imaging. Severe VM (largest trigone 23mm) was confirmed on iuMR at 21 weeks gestational age. The pattern of ventriculomegaly was suggestive of hydrocephalus secondary to aqueduct stenosis (lateral, third ventricles and proximal aqueduct involved, fourth ventricle spared and effaced CSF spaces on the surface of the brain). The head size was massively enlarged, with a linear measurement much larger

than the 97th centile on the iuMR study. The brain volume including the cerebral ventricles was 104.7 cm^3, over twice the age-matched mean volume (45.0 cm^3). When measured separately, the ventricular volume was massively increased (54.2 cm^3 compared with age-matched mean 3.5 cm^3), but the TBV was relatively normal at 50.5 cm^3, only 2 standard deviations above the mean (Figure 7.28). Congenital hydrocephalus secondary to aqueduct stenosis was confirmed on post-natal imaging.

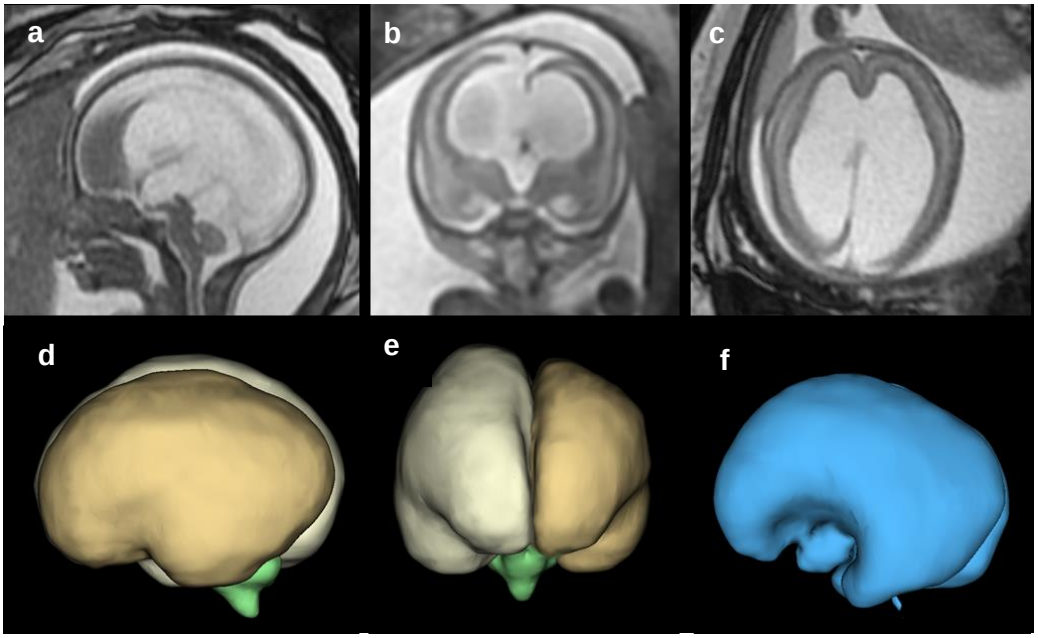


Figure 7.27 Case V1. Sagittal (a), coronal (b) and axial (c) views of the 2D ssFSE images of a 21 weeks gestation old fetus with hydrocephalus. Figures d- f show the matched surface reconstructions of the brain and the lateral view of the ventricles.

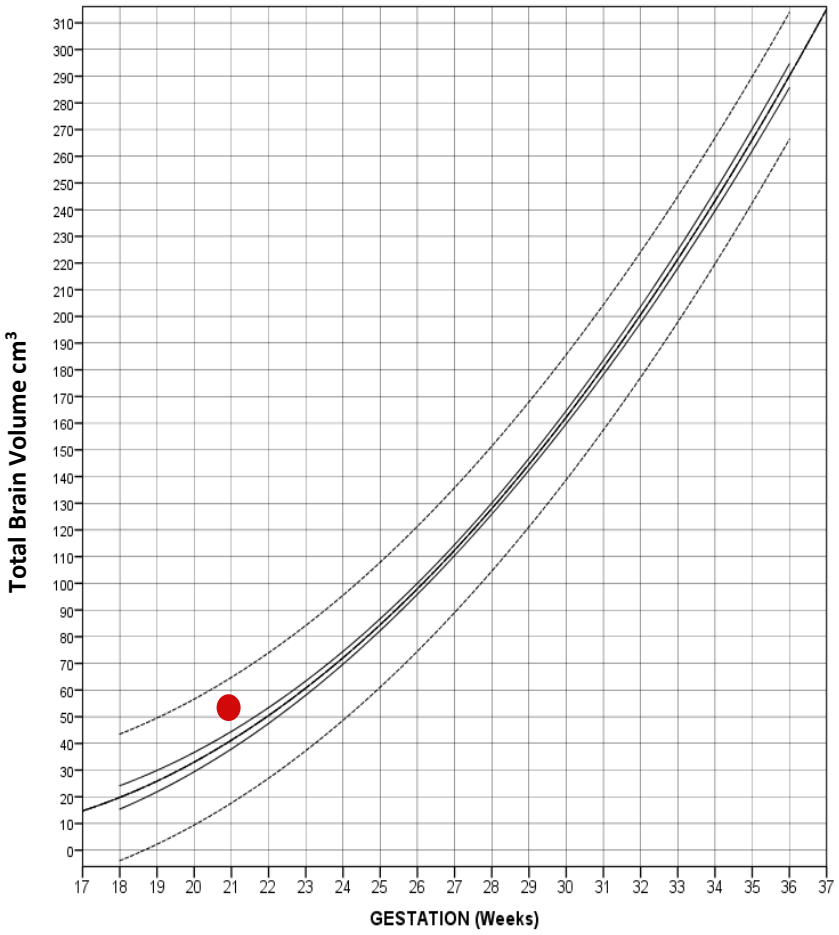


Figure 7.28 Graph of case V1 (red marker) plotted against the mean and prediction limits of normal brain volumes.

7.5.8 Megalencephaly/ Hemimegalencphaly

Abnormal neuro-glial proliferation can affect the whole brain (megalencephaly), one hemisphere only (hemimegalencephaly) or part of a hemisphere (focal megalencephaly). This condition results in abnormal disordered neocortical architecture and often occurs with other cortical abnormalities due to secondary disruption of neuronal/glial migration and organization, such as heterotopia and polymicrogyria. Although a relatively rare disorder, two cases are included showing examples of fetuses scanned as part of MERIDIAN that demonstrate how the 3D surface reconstructions and quantitative analysis (Table 7.7)

provide confirmatory evidence of the abnormality. Analysis of each cerebral hemisphere is reported and plotted on the graph against normal TBV (Figure 7.29).

Table 7.7 Details of two fetus' with megalencephaly (Case M1) and hemimegalencephaly (Case M2).

TBV and the volume of both cerebral hemispheres represented by a dot and star on the graph (Figure 7.29) for each fetus is shown

Case	Gestation	Additional Abnormalities	Hemisphere Volumes cm^3		TBV cm^3	Ventricle volume	Head size
M1	23	VM	☆ 44.2	○ 43.3	91.6	12.1	>90th Centile
M2	22	Uni lateral VM	★ 71.6	● 22.1	97.4	8.9	Normal

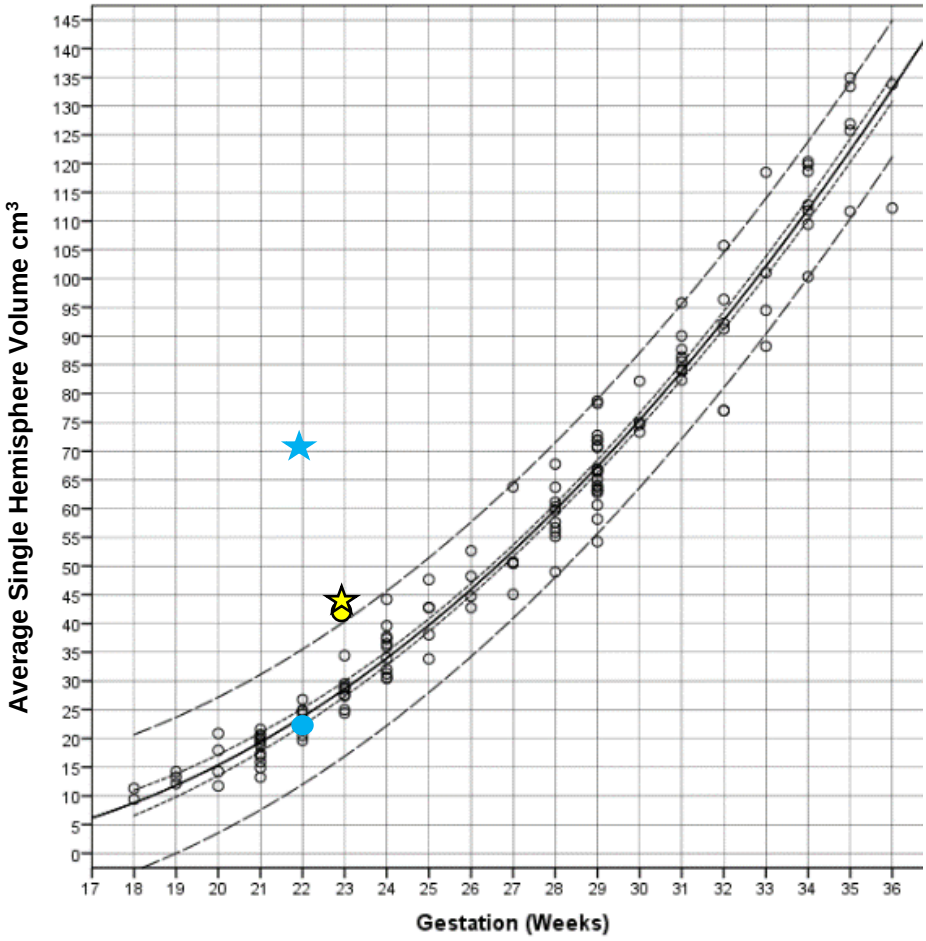
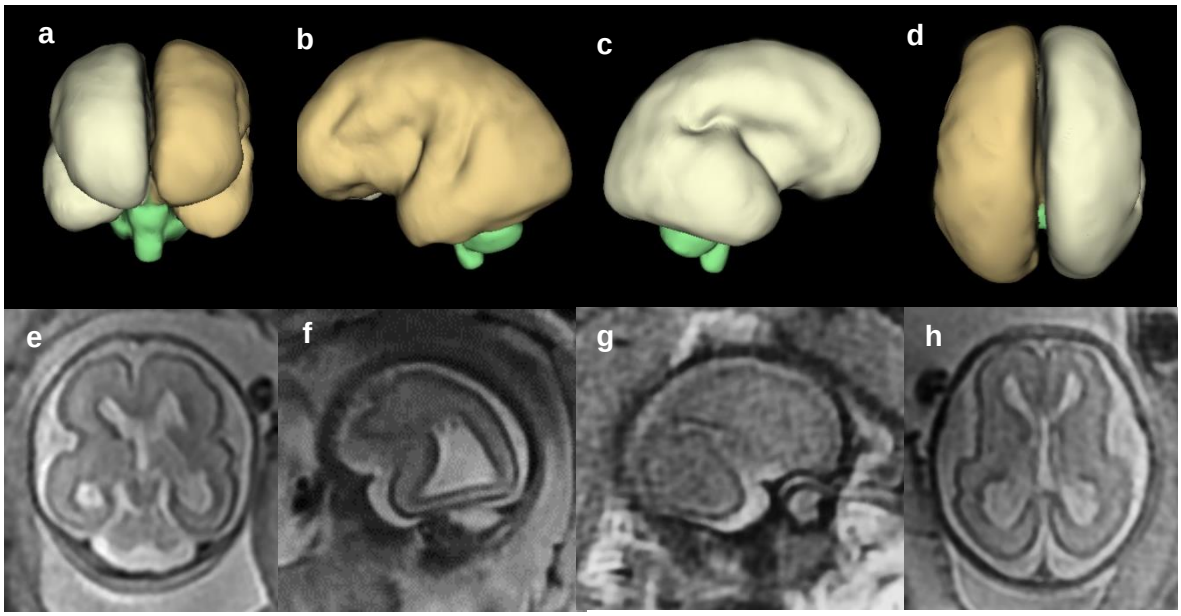


Figure 7.29 Hemisphere volumes of fetuses with megalencephaly (yellow markers) and hemimegalencephaly (blue markers) plotted on a graph of normative volume data for each hemisphere denoted by different shapes

Case Study M1 (Figure 7.30)

A 30 year old woman with singleton pregnancy was referred with suspected ACC and VM on USS at 21 weeks gestation. IuMR imaging performed at 23 weeks gestation excluded ACC and confirmed increasing VM. Also noted was a bilateral cortical formation abnormality (Figure 7.30), with enlarged brain size (TBV 91.6cm^3, >5 SD above the mean) matched by a large head size (>95th centile). A diagnosis of megalencephaly was made and this was confirmed at post mortem autopsy.

Figure 7.30 Case M1. Surface reconstructions of a 23week gestation of fetus with megalencephaly (a-d) and matched 2D ssFSE images (e-h)

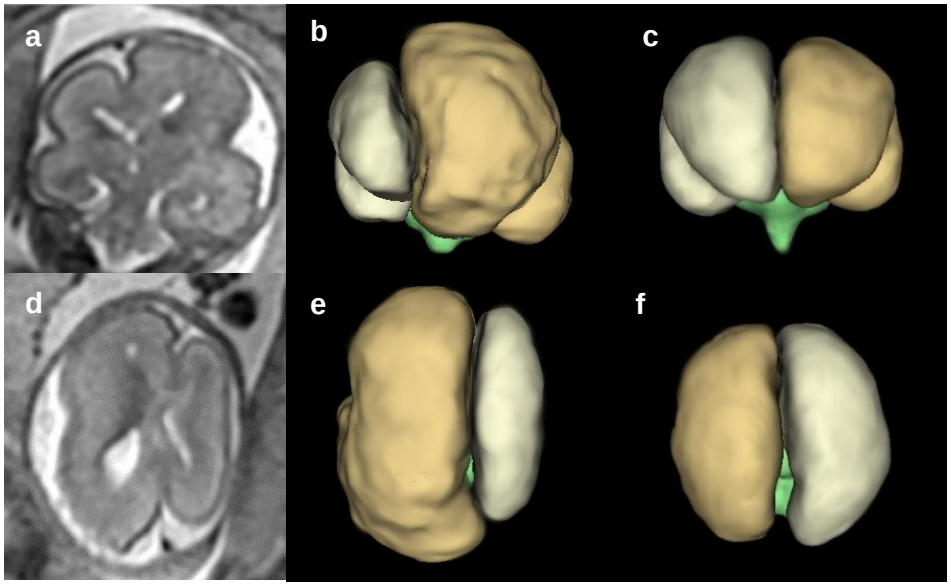


Case Study M2 (Figure 7.31)

A 28 year old with dichorionic diamniotic twin fetuses was referred for iuMR imaging at 22 weeks gestation because of unilateral ventriculomegaly in one twin on the basis of USS. IuMR confirmed the unilateral VM but one cerebral hemisphere was shown to be enlarged and malformed leading to a diagnosis of hemimegalencephaly. Head size was within normal

limits (50-90th centile) as judged by the bi-parietal skull measurement made on iuMR imaging. The full extent of the hemispheric abnormality can be seen clearly on the 3D surface reconstructions (Figure 7.31). The TBV of the twin with hemimegalencephaly was 97.4 cm^3 (10 standard deviations above the mean), while the normal twin had a TBV of 51.6cm^3, i.e. close to the 50th centile. By analysing the cerebral hemispheres of each twin separately we found that the normal hemisphere of the twin with hemimegalencephaly was very similar to the hemispheres in the normal twin (22.1 cm^3 compared with 23.7 cm^3 and 23.8 cm^3), whereas the abnormal hemisphere was over 3 times larger than the normal hemisphere (71.6 cm^3). This case shows how the segmentation and resultant volumes of anatomical sub-regions of the brain can be measured, potentially contributing to the diagnosis in cases where the pathology is more subtle.

Figure 7.31 Case M2 Images of a fetus from a twin pregnancy with hemimegalencephaly. (a) coronal, (d) axial 2D ssFSE MR imaging and (b) and (e) matched surface reconstructions. Figs (c) and (f) surface reconstructions of the normal twin.



7.6 Discussion

The use of image processing techniques to produce the 3D surfaces and printed models provide a novel and diverse way to visualise the manifestation of some of the fetal brain abnormalities described in Chapter 1. For the majority of the cases shown, the diagnosis could be made on routine 2D MR imaging, and indeed in a high proportion of the cases the 3D surfaces or models were not available until some time after the iuMR report was issued. There are though, some advantages to the resultant surface representations of the anatomy and quantitative analysis that could be useful in the diagnostic pathway. There were occasions when the surface representations demonstrated the extent of the abnormality with greater clarity and therefore allowed the diagnosis to be made with a higher degree of confidence, for example cases PF1 and PLM 1. Cortical formation abnormalities are often difficult to identify with certainty at early gestations by iuMR imaging due to the relatively smooth appearance of the normal brain before 24 weeks gestation. The electronic surface reconstructions, as with case PF1, may help in these situations.

One of the biggest advantages of manual segmentation is the generation of the volume measurements and it is this quantitative data that may provide the biggest clinical gain. Whilst it is not possible to draw any definitive conclusions about the advantages of the volume measurements due to the small numbers of cases shown, there are some interesting facts that warrant further discussion. These relate to three areas: Firstly, the ability to segment the intracranial contents or the brain parenchyma into several anatomical areas for separate analysis. For example, we were able to compare the ventricular volumes and ratio of ventricles to TBV of 51 fetuses with mild isolated VM to the same measurements from 132 normal fetuses (Figure 7.26). Analysis found the difference in volume measurements between the two groups was statistically significant. This supports the findings of Scott *et al* (277) who also undertook a similar study, albeit with a much smaller sample size. Pier *et al* (303) used ventricular volumes to attempt to predict neurodevelopmental outcome, and measured the ventricles of fetuses with isolated VM (n=193) and the ventricles of fetuses

with VM associated with other abnormalities (n=114). The results indicated that measurement of ventricular volume was no more accurate than linear measurements of the trigones of the lateral ventricles in predicting outcome. It may be a more useful clinical measure to analyse TBV and ventricular volume separately to distinguish between brain pathologies involving large ventricles but normal brain volumes (case V1), and pathologies in which large ventricles (as in cases of hydrocephalus), cause fetal brain atrophy/destruction (large ventricles and small brain volumes, case L3). Analysis of a larger number of cases is needed to determine the significance of this data.

Case study M2 (hemimegalencephaly) also highlighted the benefit of the ability to analyse separate regions of the fetal brain (Table 7.9 and Figure 7.27). Although the hemimegalencephaly case in this example was easily diagnosed on 2D images, the ability to compare the hemispheres is expected to be useful for evaluating asymmetric differences in more subtle abnormalities. We plan to use this technique in the evaluation of brainstem and cerebellar malformations, as this has been highlighted by the MERIDIAN study as a type of pathology which is difficult to diagnose on both USS and iuMR.

Secondly, there are some abnormalities where brain volumes differ from the normal range either in some cases but not others with the same abnormality, or are not affected until later gestations (e.g. holoprosencephaly, schizencephaly, lissencephaly). This information suggests that volume data may be useful as an indicator of outcome in some pregnancies but this association needs to be proven.

Thirdly, there are also those cases in which there is a disparity between head size, (defined using linear measurements such as bi-parietal diameter) and volume measurements that could potentially provide the most clinically useful information. For ten of the cases presented here there was a noticeable difference between the head size of the fetus and volume measurements. For example in Cases PLM1 and PF5 head sizes were within normal limits but TBV was much smaller than expected, and in cases PF1 and M3 head size was again considered normal, but TBV was much larger than expected for equivalent gestational

age when compared to normative data. As yet we do not know the significance, or clinical benefit, of this information and further formal studies of diagnostic impact are required.

Chapter 8

Conclusions and Future Work

The overarching aim of this thesis was to determine the diagnostic performance of iuMR as an adjunct to USS for the diagnosis of fetal brain abnormalities. Two separate but related areas have been examined; the ability of iuMR to improve the diagnostic accuracy and diagnostic confidence over ante-natal USS for the detection of fetal brain abnormalities; and the development, application and clinical evaluation of a 3D volume iuMR acquisition for fetal brain imaging. The significance of diagnosing a fetal brain abnormality prenatally is potentially huge. The expectant mother has to choose between continuing the pregnancy with uncertainty about the ultimate effects of the diagnosed abnormality or to terminate the pregnancy. An accurate and confident diagnosis is therefore vital. The immediacy and ability of USS to visualise the fetus is invaluable and, as it is safe and easily accessible, it is the undisputed primary method for screening during pregnancy. Despite this, the technical and patient-related limitations of USS, such as high maternal body mass index, reverberation artefacts and oligohydramnios, can all prevent adequate visualisation of the fetal brain.

As outlined in chapter one, diagnostic test performance is not based solely on diagnostic accuracy but a hierarchal model that has the technical efficacy of a diagnostic test at its foundation and ultimately how the test influences the outcome for the patient. The technical efficacy of routine iuMR imaging is proven, having been used as an adjunct to USS for several years but its additional value in clinical practice had not been established. Although findings of previous research suggested that iuMR improves diagnostic accuracy, the results were considered biased due to poor study design which compromised their validity (119). In addition it was unclear if those studies had investigated the further impact of iuMR imaging in the diagnostic pathway. The first aim of this research, therefore, was to establish the diagnostic capability of MR when imaging the fetal brain in utero and was addressed through the systematic review, and the MERIDIAN and Add-on studies.

The ability to acquire a 3D volume iuMR acquisition and to post-process the imaging data, has also facilitated further investigation of fetal brain anatomy and potentially lead to improved diagnostic performance. The second aim of this research was addressed in

chapters 5, and 6, which established the technical and diagnostic efficacy of the 3D MR acquisition for imaging the fetal brain in utero, and chapter 7 demonstrated its application for several brain abnormalities.

8.1 The Systematic Review and Meta-analysis

A systematic search and critical appraisal of the literature was undertaken to identify existing evidence of the ability of iuMR to diagnose fetal brain abnormalities, and to undertake a meta-analysis of the results of the studies selected. Although the MERIDIAN study had already been commissioned, there was still value in reviewing previous research so that comparisons could be made when the results of MERIDIAN were available.

The protocol for the review was written in line with the PRISMA guidelines that outlined specific inclusion criteria and this, along with the selection of studies by two independent reviewers, ensured only the most appropriate and relevant studies were included. Consequently, 773 studies were excluded during the screening process, leaving 34 full papers for final scrutiny and data extraction. One of the criteria for the meta-analysis was to only include cases from each study where diagnostic accuracy could be determined i.e. in which the diagnosis made by USS and iuMR was clear for each case and compared to a confirmed ORD. While this reduced considerably (by 62%) the number of cases for analysis it was felt that this reduction would provide a more precise calculation of diagnostic accuracy. As a result, 966/2530 complete cases were included in the analysis. The diagnostic accuracy of USS was calculated to be 75%, and for iuMR, following USS, to be 91%. More detailed analysis revealed that cortical formation abnormalities, midline and posterior fossa anomalies were the most prevalent areas of misdiagnosis by USS. Incorrect diagnoses on MR (9%), of which 5.5% were also incorrect on USS, were more likely to be false positive than false negative for the same anomalies, as well as destructive or cerebral mass lesions**.**

While our review was in progress, two other systematic reviews were published: by Rossi and Prefumo in 2014 (172) and by Van Doorn *et al* in 2015 (173). The aims of these reviews were similar to ours, but it was felt appropriate to continue with our review as it was possible that some relevant studies had been erroneously excluded by Rossi and Prefumo or by Van Doorn *et al,* and further studies had been published. Rossi and Prefumo identified and selected 13 relevant articles published between 2000 and 2012, while Van Doorrn *et al* selected 27 studies for review from the literature published between 1990 and the end of March 2014. Only 7 studies were included in all 3 systematic reviews, and an additional 15 studies were included in our report that had not been reviewed previously.

The subtle differences in selection criteria and analysis within each of the reviews did not change significantly the results, and conclusions were also similar. All confirmed that iuMR diagnosed fetal brain abnormalities more accurately than USS, particularly in the anatomical regions of the midline and posterior fossa. Analysis of the data by all three reviews found an improvement in the diagnostic accuracy of iuMR compared to USS of between 16 and 24%. Rossi and Prefumo based their diagnostic calculations on the findings from 710 fetuses. iuMR accurately detected brain abnormalities in 94%, although in some cases the measurement of accuracy was based on postnatal clinical examination alone. The review by Van Doorn reported the findings from imaging of 1184 fetuses, but only 454 of those had an ORD. Based on those numbers, Van Doorn calculated that iuMR gave an accurate diagnosis in 80% of cases and USS was accurate in 54% of cases.

All three systematic reviews came to similar conclusions with regard to the identification of compromised validity due to poor study design and inadequate reporting of outcome measures. The meta-analysis of the studies we included identified a moderate degree of variability across studies. Differences in aims and selection criteria meant sample sizes included from each study varied considerably (range n = 6 to 126) as did findings for the diagnostic accuracy of iuMR (67 to 100%). A limitation of our review was that further analysis of the causes and/or effects of heterogeneity were not possible due to the inadequate

reporting and lack of quantification of several study characteristics within the majority of the studies. For example, the previous experience of neuroradiologist of reviewing fetal iuMR imaging, which could influence diagnostic accuracy, was only recorded in a third of studies. Also 13/34 studies failed to specify the time delay between USS and iuMR and both these factors are critical to diagnostic accuracy when the rapid development and growth of the fetal brain is taken into consideration. The evaluation of the risk of bias and applicability undertaken using the QUADAS tool resulted in a judgement of a high or unclear risk of bias in at least one category for all reviewed studies due to the methodological weaknesses and the limited reporting of study outcomes. These results supported the previous accusations of bias and limited validity of previous research and confirmed the need for further investigation. The results also highlighted the need to fully assess the additional value of iuMR imaging by incorporating all elements of diagnostic performance through adequate study design.

8.2 The MERIDIAN Study

The MERIDIAN study aimed to continue the measurement of the diagnostic performance of iuMR imaging by assessing not only diagnostic accuracy but also diagnostic confidence, its influence on patient management and ultimately the impact of iuMR on patient outcome. The study addressed many of the limitations identified in previous research aiming to ensure the validity of the findings and to guide future practice within the UK. Study design was such that it was adequately powered to detect a statistical significance in diagnostic accuracy for fetuses ≤23 and ≥24 weeks gestation. A continuous cohort of participants was recruited from a wide geographical area across the UK. The iuMR findings were also compared to an USS undertaken by feto-maternal experts at tertiary level hospitals, and a time limit of two weeks between USS and iuMR was specified to ensure that any change in diagnosis between USS and iuMR was due to the accuracy of iuMR rather than due to changes in fetal condition. The

decision as to which imaging modality agreed with the ORD (i.e. gave the accurate diagnosis) was made by an independent panel of experts, blinded to the origin of the imaging reports, thus also limiting bias. MERIDIAN recruited 1101 participants, of these, 570 complete cases met the inclusion criteria and were used to calculate the diagnostic accuracy of iuMR and USS. The results of the study found a significant improvement in diagnostic accuracy on iuMR, with correct diagnoses in 93% of cases compared with the correct diagnoses on USS of 68%. IuMR corrected a wrong diagnosis by USS in 144 cases (25%), but failed to provide an accurate diagnosis in 7%. Both results have significant implications for clinical practice.

Gestational age of the fetus was regarded as an important element of the analysis due to the need to make decisions regarding the pregnancy at earlier gestations. Screening of the fetus by USS is carried out at around 18-20 weeks in the UK. If further investigations, such as amniocentesis, are needed they are performed after USS. The results of diagnostic accuracy in the age group ≤23 week's gestation were therefore particularly relevant. The final cohort of 570 complete cases comprised 369 fetuses ≤23 weeks gestation. In this age group iuMR gave the correct diagnosis for 92.4%, with USS correctly diagnosing 69.9% of cases. The results for the older group (≥24 weeks gestation, *n*= 201) were that iuMR was correct in 93.5% and USS in 64.2% of cases. This shows that when reviewing the performance of each imaging modality individually, USS was slightly more accurate in younger fetuses and iuMR performed marginally better in the older gestational age group. These findings are likely to be due to the known limitations of both modalities. In the case of iuMR, the ability to capture diagnostic images is heavily reliant on the immobility of the fetus which at younger gestations, is less likely due to the available space in which to move freely. The limitations of USS at older gestations relate directly to the progress of the pregnancy with position of the fetal head low in the pelvis and the ossification of the skull reducing the visualisation of brain anatomy by USS. The improvement in diagnostic accuracy by iuMR support the findings of

both our own systematic review and the reviews by Rossi and Perfumo and by Van Doorn *et al*. This implies that bias within previous research did not significantly affect its findings.

Though diagnostic accuracy is fundamental to diagnostic test efficacy it is only one factor contributing to the overall performance and influence of a diagnostic test. The six theoretical levels necessary for adequate diagnostic performance, outlined by Fryback and Thornbury (152), not only include technical and diagnostic accuracy at Levels 1 and 2, but also diagnostic thinking and therapeutic efficacy at Levels 3 and 4. MERIDIAN sought to address this by including a detailed analysis of the influence of diagnostic confidence and the changes in the management of the pregnancy as a result of MR findings. Assessment of diagnostic confidence was made by using the score-based weighted average method proposed by Ng and Palmer (158), which takes into account not only the level of diagnostic accuracy assigned to USS and iuMR and the differences between them, but also considers the impact of diagnostic confidence from the patient's perspective. A score is assigned according to the 'appropriate' outcome for each case this is positive when confidence has a positive impact and negative when confidence has a negative impact. For example, a diagnosis made with high confidence on iuMR has the highest positive score if the diagnosis made is correct and changes an incorrect diagnosis made with high confidence on USS. If the same scenario were judged with conventional binary measures of diagnostic confidence, both USS and iuMR would be considered equal as the scores for confidence are both high. These scenarios highlight the advantage of the score weighted method. The results of the analysis of MERIDIAN confidence scores demonstrated that iuMR had a higher proportion of correct diagnoses made with high confidence than USS (89% vs 60%). Also the confidence of iuMR had a positive impact to some degree in 31% (scores +1 to +4). iuMR was found to have a negative impact in 7% of cases (scores -1 to -3). Example scenarios might be if iuMR made a wrong diagnosis with any degree of certainty but USS was correct, or if both modalities were incorrect but the diagnosis by iuMR is made with high confidence and by

USS with low confidence. In the majority of cases (48.4%), scores were 0, indicating that the impact of iuMR was neither positive nor negative.

By assessing the influence of diagnostic confidence in such a comprehensive way, the MERIDIAN study added a unique dimension to investigations of diagnostic performance of iuMR imaging of fetal brain abnormalities. Diagnostic confidence, as far as we are aware, has not previously been examined by any other study investigating the role of iuMR in the diagnosis of fetal brain abnormalities, yet it is likely to have a significant influence on those making decisions regarding the future of a pregnancy. The clinical management of pregnancies was influenced to varying degrees (minor, significant, major or decisive) by the overall findings of iuMR in 88% of cases. Although the fetal maternal specialists were not specifically asked if the level of diagnostic confidence had any influence on changes in pregnancy management, clinical management was influenced to either a significant, major or decisive extent in 252 cases where the iuMR diagnosis was made with high confidence.

To design and conduct a research study without any limitations is difficult and MERIDIAN was no exception to this. Firstly, there may be have been element of bias in our findings as a high proportion (64%) of the iuMR examinations were performed at the primary site in Sheffield. Secondly, whilst the results of MERIDIAN provide a reliable assessment of the impact of iuMR imaging in pregnancy in the UK and support the future role of iuMR imaging in pregnancy, UK USS screening programs may not be comparable to those of other countries therefore further investigation of this may be required.

8.3 The MERIDIAN Add-on Study

The second phase of MERIDIAN, the Add-on study, was undertaken to provide data from a cohort of normal pregnancies. This was a vital addition to the main MERIDIAN study of diagnostic accuracy as it provided a normal control group to determine the negative ability of both USS and iuMR. There is a paucity of research investigating the diagnostic performance

of iuMR, as most previous studies have only included fetuses already thought to be abnormal on USS. A complete assessment of the accuracy of a diagnostic test requires both analysis of its ability to identify correctly an abnormality that is present and to correctly exclude an abnormality when none is present. It is not possible to determine this information from overall accuracy judged only by binary outcomes (i.e. correct vs. incorrect).

The nature of the Add-on study was such that a different recruitment process and inclusion criteria had to be used. It relied on women volunteering and attending for the iuMR at their convenience, and although attempts were made to try and limit the time between USS and iuMR this was not always possible. In addition, the status of the pregnancy in terms of normal development of the fetus was based on routine USS assessment. Pregnancy outcome was assumed to be normal unless an abnormality was identified by iuMR. Although these were limitations of the study, additional information regarding the diagnosis was essential to fully evaluate the value of iuMR imaging. Other studies have sought to define the diagnostic accuracy of iuMR in more detail by measuring sensitivity and specificity. Rossi and Perfumo (172) and Glenn et al (39) both assessed the sensitivity and specificity of iuMR imaging by comparing the findings of iuMR with an ORD. The major limitation of this data was that all fetuses were reviewed retrospectively and underwent iuMR imaging due to an abnormality suspected on USS. The true negative capability of iuMR was therefore not assessed.

The Add-on study recruited 198 participants without somatic or brain abnormalities reported on USS, resulting in data from 205 fetuses. Of these, iuMR confirmed the USS findings in 203 fetuses but found abnormalities in 2 fetuses. One fetus was diagnosed with VM at 26 weeks gestation, and a second fetus was thought to have a cortical abnormality at 35 weeks gestation. Neither abnormality was identified by screening USS, but follow up USS confirmed the VM and postnatal MR confirmed the cortical abnormality. As the initial USS

failed to identify the two abnormalities, one might conclude that USS was inaccurate, but that assumption would be misleading. In both cases there was a significant time delay between USS and iuMR and the abnormalities could have evolved in that period. This explains the bias resulting from a failure to restrict the time delay between the two assessments.

Data from the Add-on study was analysed in combination with the results of the main MERIDIAN study to determine the positive and negative predictive values of both USS and iuMR. Analysis of sensitivity and specificity could not be reliably calculated by the Add-on study as the sample size of 'normal' cases was not adequately powered to represent the true population, and therefore would have resulted in a distortion of the results of the NPV. However, it was possible to calculate positive and negative predictive values as this is based on the prevalence of the disease in the sample assessed. The PPVs for iuMR and USS were 93.0% and 67.9% respectively as demonstrated by combining the results from the main MERIDIAN and the Add-on studies. The NPV were 99.33% for iuMR and 98.99% for USS and support the role of USS as the primary screening method for prenatal imaging assessment in the general population as well as the benefit of iuMR in addition to USS when abnormalities are suspected.

8.4 3D Volume Imaging of the Fetal Brain

The development, clinical evaluation and application of a 3D acquisition for imaging and quantitative analysis of fetal brain development was instigated both from a need to improve further the diagnostic performance of iuMR and to take advantage of the progress of MR technology. As evidenced by the MERIDIAN study, although accuracy was high, iuMR failed to provide a correct diagnosis for 7% of the cases included. If proven to be reliable, it was possible a 3D acquisition might provide additional data, enabling a more detailed analysis of brain development, which could lead to improved diagnostic performance and introducing

the possibility of reducing the number of 2D sequences required. Although there is emerging evidence of 3D acquisitions being used for fetal imaging (120, 241, 242), the publication of sequence details has been limited and this, as well as the lack of vendor developed 3D sequences suitable for fetal imaging led to the development of our own. The 2D FIESTA formed the basis of our 3D sequence with adjustments to parameters such that the resulting scan time was short enough for acquisition during maternal suspended respiration and with increased resolution compared to the 2D FIESTA and ssFSE imaging.

The retrospective assessment evaluated the image quality of the 3D acquisition and its diagnostic capability and investigated the relationship between the two. Anecdotal evidence and measurement of CNR, which suggested that the inherent image contrast of the 3D FIESTA, compared to that of the T2 weighted ssFSE imaging, would limit its diagnostic capability proved to be unfounded. Results showed that for almost 90% of examinations (309/345) the acquired 3D acquisition was considered diagnostic, and of those 309, after exclusion of cases without an ORD, an accurate diagnosis was made in 91.4% (265/290). An unexpected finding of this assessment, after the exception of non-diagnostic cases, was that image quality did not affect diagnostic accuracy, with no statistical significance between the categories of poor, average and good. It was also interesting to note that although image quality was influenced by gestational age, with more 3D datasets classed as poor or average in the 18-23 weeks group than in the older groups, this also had little influence on diagnostic accuracy. It is difficult to know how these results compare to the performance of other 3D acquisitions as it appears that only one other study (242), as far as we are aware, has assessed the diagnostic accuracy of a 3D acquisition for fetal brain imaging *in utero*. That study found a 3D FIESTA acquisition to be marginally more accurate than 2D imaging, but less accurate than 3D USS for diagnosing brain abnormalities. Unfortunately, details of the methods of assessment were unavailable in English for appraisal.

Review of the 3D acquisitions was undertaken by the same experienced neuro-radiologist as the initial review and clinical report undertaken as part of the MERIDIAN study. Whilst this eliminated reader bias, it introduced the possibility of recall bias which in some cases may have influenced the diagnosis made. Attempts were made to address this by measures such as anonymising the images, removing prominent cases, (for example those used for publications), and introducing a long period between initial clinical reporting and the review for the 3D analysis but there may still have been in some cases an element of recall bias. A more valid and definitive assessment might have been achieved if a second expert had independently reviewed the 3D imaging but this would have introduced variation in reader experience, in itself a potential source of bias.

It is rare in clinical practice that a diagnosis is made by acquiring only a single MR sequence for any anatomical area, particularly so in fetal imaging where the fetus is likely to be very small and the range of possible abnormalities is considerable. The high accuracy of diagnosis using the 3D acquisition highlights the significant advantage of acquiring a diagnostic 3D MR imaging dataset in the fetal brain and has allowed us to reduce the number of 2D sequences in our iuMR imaging protocol. A further benefit of the 3D acquisition is that the resultant imaging data has enabled additional visual and quantitative investigation of fetal brain anatomy. This was achieved by manually segmenting fetal brain anatomy from the surrounding structures.

In manual segmentation of fetal brain anatomy, outlining freehand anatomical regions of interest, has consistently proven to be a reproducible method for calculating volumes (260, 281, 304) and our results support this. Intra and inter-rater reliability were high with ICC of 0.99 and 0.97 highlighting the advantages of the method even when used by those with limited experience of fetal brain anatomy and imaging. The software used, 3D Slicer (283), was chosen for segmentation due to its open access, ease of use and reliability, although many other software applications are available that allow the placement of manual regions of

interest and segmentation of anatomy. The comparisons between known volumes of brain models and the volumes derived by manual segmentation resulted in high agreement between the two. This confirmed that any error of measurement error directly resulting from the software was negligible.

Segmentation of anatomy using 3D Slicer has not only enabled the quantification of fetal brain volumes but also the ability to view and interact with the surfaces of the fetal brain electronically as a 3D structure and as models produced using 3D printing technology. This has led to the establishment of a novel way of visualising fetal brain anatomy and the impact of abnormalities on brain structure. This has provided confirmatory evidence in some clinical cases and the 3D printed models have been used to create a teaching file which could potentially help in training junior doctors but this is not yet proven. The segmentation process also enables brain volumes to be quantified, the measurements being derived form the number and size of the voxels in each region of interest.

A limitation of manual segmentation is the time required to manually outline the relevant anatomy on each imaging slice. This was typically 1.5 hours for a younger fetus (<25 weeks) increasing to approximately 3.5 hours for a fetus of 36 weeks gestation, due to the increasing complexity of cortical folding. An alternative to manual segmentation would be to use automated software, but at present this is not readily available. The automated methods developed for extraction of adult and paediatric brain volumes assume an immobile head enclosed by air, and hence cannot be used to extract fetal brain volumes. Some groups have made significant progress in developing automated methods, using a 3 step process. Firstly, images from several sequences acquired in multiple orientations are corrected to compensate for motion during acquisition, the resultant 2D data sets are then combined to create a high resolution 3D composite image of fetal brain anatomy from which automatic segmentation can be undertaken (266, 270, 279, 305). While these methods reduce the time needed for manual segmentation methods, they need expertise to develop the sophisticated

computer vision algorithms required. In addition whilst several papers describe the software development and methods of automation, the data published about the resultant volumes has been limited either to relatively small numbers of cases or to specific subdivisions of fetal brain anatomy (269, 276, 293, 306)

Previous methods used for segmentation to date, whether manual or automated, have used ssFSE imaging data. The potential disadvantage to this method is the nature of data acquisition which may result in erroneous measurements. As described earlier, ssFSE images are acquired a single slice at a time with the possibility of fetal movement between each which can result in incomplete capture of anatomical data. Although the motion correction methods can realign the data, any gaps in spatial coverage will be filled by interpolation of adjacent regions. Automated segmentation methods frequently rely on predefined anatomical atlases and templates, defined by manually segmenting ssFSE images again with the potential of error. The reliance of automated methods on predefined atlases may also limit their application as they may not be adaptable or may introduce significant bias when fetal brain anatomy is divergent from normal trajectories. In comparison, the 3D volume sequence data is captured as a single acquisition and movement tends to results in non-diagnostic images rather than incomplete capture of anatomical information. The key advantage to acquiring a 3D data set along with manual segmentation to quantify brain growth is its simplicity. Acquisition of a 3D imaging sequence eliminates the need for the synthesis of multiple 2D acquisitions, it does not require any specialist knowledge or bespoke software and manual segmentation is possible for all fetal brains regardless of pathology. A significant advantage of the manual segmentation of a large number of fetuses across a wide gestational age range undertaken using our method, is that the resultant data can be used to create a 3D atlas of normal appearances which has not been available previously and will provide the foundation for automated methods.

The measurement of 132 brain volumes enabled the construction of a growth chart for fetuses across a wide gestational age range (18-36 weeks) which could potentially be used as a reference in clinical practice. Growth charts provide a useful reference to monitor fetal growth, particularly by USS, and several have charted linear measurements for a number of anatomical areas, but our growth chart is the first drawn up using fetal brain volumes from such a large cohort. The growth chart provides a unique insight into fetal brain development adding significant information to previously published data. Clouchoux et al (294) measured the volumes of fetal brains using automated methods and plotted the values against gestational age and found a linear relationship between the two. This was in contrast to our results which found a quadratic model to be the best fit. When comparing the values produced at different gestational ages in the two charts, the volumes at 26 weeks gestation were comparable but at older gestations there was a disparity, ours being 30cm^3 lower than those by described Clouchoux. The reason for this difference is unknown but could be due to the limited numbers measured by our study at this gestation. The volumes measurements derived using our method were also compared to the volumes reported by Philips *et al* (284) who published the brain weights of fetuses at post mortem examination. Although we had to estimate fetal brain density to convert our volumes to weight, the results were comparable when brain oedema due to necrosis was taken in to account

The quantitative evaluation of fetal brain anatomy, to date, has focused on the methods used to extract the quantitative data but the ultimate value of this analysis has yet to be defined or proven. Linear measurements can be easily quantified on USS and are extensively used during pregnancy to assess the growth of the fetus and there may be a similar role for quantitative analysis of iuMR once 'normal' parameters have been fully defined. Manual or automated segmentation methods would require the investment of additional resources which are limited in the NHS. If, therefore, quantitative analysis of the fetal brain is to be implemented in the clinical setting it needs to provide additional clinically relevant information to help guide the management of the pregnancy and ultimately benefit the patient. Initial

investigation of brain abnormalities quantitatively has focused on ventriculomegaly. Scott *et al* and Gholipour *et al* (271, 277) investigated and reported the changes in ventricular volume and morphology in a small number of fetuses diagnosed with ventriculomegaly. While these reports demonstrated that ventricular volumes correlated with increased linear measurement of ventricle diameter on 2D imaging, it remains unclear how the volume information contributes clinically in this situation.

A proportion of the fetuses who underwent iuMR imaging as part of the MERIDIAN study were affected by the developmental brain abnormalities described at the beginning of this thesis. Post-processing of the 3D volumes acquired allowed a selection of the abnormalities to be visualized as surface reconstructions and the associated quantitative volume data for each to be compared to values from healthy fetuses. This gave an insight into the possible clinical application of quantitative volume analysis of fetal brain development by providing examples of how we have used the information in practice. This highlighted areas where this additional information could have diagnostic impact. For example, cortical formation abnormalities were more clearly defined by the surface reconstructions than by 2D iuMR imaging in a fetus of 23 weeks gestation (case PF1) and by analysing different compartments of the brain as shown in case M2. Also important to note were those cases where brain abnormalities do not appear to affect brain growth, such as isolated ACC, suggesting quantitative analysis may not provide useful information in these cases. Clearly further work is required to establish the normal and abnormal ranges for all abnormalities that can affect the fetal brain.

8.5 Summary

This work has demonstrated that iuMR imaging has the ability to provide a 25% increase in the detection of fetal brain abnormalities as an adjunct to USS, and that it can influence the management of pregnancies in a high proportion of cases. The comprehensive assessment

of diagnostic confidence in the diagnostic pathway has shown iuMR appropriately improves the confidence with which diagnoses are made. The results of the Add-on study confirmed the ability of both USS and iuMR to correctly confirm when brain development of the fetus is normal. This highlights the validity of USS as the primary screening imaging method for pregnancy and confirms the need for additional iuMR imaging when abnormalities are detected. The findings of the MERIDIAN study have major implications for clinical practice and consequently it is recommended that iuMR imaging should be performed for all pregnancies where USS raises the possibility of fetal brain abnormalities.

The 3D acquisition has been a useful addition to our routine clinical imaging protocol and was achieved in a high proportion of cases. The generation of 3D surface representations and printed models have provided a unique insight into the appearance of the developing brain. As well as providing the visual representations, manual segmentation of fetal brain anatomy produces quantitative data which will be the basis for continuing work on segmentation and 3D analysis. The measurement of fetal brain volumes in a cohort of normally developing fetuses made it possible to produce a growth chart which can be used as a reference, allowing comparison of volumes to be made when a fetal brain is affected by an abnormality. Additional information regarding any divergence in brain volume could potentially aid diagnosis or improve confidence in some cases.

8.6 Future Work

There are three areas arising from the work in thesis for further investigation that predominantly relate to the data generated by the post-processing of the 3D volume acquisitions. These include quantitative analysis of fetal brains affected by abnormalities that impact on brain growth, such as microcephaly; the development of automated methods for segmentation of brain anatomy; and the potential use of 3D printed models for parental education and counselling.

The review of fetal brain abnormalities in Chapter 7 supports the early indicators of diagnostic value in combining routine iuMR imaging with the post-processing of the 3D volume acquisitions. As the case studies have shown, there are times when there is disparity between skull size, determined by linear measurements, and brain size, determined by volume data. This information is potentially significant and further studies would identify when it would be of value in clinical situations. Areas of research that may benefit from volume analysis are those which rely heavily on head and intracranial measurement as primary indicators of an abnormality. One relevant application consists of those cases in which the fetus is thought to have microcephaly based on USS linear measurements. There have been very few iuMR studies focusing on the evaluation of fetuses with microcephaly, and consequently the potential role of iuMR imaging in this group of patients has not been adequately investigated. It is important to note that cases of isolated microcephaly were not eligible for recruitment into MERIDIAN. Previous MR studies on cases with microcephaly have focused on comparing the agreement of linear measurements of USS and MR or reporting MR biometric reference values (307, 308). As brain volumes are very difficult to quantify on USS, skull size is used as an indicator to diagnose microcephaly but the correlation is not perfect (309). Brain volume may be a more accurate marker for diagnosis of microcephaly and to predict neurodevelopmental outcome in fetuses where small head size is a concern, but a formally powered study is needed.

Research in this field is hampered by the non-standardised definition of microcephaly. Most researchers have to choose between skull sizes that are either 2 SD or 3 SD below the mean of the normal population. The choice significantly alters the proportion of individuals with pathology and therefore those considered outside the normal population. Although no definition of microcephaly is given, EUROCAT (the European Surveillance of Congenital Anomalies) reports that approximately 0.025% of pregnancies are affected each year (310). Microcephaly is often associated with other brain abnormalities which may indicate a poor

prognosis but there is an increased risk of poor neurodevelopmental outcome even in isolated microcephaly, i.e. if no other structural brain abnormality is present (311, 312).
If 2 SD below the mean is chosen as the threshold for a study, then approximately 2.5% of the normal population is included, resulting in too many false positives. Alternatively, if 3 SD below the mean is chosen then only 0.15% of the normal population will be included and it is likely that many cases with additional brain pathology will be overlooked.

Using the benefits of iuMR imaging it will be possible to study other structural brain abnormalities in fetuses with microcephaly or micrencephaly (small brain size). A primary objective of a formal study would be to determine if there is any value in using iuMRI in addition to USS by addressing the research question: 'is there a fetal head size or brain volume below which iuMR should be offered?' The answer to this question would be defined by demonstrating a clinically significant increase in diagnostic accuracy by using iuMR in addition to prenatal USS and combining this with brain volume measurements, to stratify the risk of poor outcome in cases of isolated microcephaly and micrencephaly.
Carrying out a multicentre prospective observational study, taking advantage of the proven collaboration of the MERIDIAN researchers, would make it possible to estimate the change in diagnostic accuracy of USS and iuMR in a cohort of pregnancies affected by microcephaly. It would also make it possible to determine whether measurement of skull size or an alternative antenatal assessment of brain volume provides a more accurate definition of microcephaly and prediction of risk for poor clinical outcome.

We have shown that our method for generating brain volume data is both reliable, reproducible and easy to undertake but the time burden required is currently a significant drawback. A further area of work would therefore require the investigation and development of easily accessible automated methods for the segmentation of fetal brain anatomy. This may prove challenging for cases with extensive abnormalities that greatly distort fetal brain anatomy, however it is arguably the more-subtle pathology that is of greatest interest for the

application of volume measurements and existing research suggests that this should be feasible to solve. Additionally the label maps produced through the manual segmentation in this work can be used as a reference Atlas of normal appearances and provide a foundation from which automated methods can be developed. Reducing segmentation times and subsequent analysis of brain volumes would enable quantitative comparisons of brain volumes in fetuses with abnormalities to the normative data made available through this research. Ultimately it is hoped this type of evaluation could be made on a routine basis in the clinical setting and potentially improve both the accuracy and confidence of diagnoses for the detection of fetal brain abnormalities as well as provide a clearer indicator of outcome in pregnancies.

An additional area for potential research is the use of the 3D printed brain models to improve parental understanding about the impact of abnormalities on brain development and growth. Personalised models have previously been shown to be a useful tool for educating patients affected by kidney tumours (313) but as far as we are aware 3D printed fetal brain models have not previously been produced and therefore their worth not established. Future work would investigate if parental acceptance of abnormalities and their implications are increased through being able to visualise and handle the brain models.

8.6.1 Future directions of research

- The investigation of methods to semi or fully automate the segmentation of fetal brain anatomy. This will focus on the exploration of existing software not previously applied to iuMR imaging and/or the development of new software. Initially this will focus on automated segmentation of normally developing fetal brains, with the ultimate aim of the development and successful application of automated methods regardless of the formation and structure of the fetal brain.

- A study of fetuses thought to have microcephaly following prenatal USS will combine routine 2D iuMR imaging and quantitative analysis of brain volume to define the role of iuMR imaging and post-processing in the clinical management of these cases.
- 3D iuMR imaging, in conjunction with quantitative analysis, will be used to investigate subdivisions of the fetal brain. Initial work will focus on the contents of the posterior fossa to help improve diagnostic accuracy in these cases. The accurate diagnosis of posterior fossa abnormalities remains a challenge for both USS and iuMR and further analysis of diagnostic errors within the MERIDIAN study will identify specific areas of inaccuracies and guide analysis.
- An investigation into the benefit of using 3D fetal brain models, produced using 3D printing technology, for parental understanding of the impact of abnormalities on fetal brain development.

References

1. European Surveillance of Congenital Anomalies EUROCAT. Prevelance Tables for Nervous system anomalies (per 10,000 births): EUROCAT; 2012 [Available from: http://www.eurocat-network.eu/accessprevalencedata/prevalencetables.

2. 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.

3. Griffiths P, Paley M, Whitby E. Imaging the Central Nervous System of the Fetus and Neonate. First ed. Griffiths P, Paley M, Whitby E, editors. New York: Taylor and Francis Group; 2006a 2006a. 260 p.

4. Aubry MC, Aubry JP, Dommergues M. Sonographic prenatal diagnosis of central nervous system abnormalities. Childs Nerv Syst. 2003;19(7-8):391-402.

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. Sepulveda W, Wong AE, Sepulveda S, Corral E. Fetal scalp cyst or small meningocele: differential diagnosis with three-dimensional ultrasound. Fetal diagnosis and therapy. 2011;30(1):77-80.

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

8. McLone DG, Dias MS. The Chiari II malformation: cause and impact. Childs Nerv Syst. 2003;19(7-8):540-50.

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

10. Barkovich AJ, Simon EM, Clegg NJ, Kinsman SL, Hahn JS. Analysis of the cerebral cortex in holoprosencephaly with attention to the sylvian fissures. AJNR American journal of neuroradiology. 2002;23(1):143-50.

11. Hahn JS, Barnes PD. Neuroimaging advances in holoprosencephaly: Refining the spectrum of the midline malformation. American journal of medical genetics Part C, Seminars in medical genetics. 2010;154C(1):120-32.

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 : the official journal of the International Society of Ultrasound in Obstetrics and Gynecology. 2010;36(1):10-4.

13. Herman-Sucharska I, Bekiesinska-Figatowska M, Urbanik A. Fetal central nervous system malformations on MR images. Brain Dev. 2009;31(3):185-99.

14. Wong AM, Bilaniuk LT, Ng KK, Chang YL, Chao AS, Wai YY. Lobar holoprosencephaly: prenatal MR diagnosis with postnatal MR correlation. Prenat Diagn. 2005;25(4):296-9.

15. 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 : the official journal of the International Society of Ultrasound in Obstetrics and Gynecology. 2006;27(5):509-16.

16. Mangione R, Fries N, Godard P, Capron C, Mirlesse V, Lacombe D, et al. Neurodevelopmental outcome following prenatal diagnosis of an isolated anomaly of the corpus callosum. Ultrasound in obstetrics & gynecology : the official journal of the International Society of Ultrasound in Obstetrics and Gynecology. 2011;37(3):290-5.

17. Glenn OA, Goldstein RB, Li KC, Young SJ, Norton ME, Busse RF, et al. Fetal Magnetic Resonance Imaging in the Evaluation of Fetuses Referred for Sonographically Suspected Abnormalities of the Corpus Callosum. Journal of Ultrasound in Medicine. 2005;24(6):791-804.

18. Ghi T, Carletti A, Contro E, Cera E, Falco P, Tagliavini G, et al. Prenatal diagnosis and outcome of partial agenesis and hypoplasia of the corpus callosum. Ultrasound in Obstetrics and Gynecology. 2010;35(1):35-41.

19. Francesco P, Maria-Edgarda B, Giovanni P, Dandolo G, Giulio B. Prenatal diagnosis of agenesis of corpus callosum: what is the neurodevelopmental outcome? Pediatrics international : official journal of the Japan Pediatric Society. 2006;48(3):298-304.

20. Hetts SW, Sherr EH, Chao S, Gobuty S, Barkovich AJ. Anomalies of the corpus callosum: an MR analysis of the phenotypic spectrum of associated malformations. AJR American journal of roentgenology. 2006;187(5):1343-8.

21. D'Ercole C, Girard N, Cravello L, Boubli L, Potier A, Raybaud C, et al. Prenatal diagnosis of fetal corpus callosum agenesis by ultrasonography and magnetic resonance imaging. Prenatal Diagnosis. 1998;18(3):247-53.

22. Shevell MI. Clinical and diagnostic profile of agenesis of the corpus callosum. Journal of child neurology. 2002;17(12):896-900.

23. Griffiths PD, Batty R, Connolly DA, Reeves MJ. Effects of failed commissuration on the septum pellucidum and fornix: implications for fetal imaging. Neuroradiology. 2009;51(5):347-56.

24. Levine D, Barnes PD, Robertson RR, Wong G, Mehta TS. Fast MR imaging of fetal central nervous system abnormalities. Radiology. 2003;229(1):51-61.

25. Tang PH, Bartha AI, Norton ME, Barkovich AJ, Sherr EH, Glenn OA. Agenesis of the corpus callosum: an MR imaging analysis of associated abnormalities in the fetus. AJNR American journal of neuroradiology. 2009a;30(2):257-63.

26. Toi A, Chitayat D, Blaser S. Abnormalities of the foetal cerebral cortex. Prenatal Diagnosis. 2009;29(4):355-71.

27. 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.

28. Girard N, Raybaud C, Poncet M. In vivo MR study of brain maturation in normal fetuses. AJNR American journal of neuroradiology. 1995;16(2):407-13.

29. 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.

30. Griffiths P, Morris J, Larroche J-C, Reeves M. Atlas of Fetal and Postnatal Brain MR. First Eition ed. United States of America: MOSBY, Elsevier; 2010. 266 p.

31. 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.

32. Nishimaki S, Endo M, Seki K, Yokota S. Hemimegalencephaly misdiagnosed as a congenital brain tumor by fetal cerebral ultrasonography. Prenat Diagn. 2004;24(4):257-9.

33. Nakahashi M, Sato N, Yagishita A, Ota M, Saito Y, Sugai K, et al. Clinical and imaging characteristics of localized megalencephaly: a retrospective comparison of diffuse hemimegalencephaly and multilobar cortical dysplasia. Neuroradiology. 2009;51(12):821-30.

34. Agid R, Lieberman S, Nadjari M, Gomori JM. Prenatal MR diffusion-weighted imaging in a fetus with hemimegalencephaly. Pediatric radiology. 2006;36(2):138-40.

35. Raybaud C, Levrier O, Brunel H, Girard N, Farnarier P. MR imaging of fetal brain malformations. Childs Nerv Syst. 2003;19(7-8):455-70.

36. Fogliarini C, Chaumoitre K, Chapon F, Fernandez C, Levrier O, Figarella-Branger D, et al. Assessment of cortical maturation with prenatal MRI: part II: abnormalities of cortical maturation. European radiology. 2005;15(9):1781-9.

37. Garel C, Delezoide AL, Elmaleh-Berges M, Menez F, Fallet-Bianco C, Vuillard E, et al. Contribution of fetal MR imaging in the evaluation of cerebral ischemic lesions. American Journal of Neuroradiology. 2004;25(9):1563-8.

38. Blondiaux E, Sileo C, Nahama-Allouche C, Moutard ML, Gelot A, Jouannic JM, et al. Periventricular nodular heterotopia: prenatal ultrasound and magnetic resonance findings. Ultrasound in obstetrics & gynecology : the official journal of the International Society of Ultrasound in Obstetrics and Gynecology. 2012.

39. Glenn OA, Cuneo AA, Barkovich AJ, Hashemi Z, Bartha AI, Xu D. Malformations of Cortical Development: Diagnostic Accuracy of Fetal MR Imaging. Radiology. 2012;263(3):843-55.

40. Barkovich AJ. Morphologic characteristics of subcortical heterotopia: MR imaging study. AJNR American journal of neuroradiology. 2000;21(2):290-5.

41. Greco P, Resta M, Vimercati A, Dicuonzo F, Loverro G, Vicino M, et al. Antenatal diagnosis of isolated lissencephaly by ultrasound and magnetic resonance imaging. Ultrasound in obstetrics & gynecology : the official journal of the International Society of Ultrasound in Obstetrics and Gynecology. 1998;12(4):276-9.

42. Levine D, Barnes PD. Cortical maturation in normal and abnormal fetuses as assessed with prenatal MR imaging. Radiology. 1999;210(3):751-8.

43. Li Y, Estroff JA, Mehta TS, Robertson RL, Robson CD, Poussaint TY, et al. Ultrasound and MRI of fetuses with ventriculomegaly: can cortical development be used to predict postnatal outcome? AJR American journal of roentgenology. 2011;196(6):1457-67.

44. Girard N, Chaumoitre K, Chapon F, Pineau S, Barberet M, Brunel H. Fetal magnetic resonance imaging of acquired and developmental brain anomalies. Seminars in perinatology. 2009;33(4):234-50.

45. Leventer RJ, Jansen A, Pilz DT, Stoodley N, Marini C, Dubeau F, et al. Clinical and imaging heterogeneity of polymicrogyria: a study of 328 patients. Brain : a journal of neurology. 2010;133(Pt 5):1415-27.

46. Denis D, Maugey-Laulom B, Carles D, Pedespan JM, Brun M, Chateil JF. Prenatal diagnosis of schizencephaly by fetal magnetic resonance imaging. Fetal diagnosis and therapy. 2001;16(6):354-9.

47. Garel C. The role of MRI in the evaluation of the fetal brain with an emphasis on biometry, gyration and parenchyma. Pediatric radiology. 2004;34(9):694-9.

48. Howe DT, Rankin J, Draper ES. Schizencephaly prevalence, prenatal diagnosis and clues to etiology: a register-based study. Ultrasound in obstetrics & gynecology : the official journal of the International Society of Ultrasound in Obstetrics and Gynecology. 2012;39(1):75-82.

49. Barkovich AJ. Developmental disorders of the midbrain and hindbrain. Frontiers in neuroanatomy. 2012;6:7.

50. Limperopoulos C, Robertson RL, Jr., Khwaja OS, Robson CD, Estroff JA, Barnewolt C, et al. How accurately does current fetal imaging identify posterior fossa anomalies? AJR American journal of roentgenology. 2008;190(6):1637-43.

51. Guibaud L. Practical approach to prenatal posterior fossa abnormalities using MRI. Pediatric radiology. 2004;34(9):700-11.

52. Zalel Y, Gilboa Y, Gabis L, Ben-Sira L, Hoffman C, Wiener Y, et al. Rotation of the vermis as a cause of enlarged cisterna magna on prenatal imaging. Ultrasound in obstetrics & gynecology : the official journal of the International Society of Ultrasound in Obstetrics and Gynecology. 2006;27(5):490-3.

53. Guibaud L. Contribution of fetal cerebral MRI for diagnosis of structural anomalies. Prenat Diagn. 2009;29(4):420-33.

54. Klein O, Pierre-Kahn A, Boddaert N, Parisot D, Brunelle F. Dandy-Walker malformation: prenatal diagnosis and prognosis. Childs Nerv Syst. 2003;19(7-8):484-9.

55. Patek KJ, Kline-Fath BM, Hopkin RJ, Pilipenko VV, Crombleholme TM, Spaeth CG. Posterior fossa anomalies diagnosed with fetal MRI: associated anomalies and neurodevelopmental outcomes. Prenat Diagn. 2012;32(1):75-82.

56. Stazzone MM, Hubbard AM, Bilaniuk LT, Harty MP, Meyer JS, Zimmerman RA, et al. Ultrafast MR imaging of the normal posterior fossa in fetuses. AJR American journal of roentgenology. 2000;175(3):835-9.

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

58. Limperopoulos C, Robertson RL, Estroff JA, Barnewolt C, Levine D, Bassan H, et al. Diagnosis of inferior vermian hypoplasia by fetal magnetic resonance imaging: potential pitfalls and neurodevelopmental outcome. American journal of obstetrics and gynecology. 2006;194(4):1070-6.

59. Guibaud L, Larroque A, Ville D, Sanlaville D, Till M, Gaucherand P, et al. Prenatal diagnosis of 'isolated' Dandy-Walker malformation: imaging findings and prenatal counselling. Prenat Diagn. 2012;32(2):185-93.

60. . G, Contro E, Carletti A, Ghi T, Campobasso G, Rembouskos G, et al. Prenatal diagnosis and outcome of fetal posterior fossa fluid collections. Ultrasound in obstetrics & gynecology : the official journal of the International Society of Ultrasound in Obstetrics and Gynecology. 2012;39(6):625-31.

61. Ertl-Wagner B, Lienemann A, Strauss A, Reiser MF. Fetal magnetic resonance imaging: indications, technique, anatomical considerations and a review of fetal abnormalities. European radiology. 2002;12(8):1931-40.

62. Righini A, Parazzini C, Doneda C, Arrigoni F, Rustico M, Re TJ, et al. Fetal MRI features related to the Chiari malformations. Neurological sciences : official journal of the Italian Neurological Society and of the Italian Society of Clinical Neurophysiology. 2011;32 Suppl 3:S279-81.

63. Ando K, Ishikura R, Ogawa M, Shakudo M, Tanaka H, Minagawa K, et al. MRI tight posterior fossa sign for prenatal diagnosis of Chiari type II malformation. Neuroradiology. 2007;49(12):1033-9.

64. Abele TA, Lee SL, Twickler DM. MR imaging quantitative analysis of fetal chiari II malformations and associated open neural tube defects: Balanced SSFP versus half-fourier RARE and interobserver reliability. Journal of magnetic resonance imaging : JMRI. 2013.

65. Griffiths PD, Widjaja E, Paley MN, Whitby EH. Imaging the fetal spine using in utero MR: diagnostic accuracy and impact on management. Pediatric radiology. 2006;36(9):927-33.

66. von Koch CS, Glenn OA, Goldstein RB, Barkovich AJ. Fetal magnetic resonance imaging enhances detection of spinal cord anomalies in patients with sonographically detected bony anomalies of the spine. Journal of ultrasound in medicine : official journal of the American Institute of Ultrasound in Medicine. 2005;24(6):781-9.

67. Blaicher W, Mittermayer C, Messerschmidt A, Deutinger J, Bernaschek G, Prayer D. Fetal skeletal deformities - the diagnostic accuracy of prenatal ultrasonography and fetal magnetic resonance imaging. Ultraschall in der Medizin (Stuttgart, Germany : 1980). 2004;25(3):195-9.

68. Patel S, Barkovich AJ. Analysis and classification of cerebellar malformations. AJNR American journal of neuroradiology. 2002;23(7):1074-87.

69. Shekdar K. Posterior fossa malformations. Seminars in ultrasound, CT, and MR. 2011;32(3):228-41.

70. França CM, Mugayar LR. Intrauterine infections: A literature review. Special Care in Dentistry. 2004;24(5):250-3.

71. Barkovich AJ, Girard N. Fetal brain infections. Childs Nerv Syst. 2003;19(7):501-7.

72. Spinillo A, Capuzzo E, Stronati M, Ometto A, Orcesi S, Fazzi E. Effect of preterm premature rupture of membranes on neurodevelopmental outcome: follow up at two years of age. BJOG: An International Journal of Obstetrics & Gynaecology. 1995;102(11):882-7.

73. Pereira L, Maidji E, McDonagh S, Tabata T. Insights into viral transmission at the uterine–placental interface. Trends in Microbiology. 2005;13(4):164-74.

74. Bale Jr J. Fetal infections and brain development. Clinics in perinatology. 2009;36(3):639.

75. Kravetz JD, Federman DG. Toxoplasmosis in pregnancy. The American journal of medicine. 2005;118(3):212-6.

76. Hill D, Dubey JP. Toxoplasma gondii: transmission, diagnosis and prevention. Clinical Microbiology and Infection. 2002;8(10):634-40.

77. Yamamoto R, Ishii K, Shimada M, Hayashi S, Hidaka N, Nakayama M, et al. Significance of maternal screening for toxoplasmosis, rubella, cytomegalovirus and herpes simplex virus infection in cases of fetal growth restriction. The journal of obstetrics and gynaecology research. 2013;39(3):653-7.

78. Stagno S, Pass RF, Cloud G, Britt WJ, Henderson RE, Walton PD, et al. Primary cytomegalovirus infection in pregnancy. Incidence, transmission to fetus, and clinical outcome. JAMA. 1986;256(14):1904-8.

79. Vyse AJ, Hesketh LM, Pebody RG. The burden of infection with cytomegalovirus in England and Wales: how many women are infected in pregnancy? Epidemiology and Infection. 2008;137(4):526-33.

80. Leruez-Ville M, Magny J-F, Couderc S, Pichon C, Parodi M, Bussières L, et al. Risk Factors for Congenital Cytomegalovirus Infection Following Primary and Nonprimary Maternal Infection: A Prospective Neonatal Screening Study Using Polymerase Chain Reaction in Saliva. Clinical Infectious Diseases. 2017:cix337.

81. Malinger G, Lev D, Ben-Sira L, Hoffmann C, Herrera M, Vinals F, et al. Can syndromic macrocephaly be diagnosed in utero? Ultrasound in obstetrics & gynecology : the official journal of the International Society of Ultrasound in Obstetrics and Gynecology. 2011;37(1):72-81.

82. Popa RT, editor Imaging patterns in fetal CNS infections1970: European Congress of Radiology 2012.

83. Doneda C. Early Cerebral Lesions in Cytomegalovirus Infection: Prenatal MR Imaging. Radiology. 2010;255(2):613-21.

84. Benoist G, Salomon L, Mohlo M, Suarez B, Jacquemard F, Ville Y. Cytomegalovirus-related fetal brain lesions: comparison between targeted ultrasound examination and magnetic resonance imaging. Ultrasound in Obstetrics & Gynecology. 2008;32(7):900-5.

85. Boppana SB, Ross SA, Fowler KB. Congenital cytomegalovirus infection: clinical outcome. Clinical infectious diseases. 2013;57(suppl 4):S178-S81.

86. Ozduman K, Pober BR, Barnes P, Copel JA, Ogle EA, Duncan CC, et al. Fetal stroke. Pediatr Neurol. 2004;30(3):151-62.

87. Ballabh P. Intraventricular hemorrhage in premature infants: mechanism of disease. Pediatric research. 2010;67(1):1-8.

88. Rorke LB, Zimmerman RA. Prematurity, postmaturity, and destructive lesions in utero. AJNR American journal of neuroradiology. 1992;13(2):517-36.

89. Espinoza JP, Caradeux J, Norwitz ER, Illanes SE. Fetal and Neonatal Alloimmune Thrombocytopenia. Reviews in Obstetrics and Gynecology. 2013;6(1):e15-21.

90. Herman JH, Jumbelic MI, Ancona RJ, Kickler TS. In utero cerebral hemorrhage in alloimmune thrombocytopenia. The American journal of pediatric hematology/oncology. 1986;8(4):312-7.

91. Govaert P. Prenatal stroke. Seminars in Fetal and Neonatal Medicine. 2009;14(5):250-66.

92. Bhattacharya JJ, Thammaroj J. VEIN OF GALEN MALFORMATIONS. Journal of Neurology, Neurosurgery & Psychiatry. 2003;74(suppl 1):i42-i4.

93. Raybaud CA, Strother CM, Hald JK. Aneurysms of the vein of Galen: embryonic considerations and anatomical features relating to the pathogenesis of the malformation. Neuroradiology. 1989;31(2):109-28.

94. Byrd SE, Abramowicz JS, Kent P, Kimura RE, Elias D, Heydeman PT. Fetal MR imaging of posterior intracranial dural sinus thrombosis: a report of three cases with variable outcomes. Pediatric radiology. 2012;42(5):536-43.

95. Faye-Petersen OM, Crombleholme TM. Twin-to-twin transfusion syndrome. NeoReviews. 2008;9(9):e380-e92.

96. Kline-Fath BM, Calvo-Garcia MA, O'Hara SM, Crombleholme TM, Racadio JM. Twin–twin transfusion syndrome: cerebral ischemia is not the only fetal MR imaging finding. Pediatric radiology. 2007;37(1):47-56.

97. Mari G, Roberts A, Detti L, Kovanci E, Stefos T, Bahado-Singh RO, et al. Perinatal morbidity and mortality rates in severe twin-twin transfusion syndrome: Results of the International Amnioreduction Registry. American journal of obstetrics and gynecology. 2001;185(3):708-15.

98. Van Heteren CF, Nijhuis JG, Semmekrot BA, Mulders LG, Van Den Berg PP. Risk for surviving twin after fetal death of co-twin in twin–twin transfusion syndrome. Obstetrics & Gynecology. 1998;92(2):215-9.

99. Pharoah P, Adi Y. Consequences of in-utero death in a twin pregnancy. The Lancet. 2000;355(9215):1597-602.

100. 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.

101. Prayer D, Brugger PC, Kasprian G, Witzani L, Helmer H, Dietrich W, et al. MRI of fetal acquired brain lesions. Eur J Radiol. 2006;57(2):233-49.

102. Baldoli C, Righini A, Parazzini C, Scotti G, Triulzi F. Demonstration of acute ischemic lesions in the fetal brain by diffusion magnetic resonance imaging. Annals of neurology. 2002;52(2):243-6.

103. Canapicchi R, Cioni G, Strigini FAL, Abbruzzese A, Bartalena L, Lencioni G. Prenatal diagnosis of periventricular hemorrhage by fetal brain magnetic resonance imaging. Childs Nerv Syst. 1998;14(12):689-92.

104. Davis GH. Fetal hydrocephalus. Clinics in perinatology. 2003;30(3):531-9.

105. Cardoza JD, Goldstein RB, Filly RA. Exclusion of fetal ventriculomegaly with a single measurement: the width of the lateral ventricular atrium. Radiology. 1988;169(3):711-4.

106. McKechnie L, Vasudevan C, Levene M. Neonatal outcome of congenital ventriculomegaly. Seminars in fetal & neonatal medicine. 2012;17(5):301-7.

107. Beeghly M, Ware J, Soul J, du Plessis A, Khwaja O, Senapati GM, et al. Neurodevelopmental outcome of fetuses referred for ventriculomegaly. Ultrasound in obstetrics & gynecology : the official journal of the International Society of Ultrasound in Obstetrics and Gynecology. 2010;35(4):405-16.

108. Garel C, Luton D, Oury JF, Gressens P. Ventricular dilatations. Childs Nerv Syst. 2003;19(7-8):517-23.

109. Schrander-Stumpel C, Fryns JP. Congenital hydrocephalus: nosology and guidelines for clinical approach and genetic counselling. European journal of pediatrics. 1998;157(5):355-62.

110. Breeze AC, Alexander PM, Murdoch EM, Missfelder-Lobos HH, Hackett GA, Lees CC. Obstetric and neonatal outcomes in severe fetal ventriculomegaly. Prenat Diagn. 2007;27(2):124-9.

111. Vergani P, Locatelli A, Strobelt N, Cavallone M, Ceruti P, Paterlini G, et al. Clinical outcome of mild fetal ventriculomegaly. American journal of obstetrics and gynecology. 1998;178(2):218-22.

112. Manganaro L, Savelli S, Francioso A, Di Maurizio M, Coratella F, Vilella G, et al. Role of fetal MRI in the diagnosis of cerebral ventriculomegaly assessed by ultrasonography. La Radiologia medica. 2009;114(7):1013-23.

113. Griffiths PD, Reeves MJ, Morris JE, Mason G, Russell SA, Paley MN, et al. A prospective study of fetuses with isolated ventriculomegaly investigated by antenatal sonography and in utero MR imaging. AJNR American journal of neuroradiology. 2010;31(1):106-11.

114. Garel C, Alberti C. Coronal measurement of the fetal lateral ventricles: Comparison between ultrasonography and magnetic resonance imaging. Ultrasound in Obstetrics and Gynecology. 2006;27(1):23-7.

115. Levine D, Feldman HA, Tannus JF, Estroff JA, Magnino M, Robson CD, et al. Frequency and cause of disagreements in diagnoses for fetuses referred for ventriculomegaly. Radiology. 2008;247(2):516-27.

116. Girard NJ, Chaumoitre K. The brain in the belly: what and how of fetal neuroimaging? Journal of magnetic resonance imaging : JMRI. 2012;36(4):788-804.

117. Dashe JS, McIntire DD, Twickler DM. Maternal obesity limits the ultrasound evaluation of fetal anatomy. Journal of ultrasound in medicine : official journal of the American Institute of Ultrasound in Medicine. 2009;28(8):1025-30.

118. Michailidis GD, Papageorgiou P, Economides DL. Assessment of fetal anatomy in the first trimester using two- and three-dimensional ultrasound. The British journal of radiology. 2002;75(891):215-9.

119. Malinger G, Lev D, Lerman-Sagie T. Is fetal magnetic resonance imaging superior to neurosonography for detection of brain anomalies? Ultrasound in obstetrics & gynecology : the official journal of the International Society of Ultrasound in Obstetrics and Gynecology. 2002;20(4):317-21.

120. Amini H, Axelsson O, Raiend M, Wikstrom J. The clinical impact of fetal magnetic resonance imaging on management of CNS anomalies in the second trimester of pregnancy. Acta obstetricia et gynecologica Scandinavica. 2010;89(12):1571-81.

121. Antonsson P, Sundberg A, Kublickas M, Pilo C, Ghazi S, Westgren M, et al. Correlation between ultrasound and autopsy findings after 2nd trimester terminations of pregnancy. Journal of perinatal medicine. 2008;36(1):59-69.

122. Boyd PA, Tondi F, Hicks NR, Chamberlain PF. Autopsy after termination of pregnancy for fetal anomaly: retrospective cohort study. BMJ (Clinical research ed). 2004;328(7432):137.

123. Carroll SG, Porter H, Abdel-Fattah S, Kyle PM, Soothill PW. Correlation of prenatal ultrasound diagnosis and pathologic findings in fetal brain abnormalities. Ultrasound in obstetrics & gynecology : the official journal of the International Society of Ultrasound in Obstetrics and Gynecology. 2000;16(2):149-53.

124. Smith FW, Adam AH, Phillips WD. NMR imaging in pregnancy. Lancet. 1983;1(8314-5):61-2.

125. Johnson IR, Symonds EM, Kean DM, Worthington BS, Broughton Pipkin F, Hawkes RC, et al. Imaging the pregnant human uterus with nuclear magnetic resonance. American journal of obstetrics and gynecology. 1984;148(8):1136-9.

126. McCarthy SM, Filly RA, Stark DD, Callen PW, Golbus MS, Hricak H. Magnetic resonance imaging of fetal anomalies in utero: early experience. AJR American journal of roentgenology. 1985;145(4):677-82.

127. Sonigo PC, Rypens FF, Carteret M, Delezoide AL, Brunelle FO. MR imaging of fetal cerebral anomalies. Pediatric radiology. 1998;28(4):212-22.

128. Daffos F, Forestier F, Mac Aleese J, Aufrant C, Mandelbrot L, Cabanis EA, et al. Fetal curarization for prenatal magnetic resonance imaging. Prenat Diagn. 1988;8(4):312-4.

129. Levine D, Hatabu H, Gaa J, Atkinson MW, Edelman RR. Fetal anatomy revealed with fast MR sequences. AJR American journal of roentgenology. 1996;167(4):905-8.

130. Huisman TA, Martin E, Kubik-Huch R, Marincek B. Fetal magnetic resonance imaging of the brain: technical considerations and normal brain development. European radiology. 2002;12(8):1941-51.

131. Westbrook C, Kaut Roth C, Talbot J. MRI in Practice. Third Edition ed. Oxford UK: Blackwell Publishing Ltd; 2006 2006. 1- 410 p.

132. Chavhan GB, Babyn PS, Jankharia BG, Cheng HL, Shroff MM. Steady-state MR imaging sequences: physics, classification, and clinical applications. Radiographics : a review publication of the Radiological Society of North America, Inc. 2008;28(4):1147-60.

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

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

135. 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 : the official journal of the International Society of Ultrasound in Obstetrics and Gynecology. 2007;30(3):318-24.

136. Edwards MJ, Saunders RD, Shiota K. Effects of heat on embryos and foetuses. International journal of hyperthermia : the official journal of European Society for Hyperthermic Oncology, North American Hyperthermia Group. 2003;19(3):295-324.

137. Formica D, Silvestri S. Biological effects of exposure to magnetic resonance imaging: an overview. Biomedical engineering online. 2004;3:11.

138. Hepper PG, Shahidullah BS. Development of fetal hearing. Archives of disease in childhood. 1994;71(2):F81-7.

139. Glover P, Hykin J, Gowland P, Wright J, Johnson I, Mansfield P. An assessment of the intrauterine sound intensity level during obstetric echo-planar magnetic resonance imaging. The British journal of radiology. 1995;68(814):1090-4.

140. Gerhardt KJ, Pierson LL, Huang X, Abrams RM, Rarey KE. Effects of intense noise exposure on fetal sheep auditory brain stem response and inner ear histology. Ear and hearing. 1999;20(1):21-32.

141. Kok RD, de Vries MM, Heerschap A, van den Berg PP. Absence of harmful effects of magnetic resonance exposure at 1.5 T in utero during the third trimester of pregnancy: a follow-up study. Magnetic resonance imaging. 2004;22(6):851-4.

142. 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.

143. 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.
144. Church CC, Miller MW. Quantification of risk from fetal exposure to diagnostic ultrasound. Progress in biophysics and molecular biology. 2007;93(1-3):331-53.

145. Chambers CD, Johnson KA, Dick LM, Felix RJ, Jones KL. Maternal fever and birth outcome: a prospective study. Teratology. 1998;58(6):251-7.

146. Graham JM, Jr., Edwards MJ, Edwards MJ. Teratogen update: gestational effects of maternal hyperthermia due to febrile illnesses and resultant patterns of defects in humans. Teratology. 1998;58(5):209-21.

147. 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 : JMRI. 2013;37(3):501-30.

148. MHRA. Safety Guidelines for Magnetic Resonance Imaging Equipment in Clinical Use. 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.

149. ICNIRP TICoN-IRP. Icnirp Statement Related to the Use of Security and Similar Devices Utilizing Electromagnetic Fields. Health Physics. 2004;87(2):187-96.

150. Bekiesinska-Figatowska M. Fetal MRI: Is it safe? Journal of Pediatric Neuroradiology. 2012;1(3):155-9.

151. Glasziou P, Irwig L, Deeks JJ. When should a new test become the current reference standard? Annals of internal medicine. 2008;149(11):816-22.

152. Fryback DG, Thornbury JR. The efficacy of diagnostic imaging. Medical decision making : an international journal of the Society for Medical Decision Making. 1991;11(2):88-94.

153. Metz CE. ROC analysis in medical imaging: a tutorial review of the literature. Radiological physics and technology. 2008;1(1):2-12.

154. Alberg AJ, Park JW, Hager BW, Brock MV, Diener-West M. The use of "overall accuracy" to evaluate the validity of screening or diagnostic tests. Journal of general internal medicine. 2004;19(5 Pt 1):460-5.

155. Simundic A. Measures of diagnostic accuracy: basic definitions. eJIFCC 2008; 19 (4). Avialable at http://www ifcc org/ Verified October. 2013.

156. Altman DG, Bland JM. Statistics Notes: Diagnostic tests 2: predictive values. BMJ (Clinical research ed). 1994;309(6947):102.

157. Breeze AC, Cross JJ, Hackett GA, Jessop FA, Joubert I, Lomas DJ, et al. Use of a confidence scale in reporting postmortem fetal magnetic resonance imaging. Ultrasound in obstetrics & gynecology : the official journal of the International Society of Ultrasound in Obstetrics and Gynecology. 2006;28(7):918-24.

158. Ng CS, Palmer CR. Analysis of diagnostic confidence and diagnostic accuracy: a unified framework. The British journal of radiology. 2007;80(951):152-60.

159. Meyer AN, Payne VL, Meeks DW, Rao R, Singh H. Physicians' diagnostic accuracy, confidence, and resource requests: a vignette study. JAMA internal medicine. 2013;173(21):1952-8.

160. Berner ES, Graber ML. Overconfidence as a cause of diagnostic error in medicine. The American journal of medicine. 2008;121(5 Suppl):S2-23.

161. Rosenquist CJ. Pitfalls in the use of diagnostic tests. Clin Radiol. 1989;40(5):448-50.
162. Gazelle GS, McMahon PM, Siebert U, Beinfeld MT. Cost-effectiveness analysis in the assessment of diagnostic imaging technologies. Radiology. 2005;235(2):361-70.

163. NICE NIfHaCE. Guide to the methods of technology appraisal 2013. http://publications.nice.org.uk/pmg92013.

164. Chung JH, Pelayo R, Hatfield TJ, Speir VJ, Wu J, Caughey AB. Limitations of the fetal anatomic survey via ultrasound in the obese obstetrical population. The journal of maternal-fetal & neonatal medicine : the official journal of the European Association of Perinatal Medicine, the Federation of Asia and Oceania Perinatal Societies, the International Society of Perinatal Obstet. 2012;25(10):1945-9.

165. Whitby EH, Paley MN, Sprigg A, Rutter S, Davies NP, Wilkinson ID, et al. Comparison of ultrasound and magnetic resonance imaging in 100 singleton pregnancies with suspected brain abnormalities. BJOG: An International Journal of Obstetrics & Gynaecology. 2004;111(8):784-92.

166. Papaioannou G, Loggitsi D, Kampas I. Imaging findings and utility of fetal central nervous system MRI. Pediatric radiology. 2010;40 (6):1126.

167. Patenaude Y, Pugash D, Lim K, Morin L, Lim K, Bly S, et al. The use of magnetic resonance imaging in the obstetric patient. Journal of obstetrics and gynaecology Canada : JOGC = Journal d'obstetrique et gynecologie du Canada : JOGC. 2014;36(4):349-55.

168. Nabavizadeh SA, Zarnow D, Bilaniuk LT, Schwartz ES, Zimmerman RA, Vossough A. Correlation of Prenatal and Postnatal MRI Findings in Schizencephaly. AJNR American journal of neuroradiology. 2014.

169. Egana-Ugrinovic G, Sanz-Cortes M, Couve-Perez C, Figueras F, Gratacos E. Corpus callosum differences assessed by fetal MRI in late-onset intrauterine growth restriction and its association with neurobehavior. Prenat Diagn. 2014.

170. Kubik-Huch RA, Huisman TA, Wisser J, Gottstein-Aalame N, Debatin JF, Seifert B, et al. Ultrafast MR imaging of the fetus. AJR American journal of roentgenology. 2000;174(6):1599-606.

171. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. Journal of clinical epidemiology. 2009;62(10):1006-12.

172. Rossi AC, 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 in Obstetrics & Gynecology. 2014;44(4):388-93.

173. van Doorn M, Oude Rengerink K, Newsum EA, Reneman L, Majoie CB, Pajkrt E. Added value of fetal MRI in fetuses with suspected brain abnormalities on

neurosonography: a systematic review and meta-analysis. The Journal of Maternal-Fetal & Neonatal Medicine. 2015:1-13.

174. Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gotzsche PC, Ioannidis JP, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. Journal of clinical epidemiology. 2009;62(10):e1-34.

175. Whiting PF, Rutjes AW, Westwood ME, Mallett S, Deeks JJ, Reitsma JB, et al. QUADAS-2: a revised tool for the quality assessment of diagnostic accuracy studies. Annals of internal medicine. 2011;155(8):529-36.

176. Corp LS. Stata Statistical Software Release 12. 2011.

177. Elbourne DR, Altman DG, Higgins JP, Curtin F, Worthington HV, Vail A. Meta-analyses involving cross-over trials: methodological issues. International journal of epidemiology. 2002;31(1):140-9.

178. Becker MP, Balagtas CC. Marginal modeling of binary cross-over data. Biometrics. 1993:997-1009.

179. Higgins J, Thompson SG. Quantifying heterogeneity in a meta-analysis. Statistics in medicine. 2002;21(11):1539-58.

180. DerSimonian R, Laird N. Meta-analysis in clinical trials. Controlled clinical trials. 1986;7(3):177-88.

181. Benacerraf BR, Shipp TD, Bromley B, Levine D. What does magnetic resonance imaging add to the prenatal sonographic diagnosis of ventricidomegaly? Journal of Ultrasound in Medicine. 2007;26(11):1513-22.

182. Benoist G, Salomon LJ, Mohlo M, Suarez B, Jacquemard F, Ville Y. Cytomegalovirus-related fetal brain lesions: Comparison between targeted ultrasound examination and magnetic resonance imaging. Ultrasound in Obstetrics and Gynecology. 2008;32(7):900-5.

183. Blaicher W, Prayer D, Bernaschek G. Magnetic resonance imaging and ultrasound in the assessment of the fetal central nervous system. Journal of perinatal medicine. 2003;31(6):459-68.

184. Colleoni GG, Contro E, Carletti A, Ghi T, Campobasso G, Rembouskos G, et al. Prenatal diagnosis and outcome of fetal posterior fossa fluid collections. Ultrasound in Obstetrics & Gynecology. 2012;39(6):625-31.

185. Frates MC. Fetal Anomalies: Comparison of MR Imaging and US for Diagnosis. Radiology. 2004;232(2):398-404.

186. Garcia-Flores J, Recio M, Uriel M, Canamares M, Cruceyra M, Tamarit I, et al. Fetal magnetic resonance imaging and neurosonography in congenital neurological anomalies: Supplementary diagnostic and postnatal prognostic value. Journal of Maternal-Fetal and Neonatal Medicine. 2013;26(15):1517-23.

187. Hagmann CF, Robertson NJ, Leung WC, Chong KW, Chitty LS. Foetal brain imaging: ultrasound or MRI. A comparison between magnetic resonance imaging and

a dedicated multidisciplinary neurosonographic opinion. Acta Paediatr. 2008;97(4):414-9.

188. Hamisa M, Dabees N, Ataalla WM, Ziada DH. Magnetic resonance imaging versus Ultrasound examination in detection of prenatal fetal brain anomalies. Egyptian Journal of Radiology and Nuclear Medicine. 2013;44(3):665-72.

189. Hosny IA, Elghawabi HS. Ultrafast MRI of the fetus: an increasingly important tool in prenatal diagnosis of congenital anomalies. Magnetic resonance imaging. 2010;28(10):1431-9.

190. Ismail KM, Ashworth JR, Martin WL, Chapman S, McHugo J, Whittle MJ, et al. Fetal magnetic resonance imaging in prenatal diagnosis of central nervous system abnormalities: 3-year experience. The journal of maternal-fetal & neonatal medicine : the official journal of the European Association of Perinatal Medicine, the Federation of Asia and Oceania Perinatal Societies, the International Society of Perinatal Obstet. 2002;12(3):185-90.

191. Kul S, Korkmaz HA, Cansu A, Dinc H, Ahmetoglu A, Guven S, et al. Contribution of MRI to ultrasound in the diagnosis of fetal anomalies. Journal of magnetic resonance imaging : JMRI. 2012;35(4):882-90.

192. Lipitz S, Hoffmann C, Feldman B, Tepperberg-Dikawa M, Schiff E, Weisz B. Value of prenatal ultrasound and magnetic resonance imaging in assessment of congenital primary cytomegalovirus infection. Ultrasound in obstetrics & gynecology : the official journal of the International Society of Ultrasound in Obstetrics and Gynecology. 2010;36(6):709-17.

193. Malinger G, Ben-Sira L, Lev D, Ben-Aroya Z, Kidron D, Lerman-Sagie T. Fetal brain imaging: A comparison between magnetic resonance imaging and dedicated neurosonography. Ultrasound in Obstetrics and Gynecology. 2004;23(4):333-40.

194. Manganaro L, Bernardo S, La Barbera L, Noia G, Masini L, Tomei A, et al. Role of foetal MRI in the evaluation of ischaemic-haemorrhagic lesions of the foetal brain. Journal of perinatal medicine. 2012;40(4):419-26.

195. Paladini D, Quarantelli M, Sglavo G, Pastore G, Cavallaro A, D'Armiento MR, et al. Accuracy of neurosonography and MRI in clinical management of fetuses referred with central nervous system abnormalities. Ultrasound in obstetrics & gynecology : the official journal of the International Society of Ultrasound in Obstetrics and Gynecology. 2014;44(2):188-96.

196. Peruzzi P, Corbitt RJ, Raffel C. Magnetic resonance imaging versus ultrasonography for the in utero evaluation of central nervous system anomalies. Journal of neurosurgery Pediatrics. 2010;6(4):340-5.

197. Phua HT, Chiou LO, Stringer D, Tan JVK, Yeo GSH. Magnetic resonance imaging of the fetal central nervous system in Singapore. Annals of the Academy of Medicine Singapore. 2009;38(9):774-81.

198. Rajeswaran R, Chandrasekharan A, Joseph S, Venkata Sai P, Dev B, Reddy S. Ultrasound versus MRI in the diagnosis of fetal head and trunk anomalies. The Journal of Maternal-Fetal & Neonatal Medicine. 2009;22(2):115-23.

199. Resta M, Greco P, D'Addario V, Florio C, Dardes N, Caruso G, et al. Magnetic resonance imaging in pregnancy: study of fetal cerebral malformations. Ultrasound in Obstetrics & Gynecology. 1994;4(1):7-20.

200. Rubod C, Robert Y, Tillouche N, Devisme L, Houfflin-Debarge V, Puech F. Role of fetal ultrasound and magnetic resonance imaging in the prenatal diagnosis of migration disorders. Prenatal Diagnosis. 2005;25(13):1181-7.

201. Saleem SN, Said AH, Abdel-Raouf M, El-Kattan EA, Zaki MS, Madkour N, et al. Fetal MRI in the evaluation of fetuses referred for sonographically suspected neural tube defects (NTDs): Impact on diagnosis and management decision. Neuroradiology. 2009;51(11):761-72.

202. Simon EM, Goldstein RB, Coakley FV, Filly RA, Broderick KC, Musci TJ, et al. Fast MR imaging of fetal CNS anomalies in utero. AJNR American journal of neuroradiology. 2000;21(9):1688-98.

203. Sohn YS, Kim MJ, Kwon JY, Kim YH, Park YW. The usefulness of fetal MRI for prenatal diagnosis. Yonsei medical journal. 2007;48(4):671-7.

204. Twickler DM, Magee KP, Caire J, Zaretsky M, Fleckenstein JL, Ramus RM. Second-opinion magnetic resonance imaging for suspected fetal central nervous system abnormalities. American journal of obstetrics and gynecology. 2003;188(2):492-6.

205. Wang GB, Shan RQ, Ma YX, Shi H, Chen LG, Liu W, et al. Fetal central nervous system anomalies: Comparison of magnetic resonance imaging and ultrasonography for diagnosis. Chinese Medical Journal. 2006;119(15):1272-7.

206. We JS, Young L, Park IY, Shin JC, Im SA. Usefulness of additional fetal magnetic resonance imaging in the prenatal diagnosis of congenital abnormalities. Archives of gynecology and obstetrics. 2012;286(6):1443-52.

207. Whitby EH, Paley MN, Sprigg A, Rutter S, Davies NP, Wilkinson ID, et al. Comparison of ultrasound and magnetic resonance imaging in 100 singleton pregnancies with suspected brain abnormalities. BJOG : an international journal of obstetrics and gynaecology. 2004;111(8):784-92.

208. Whitby EH, Variend S, Rutter S, Paley MNJ, Wilkinson ID, Davies NP, et al. Corroboration of in utero MRI using post-mortem MRI and autopsy in foetuses with CNS abnormalities. Clinical Radiology. 2004;59(12):1114-20.

209. Yuh WT, Nguyen HD, Fisher DJ, Tali ET, Gao F, Simonson TM, et al. MR of fetal central nervous system abnormalities. Ajnr: American Journal of Neuroradiology. 1994;15(3):459-64.

210. Manganaro L, Bernardo S, La Barbera L, Noia G, Masini L, Tomei A, et al. Role of foetal MRI in the evaluation of ischaemic-haemorrhagic lesions of the foetal brain. Journal of perinatal medicine. 2012;40(4):419-26.

211. Resta M, Greco P, Daddario V, Florio C, Dardes N, Caruso G, et al. MAGNETIC-RESONANCE-IMAGING IN PREGNANCY - STUDY OF FETAL CEREBRAL MALFORMATIONS. Ultrasound in Obstetrics & Gynecology. 1994;4(1):7-20.

212. Saleem SN, Said AH, Abdel-Raouf M, El-Kattan EA, Zaki MS, Madkour N, et al. Fetal MRI in the evaluation of fetuses referred for sonographically suspected neural tube

defects (NTDs): impact on diagnosis and management decision. Neuroradiology. 2009;51(11):761-72.

213. Twickler DM, Magee KP, Caire J, Zaretsky M, Fleckenstein JL, Ramus RM. Second-opinion magnetic resonance imaging for suspected fetal central nervous system abnormalities. American journal of obstetrics and gynecology. 2003;188(2):492-6.

214. Malinger G, Ben-Sira L, Lev D, Ben-Aroya Z, Kidron D, Lerman-Sagie T. Fetal brain imaging: a comparison between magnetic resonance imaging and dedicated neurosonography. Ultrasound in obstetrics & gynecology : the official journal of the International Society of Ultrasound in Obstetrics and Gynecology. 2004;23(4):333-40.

215. Garcia-Flores J, Recio M, Uriel M, Canamares M, Cruceyra M, Tamarit I, et al. Fetal magnetic resonance imaging and neurosonography in congenital neurological anomalies: supplementary diagnostic and postnatal prognostic value. Journal of Maternal-Fetal & Neonatal Medicine. 2013;26(15):1517-23.

216. Wang GB, Shan RQ, Ma YX, Shi H, Chen LG, Liu W, et al. Fetal central nervous system anomalies: comparison of magnetic resonance imaging and ultrasonography for diagnosis. Chin Med J (Engl). 2006;119(15):1272-7.

217. Whitby EH, Variend S, Rutter S, Paley MN, Wilkinson ID, Davies NP, et al. Corroboration of in utero MRI using post-mortem MRI and autopsy in foetuses with CNS abnormalities. Clinical Radiology. 2004;59(12):1114-20.

218. Frates MC, Kumar AJ, Benson CB, Ward VL, Tempany CM. Fetal anomalies: comparison of MR imaging and US for diagnosis. Radiology. 2004;232(2):398-404.

219. Garcia-Flores J, Recio M, Uriel M, Canamares M, Cruceyra M, Tamarit I, et al. Fetal magnetic resonance imaging and neurosonography in congenital neurological anomalies: supplementary diagnostic and postnatal prognostic value. The journal of maternal-fetal & neonatal medicine : the official journal of the European Association of Perinatal Medicine, the Federation of Asia and Oceania Perinatal Societies, the International Society of Perinatal Obstet. 2013;26(15):1517-23.

220. Hagmann CF, Robertson NJ, Leung WC, Chong KW, Chitty LS. Foetal brain imaging: ultrasound or MRI. A comparison between magnetic resonance imaging and a dedicated multidisciplinary neurosonographic opinion. Acta Paediatrica. 2008;97(4):414-9.

221. We JS, Young L, Park IY, Shin JC, Im SA. Usefulness of additional fetal magnetic resonance imaging in the prenatal diagnosis of congenital abnormalities. Archives of gynecology and obstetrics. 2012;286(6):1443-52.

222. Blaicher W, Prayer D, Mittermayer C, Pollak A, Bernert G, Deutinger J, et al. Magnetic resonance imaging in foetuses with bilateral moderate ventriculomegaly and suspected anomaly the corpus callosum on ultrasound scan. Ultraschall in Der Medizin. 2003;24(4):255-60.

223. Doneda C, Parazzini C, Righini A, Rustico M, Tassis B, Fabbri E, et al. Early cerebral lesions in cytomegalovirus infection: Prenatal MR imaging. Radiology. 2010;255(2):613-21.

224. Malinger G, Lev D, Ben-Sira L, Hoffmann C, Herrera M, Vinals F, et al. Can syndromic macrocephaly be diagnosed in utero? Ultrasound in Obstetrics & Gynecology. 2011;37(1):72-81.

225. Higgins JPT, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. BMJ (Clinical research ed). 2003;327(7414):557-60.

226. NIHR. Magnetic resonance imaging to enhance the diagnosis of fetal developmental brain abnormalities in utero http://www.nets.nihr.ac.uk/projects/hta/090601: NIHR; 2011 [

227. Eshed I, Althoff CE, Hamm B, Hermann K-GA. Claustrophobia and premature termination of magnetic resonance imaging examinations. Journal of Magnetic Resonance Imaging. 2007;26(2):401-4.

228. Dewey M, Schink T, Dewey CF. Frequency of referral of patients with safety-related contraindications to magnetic resonance imaging. European Journal of Radiology.63(1):124-7.

229. Anzilotti K, Jr., Schweitzer ME, Hecht P, Wapner K, Kahn M, Ross M. Effect of foot and ankle MR imaging on clinical decision making. Radiology. 1996;201(2):515-7.

230. Omary RA, Kaplan PA, Dussault RG, Hornsby PP, Carter CT, Kahler DM, et al. The impact of ankle radiographs on the diagnosis and management of acute ankle injuries. Academic radiology. 1996;3(9):758-65.

231. Likert R. A technique for the measurement of attitudes. Archives of Psychology. 1932;22 140:55.

232. Bigley J, Griffiths PD, Prydderch A, Romanowski CA, Miles L, Lidiard H, et al. Neurolinguistic programming used to reduce the need for anaesthesia in claustrophobic patients undergoing MRI. The British journal of radiology. 2010;83(986):113-7.

233. Parikh R, Mathai A, Parikh S, Chandra Sekhar G, Thomas R. Understanding and using sensitivity, specificity and predictive values. Indian Journal of Ophthalmology. 2008;56(1):45-50.

234. 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.

235. Lange K, Brunner E. Analysis of predictive values based on individual risk factors in multi-modality trials. Diagnostics. 2013;3(1):192-209.

236. NICE Clinical Guidelines N. Antenatal Care: Routine Care for the Healthy Pregnant Woman. In: (UK). NCCfWsaCsH, editor. London: RCOG Press; 2008. p. 1-454.

237. Malhotra RK, Indrayan A. A simple nomogram for sample size for estimating sensitivity and specificity of medical tests. Indian Journal of Ophthalmology. 2010;58(6):519-22.

238. Statistics OfN. Conceptions in England and Wales: 2015 https://www.ons.gov.uk/peoplepopulationandcommunity/birthsdeathsandmarriages/conceptionandfertilityrates/bulletins/conceptionstatistics/20152017 [

239. Leeflang MMG, Rutjes AWS, Reitsma JB, Hooft L, Bossuyt PMM. Variation of a test's sensitivity and specificity with disease prevalence. CMAJ : Canadian Medical Association Journal. 2013;185(11):E537-E44.

240. Salomon LJ, Ouahba J, Delezoide AL, Vuillard E, Oury JF, Sebag G, et al. Third-trimester fetal MRI in isolated 10- to 12-mm ventriculomegaly: is it worth it? BJOG : an international journal of obstetrics and gynaecology. 2006;113(8):942-7.

241. SUN Z-y, XIA L-m, PANG Y. Preliminary application of three dimensional magnetic resonance imaging of fetus. Radiologic Practice. 2011;9:029.

242. Pang Y, Xia L-M, Sun Z-Y, Chen X-L, Yang X-H. 3 D MRI investigation on fetal surface malformations. Chinese Journal of Magnetic Resonance Imaging. 2012;3(3):194-9.

243. Liu J, Glenn OA, Xu D. Fast, free-breathing, in vivo fetal imaging using time-resolved 3D MRI technique: preliminary results. Quantitative imaging in medicine and surgery. 2014;4(2):123-8.

244. Studholme C. Mapping fetal brain development in utero using magnetic resonance imaging: the Big Bang of brain mapping. Annual review of biomedical engineering. 2011;13:345-68.

245. 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.

246. Reeder SB, Du YP, Lima JA, Bluemke DA. Advanced cardiac MR imaging of ischemic heart disease. Radiographics : a review publication of the Radiological Society of North America, Inc. 2001;21(4):1047-74.

247. Slavin GS, Saranathan M. FIESTA-ET: High-resolution cardiac imaging using echo-planar steady-state free precession. Magnetic Resonance in Medicine. 2002;48(6):934-41.

248. De Salles AA, Solberg TD, Pedroso A, Espinoza D, Villablanca P. Three-dimensional fast imaging employing steady-state acquisition magnetic resonance imaging for stereotactic radiosurgery of trigeminal neuralgia. Neurosurgery. 2005;56(3):E628.

249. Hatipoglu HG, Durakoglugil T, Ciliz D, Yüksel E. Comparison of FSE T2W and 3D FIESTA sequences in the evaluation of posterior fossa cranial nerves with MR cisternography. Diagnostic and interventional radiology. 2007;13(2):56.

250. Nemoto O, Fujikawa A, Tachibana A. Three-dimensional fast imaging employing steady-state acquisition MRI and its diagnostic value for lumbar foraminal stenosis. European Journal of Orthopaedic Surgery & Traumatology. 2014;24(1):209-14.

251. Chung H-W, Chen C-Y, Zimmerman RA, Lee K-W, Lee C-C, Chin S-C. T2-Weighted Fast MR Imaging with True FISP Versus HASTE. American Journal of Roentgenology. 2000;175(5):1375-80.

252. Barrett H MK. Foundations of Image Science. Salah BEA, editor. New Jersey USA: John Wiley and Sons; 2004.

253. 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.

254. Chang CH, Yu CH, Chang FM, Ko HC, Chen HY. The assessment of normal fetal brain volume by 3-D ultrasound. Ultrasound in medicine & biology. 2003;29(9):1267-72.

255. Benavides-Serralde A, Hernandez-Andrade E, Fernandez-Delgado J, Plasencia W, Scheier M, Crispi F, et al. Three-dimensional sonographic calculation of the volume of intracranial structures in growth-restricted and appropriate-for-gestational age fetuses. Ultrasound in obstetrics & gynecology : the official journal of the International Society of Ultrasound in Obstetrics and Gynecology. 2009;33(5):530-7.

256. Endres LK, Cohen L. Reliability and validity of three-dimensional fetal brain volumes. Journal of ultrasound in medicine. 2001;20(12):1265-9.

257. Gong QY, Roberts N, Garden AS, Whitehouse GH. Fetal and Fetal Brain Volume Estimation in the Third Trimester of Human Pregnancy Using Gradient Echo MR Imaging. Magnetic resonance imaging.16(3):235-40.

258. Andreas T, Wedegartner U, Tchirikov M, Hecher K, Schroder HJ. Fetal brain volume measurements by magnetic resonance imaging. Ultrasound in obstetrics & gynecology : the official journal of the International Society of Ultrasound in Obstetrics and Gynecology. 2006;27(5):588-9.

259. Duncan KR, Issa B, Moore R, Baker PN, Johnson IR, Gowland PA. A comparison of fetal organ measurements by echo-planar magnetic resonance imaging and ultrasound. BJOG: An International Journal of Obstetrics & Gynaecology. 2005;112(1):43-9.

260. Kazan-Tannus JF, Dialani V, Kataoka ML, Chiang G, Feldman HA, Brown JS, et al. MR volumetry of brain and CSF in fetuses referred for ventriculomegaly. AJR American journal of roentgenology. 2007;189(1):145-51.

261. Rousseau F, Glenn O, Iordanova B, Rodriguez-Carranza C, Vigneron D, Barkovich J, et al. A novel approach to high resolution fetal brain MR imaging. In: Duncan JS, Gerig G, editors. Medical Image Computing and Computer-Assisted Intervention - Miccai 2005, Pt 1. Lecture Notes in Computer Science. 37492005. p. 548-55.

262. 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.

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

264. 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.

265. 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 GM, editors. Computational Intelligence Methods for Bioinformatics and Biostatistics. Lecture Notes in Bioinformatics. 54882009. p. 188-+.

266. Kim K, Habas PA, Rousseau F, Glenn OA, Barkovich AJ, Studholme C. Intersection based motion correction of multislice MRI for 3-D in utero fetal brain image formation. IEEE transactions on medical imaging. 2010;29(1):146-58.

267. Studholme C, Rousseau F. Quantifying and modelling tissue maturation in the living human fetal brain. International journal of developmental neuroscience : the official journal of the International Society for Developmental Neuroscience. 2014;32:3-10.

268. 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.

269. Habas PA, Kim K, Rousseau F, Glenn OA, Barkovich AJ, Studholme C. Atlas-based segmentation of the germinal matrix from in utero clinical MRI of the fetal brain. Medical image computing and computer-assisted intervention : MICCAI International Conference on Medical Image Computing and Computer-Assisted Intervention. 2008;11(Pt 1).

270. 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.

271. Gholipour A, Akhondi-Asl A, Estroff JA, Warfield SK. Multi-atlas multi-shape segmentation of fetal brain MRI for volumetric and morphometric analysis of ventriculomegaly. NeuroImage. 2012;60(3):1819-31.

272. Rousseau F, Habas PA, Studholme C. A supervised patch-based approach for human brain labeling. IEEE transactions on medical imaging. 2011;30(10):1852-62.

273. 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 PAPI. 2012:97-104.

274. Habas PA, Kim K, Rousseau F, Glenn OA, Barkovich AJ, Studholme C. A spatio-temporal atlas of the human fetal brain with application to tissue segmentation. Medical image computing and computer-assisted intervention : MICCAI International Conference on Medical Image Computing and Computer-Assisted Intervention. 2009;12(Pt 1):289-96.

275. Habas PA, Scott JA, Roosta A, Rajagopalan V, Kim K, Rousseau F, et al. Early folding patterns and asymmetries of the normal human brain detected from in utero MRI. Cerebral cortex (New York, NY : 1991). 2012;22(1):13-25.

276. 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 journal of developmental neuroscience : the official journal of the International Society for Developmental Neuroscience. 2011;29(5):529-36.

277. Scott JA, Habas PA, Rajagopalan V, Kim K, Barkovich AJ, Glenn OA, et al. Volumetric and surface-based 3D MRI analyses of fetal isolated mild ventriculomegaly : Brain morphometry in ventriculomegaly. Brain structure & function. 2013;218(3):645-55.

278. Gholipour A, Akhondi-Asl A, Estroff JA, Warfield SK. Multi-atlas multi-shape segmentation of fetal brain MRI for volumetric and morphometric analysis of ventriculomegaly. NeuroImage. 2012;60(3):1819-31.

279. Keraudren K, Kuklisova-Murgasova M, Kyriakopoulou V, Malamateniou C, Rutherford MA, Kainz B, et al. Automated fetal brain segmentation from 2D MRI slices for motion correction. NeuroImage. 2014;101:633-43.

280. Kainz B, Keraudren K, Kyriakopoulou V, Rutherford M, Hajnal JV, Rueckert D, editors. Fast fully automatic brain detection in fetal MRI using dense rotation invariant image descriptors. 2014 IEEE 11th International Symposium on Biomedical Imaging (ISBI); 2014 April 29 2014-May 2 2014.

281. Damodaram MS, Story L, Eixarch E, Patkee P, Patel A, Kumar S, et al. Foetal volumetry using magnetic resonance imaging in intrauterine growth restriction. Early human development. 2012;88 Suppl 1:S35-40.

282. Paddock M, Akram R, Jarvis DA, Armitage P, Song S, Madhuvrata P, et al. The assessment of fetal brain growth in diabetic pregnancy using in utero magnetic resonance imaging. Clin Radiol. 2017.

283. 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.

284. Phillips JB, Billson VR, Forbes AB. Autopsy standards for fetal lengths and organ weights of an Australian perinatal population. Pathology. 2009;41(6):515-26.

285. Breeze AC, Gallagher FA, Lomas DJ, Smith GC, Lees CC. Postmortem fetal organ volumetry using magnetic resonance imaging and comparison to organ weights at conventional autopsy. Ultrasound in obstetrics & gynecology : the official journal of the International Society of Ultrasound in Obstetrics and Gynecology. 2008;31(2):187-93.

286. Anquez J, Angelini E, Bloch I, Merzoug V, Bellaiche-Millischer A-E, Adamsbaum C, editors. Interest of the Steady State Free Precession (SSFP) sequence for 3D modeling of the whole fetus. Engineering in Medicine and Biology Society, 2007 EMBS 2007 29th Annual International Conference of the IEEE; 2007: IEEE.

287. Schierlitz L, Dumanli H, Robinson JN, Burrows PE, Schreyer AG, Kikinis R, et al. Three-dimensional magnetic resonance imaging of fetal brains. Lancet. 2001;357(9263):1177-8.

288. Oyama R, Jakab M, Kikuchi A, Sugiyama T, Kikinis R, Pujol S. Towards improved ultrasound-based analysis and 3D visualization of the fetal brain using the 3D Slicer. Ultrasound in obstetrics & gynecology : the official journal of the International Society of Ultrasound in Obstetrics and Gynecology. 2013;42(5):609-10.

289. Kainz B, Steinberger M, Wein W, Kuklisova-Murgasova M, Malamateniou C, Keraudren K, et al. Fast Volume Reconstruction From Motion Corrupted Stacks of 2D Slices. IEEE transactions on medical imaging. 2015;34(9):1901-13.

290. Rajagopalan V, Scott J, Habas PA, Kim K, Corbett-Detig J, Rousseau F, et al. Local tissue growth patterns underlying normal fetal human brain gyrification quantified in

utero. The Journal of neuroscience : the official journal of the Society for Neuroscience. 2011;31(8):2878-87.

291. Clouchoux C, Kudelski D, Gholipour A, Warfield SK, Viseur S, Bouyssi-Kobar M, et al. Quantitative in vivo MRI measurement of cortical development in the fetus. Brain structure & function. 2012;217(1):127-39.

292. Vatansever D, Kyriakopoulou V, Allsop JM, Fox M, Chew A, Hajnal JV, et al. Multidimensional analysis of fetal posterior fossa in health and disease. Cerebellum (London, England). 2013;12(5):632-44.

293. Scott JA, Hamzelou KS, Rajagopalan V, Habas PA, Kim K, Barkovich AJ, et al. 3D morphometric analysis of human fetal cerebellar development. Cerebellum (London, England). 2012;11(3):761-70.

294. Clouchoux C, Guizard N, Evans AC, du Plessis AJ, Limperopoulos C. Normative fetal brain growth by quantitative in vivo magnetic resonance imaging. American journal of obstetrics and gynecology. 2012;206(2).

295. Egana-Ugrinovic G, Sanz-Cortes M, Figueras F, Bargallo N, Gratacos E. Differences in cortical development assessed by fetal MRI in late-onset intrauterine growth restriction. American journal of obstetrics and gynecology. 2013;209(2):126 e1-8.

296. Jarvis DA, Armitage P, Dean A, Griffiths PD. Surface reconstructions of foetal brain abnormalities using ultrafast steady state 3D acquisitions. Clin Radiol. 2014.

297. Jarvis D, Griffiths PD. Clinical applications of 3D volume MR imaging of the fetal brain in utero. Prenatal Diagnosis. 2017.

298. Garel C, Chantrel E, Brisse H, Elmaleh M, Luton D, Oury JF, et al. Fetal cerebral cortex: normal gestational landmarks identified using prenatal MR imaging. AJNR American journal of neuroradiology. 2001;22(1):184-9.

299. Garel C, Chantrel E, Elmaleh M, Brisse H, Sebag G. Fetal MRI: normal gestational landmarks for cerebral biometry, gyration and myelination. Childs Nervous System. 2003;19(7-8):422-5.

300. Griffiths PD, Brackley K, Bradburn M, Connolly DJ, Gawne-Cain ML, Griffiths DI, et al. Anatomical subgroup analysis of the MERIDIAN cohort: failed commissuration. Ultrasound in Obstetrics & Gynecology. 2017.

301. Williams F, Griffiths PD. In utero MR imaging in fetuses at high risk of lissencephaly. The British journal of radiology. 2017;90(0):20160902.

302. 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. Lancet. 2017;389(10068):538-46.

303. Pier DB, Levine D, Kataoka ML, Estroff JA, Werdich XQ, Ware J, et al. Magnetic resonance volumetric assessments of brains in fetuses with ventriculomegaly correlated to outcomes. Journal of ultrasound in medicine : official journal of the American Institute of Ultrasound in Medicine. 2011;30(5):595-603.

304. Grossman R, Hoffman C, Mardor Y, Biegon A. Quantitative MRI measurements of human fetal brain development in utero. NeuroImage. 2006;33(2):463-70.

305. 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.

306. 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.

307. Hatab MR, Kamourieh SW, Twickler DM. MR volume of the fetal cerebellum in relation to growth. Journal of Magnetic Resonance Imaging. 2008;27(4):840-5.

308. Tilea B, Alberti C, Adamsbaum C, Armoogum P, Oury JF, Cabrol D, et al. Cerebral biometry in fetal magnetic resonance imaging: new reference data. Ultrasound in Obstetrics and Gynecology. 2009;33(2):173-81.

309. Guibaud L, Lacalm A. Diagnostic imaging tools to elucidate decreased cephalic biometry and fetal microcephaly: a systematic analysis of the central nervous system. Ultrasound in Obstetrics & Gynecology. 2016;48(1):16-25.

310. EUROCAT Esoca. European surveillance of congenital anomalies -Prevalence Tables 2011-2015 http://www.eurocat-network.eu/accessprevalencedata/prevalencetables2011-2015 [Available from: http://www.eurocat-network.eu/accessprevalencedata/prevalencetables.

311. Gilmore EC, Walsh CA. Genetic causes of microcephaly and lessons for neuronal development. Wiley Interdisciplinary Reviews: Developmental Biology. 2013;2(4):461-78.

312. Deloison B, Chalouhi GE, Bernard JP, Ville Y, Salomon LJ. Outcomes of fetuses with small head circumference on second-trimester ultrasonography. Prenatal diagnosis. 2012;32(9):869-74.

313. Bernhard J-C, Isotani S, Matsugasumi T, Duddalwar V, Hung AJ, Suer E, et al. Personalized 3D printed model of kidney and tumor anatomy: a useful tool for patient education. World Journal of Urology. 2016;34(3):337-45.

Appendix 1

The MERIDIAN Study Patient Information Sheet

Invitation paragraph

Thank you for your cooperation, we do appreciate you taking the time to help us at what is a difficult time for you. We would like to ask you to consider taking part in a research project which uses new methods of looking at a baby's brain while still in the womb. The project involves magnetic resonance imaging (MRI), which is a type of scan already used in many hospitals for other reasons. Please read this information sheet carefully and if there is anything that is not clear or you need more information, please do not hesitate to ask us. Even if we cannot speak to you immediately, one of our team will get back to you.

Why is the project happening?

Ultrasound scanning is used throughout the country to check for possible problems during pregnancy. Although this technique is good, in fact no medical test is perfect and in some cases ultrasound does not provide all the information needed to make a full assessment of the unborn baby's brain development. Newer MRI scanners like the ones we are using in this research project are able to scan much more quickly than we could ten years or so ago. This is very useful as a baby often moves during the scan and these faster scanners still allow us to take good, clear pictures of the baby's brain and hence sometimes gather more information about any possible problems.

What is the aim of the project?

The aim of the project is to find out how and when MRI should be used to improve the information available to parents before birth about the health of their baby. In particular we are concentrating on situations where ultrasound scanning suggests there is a problem with the growth and development of their baby's brain.

Why have I been chosen?

As you are aware there may have been a problem with your baby's brain shown on the ultrasound scan performed by your doctor. We believe that MRI scanning may be able to provide you with more information regarding this.

Do I have to take part?

No. Your participation in this study is voluntary. You may decline to participate. If you decide to participate, you will be given this information sheet to keep, and you will be asked to sign

a written consent form. You can still withdraw at any time. You do not have to give a reason if you withdraw from the study prior to its completion. This will not affect your treatment.

What will happen to me if I take part?

If you decide to take part, we will first ask you some routine questions to make sure that MRI is a safe procedure for you. If you have a heart pacemaker, you have had previous brain or heart surgery, or you have suffered an injury to your eye (such as a metal splinter) you should inform us so we may check this before the MRI takes place. You will be seen by a member of staff in the MRI department before your scan and they will explain to you what will happen during the scan. You will also be able to ask questions before and after the scan takes place.

The MRI will either take place at the Academic Unit of Radiology in the Royal Hallamshire Hospital in Sheffield or it will be arranged by your doctor in the radiology department of your hospital. The MRI scan normally takes around 30 minutes in total, although this may be longer if you are carrying twins or if your baby is particularly active during the scan. You will be asked to lie very still. During the scan you will hear the loud noise made by the MRI scanner while it is working. You will receive earplugs or headphones before the scan starts to reduce this noise. Some people may feel enclosed inside the scanner, and possibly experience feelings of "claustrophobia", so you may wish to have another person present in the scanner room with you (for instance your partner, a close relative or friend). This is OK as long as they complete a visitor safety questionnaire so that we know they are safe to enter the scanner room.

Following your scan we will ask your doctor to let us know how useful the information from the MRI scan has been. We are also very interested in your views about the MRI scan, and we will ask you to fill out two questionnaires, both of them after you have seen your doctor and discussed the scan results, one of them a few months after the other. Once you have completed a questionnaire you can give it to a member of staff in clinic or return it to a member of the research team in a stamped addressed envelope which we will provide.

With your agreement (which is included on the consent form) we would like to be able to use some of the pictures, or "images", from your scan for teaching purposes or where appropriate in other publications relevant to this research. None of your personal details would ever be printed on these images. We may also, with your agreement (which is included on the consent form), wish to gather some information about what happens later on in your pregnancy and around the time of delivery. Finally, in order to check how useful and

accurate the information from your MRI scan has been we would like to see the results of any tests performed postnatally by your doctors up to 6 months term corrected after delivery. Sometimes this information can be collected entirely from your medical records, and those of your child, and we may not need to contact you directly. If this is not possible however, then either a member of the research team, your midwife or consultant obstetrician would contact you to help us check these details.

We may also wish (which is included on the consent form) to contact you regarding future studies into your child's development. It is entirely your choice whether you agree to the use of images for teaching purposes, providing us with information after your child is born, or participation in any future studies as your child grows. It will not affect your care you receive if you decide not to take any of these options. Please note that the doctor who performed your ultrasound test will be informed of the results of the MRI study. They will in fact receive a full report which will be discussed with you when you next see them.

What are the possible disadvantages and risks of taking part?

There are no known problems regarding the use of MRI scanning in pregnant women. There are some possible disadvantages to having an MRI scan, as some people can find being in the scanner uncomfortable or unpleasant (please see paragraph 7 above "What will happen to me if I take part"). It is important to point out though that most people experience little or no problem at all when they are having their MRI scan.

It is possible that the information from your MRI scan might be different from the information shown on your ultrasound scan. This can happen because no single medical test is perfect, and sometimes information provided by tests such as ultrasound and MRI may be incomplete or difficult to interpret. If this occurs your doctor will discuss this with you, and it will be up to you and your doctor to decide between you how best to use the information provided by each of your medical tests.

What are the possible benefits of taking part?

Researchers, doctors and other health care professionals who are involved in scanning babies before birth could benefit from this research by gaining a better understanding of how and when to perform MRI scans for pregnant women. In the future, other pregnant women who have been told their baby might have a problem could benefit from the results of this research. As a result of the MRI scan you might also gain some more information about your current pregnancy and your baby's condition.

What happens if the research study stops earlier than expected?

If this is the case, the reason(s) will be explained to you by one or our research team.

Will my taking part in this project be kept confidential?

All data obtained in the study will be kept confidential. All information provided by you or recorded by the research team will be kept under code number and will only be linked together with your name where we need to contact you to make an appointment or request some further details from you. Data will be made available only to the persons conducting the study, your referring consultant and any other individuals where you have given specific permission for us to do so (for instance your GP). All information will be kept in a locked room at the Academic Unit of Radiology in the University of Sheffield, within the hospital clinic or radiology department where your MRI scan takes place. Copies will also be stored in a locked room and on a secure electronic database at the University of Sheffield School for Health and Related Research (ScHARR). The questionnaires you complete after your MRI scan will be stored by a member of the research team in a locked room within the University of Newcastle.

Will I get travel expenses?

We will be able to reimburse reasonable travel expenses if you are asked to travel to Sheffield for your MRI scan (and you would not normally have your scans or other hospital appointments there). Please ask the radiologist or another member of staff when you attend for your MRI scan, or contact the Academic Unit of Radiology in Sheffield for details (address and phone number are shown at the end of this information sheet).

What will happen to the results of the research project?

Researchers may present the results of this project in research conferences, or they may publish in scientific or medical journals. None of your personal details will be identifiable.

Who has reviewed the project?

This study has been reviewed and commissioned by the National Institute for Health Research (NIHR) Health Technology Assessment Programme. This is a part of the National Health Service (NHS) involved in medical research. Ethical review is provided by means of the Integrated Research Application System (IRAS), and has been approved by a research ethics committee (South Yorkshire REC, reference: 11/YH/0006).

What if something goes wrong?

Since there are no known health risks specifically associated with this study, it is very unlikely that you will be harmed as a result of taking part. In the event that something does go wrong and you are harmed during the research, and this is due to someone's negligence, then you may have grounds for legal action for compensation against the University of Sheffield. You may however have to pay your own legal costs. The normal National Health Service complaints procedure will still be available to you.

What if I wish to make a complaint?

If you wish to raise a complaint about the way you have been dealt with, or about any harm you feel you have suffered, you can contact Professor Paul Griffiths in the Academic Unit of Radiology at the University of Sheffield via email (p.griffiths@sheffield.ac.uk), phone (0114 2712587) or send a letter to: Professor P D Griffiths, Academic Unit of Radiology, University of Sheffield, C floor Royal Hallamshire Hospital, S10 2JF.

Alternatively, you can contact the patient advisory and complaints service at your local hospital or NHS Trust (*Details of relevant local Patient Services Team(PST)/Patient Advisory and Liaison Service (PALS) office to be provided here specific to participating site*).

Involvement of general practitioner (GP)

Your GP will not be notified of your involvement in this study unless you specifically ask us to do so.

Who is organising and funding the research?

The funding of this research is obtained from the National Institute for Health Research (NIHR), which is a part of the NHS involved in medical research. The project is part of the NIHR Heath Technology Assessment (HTA) programme.

The sponsors of this study will pay the Academic Unit of Radiology for the cost of the MRI scan and also for your reasonable travel expenses to allow you to come for your MRI scan. The doctor conducting the research will not be paid specifically to perform the scan and therefore he/she has no conflict of interest in your care.

Contact for further information

If you would like further information about the study, please contact Professor Paul Griffiths at the Academic Unit of Radiology in Sheffield. Alternatively you can contact the person detailed below who is a member of our research team based at your local hospital or clinic.

Paul D Griffiths
Professor of Radiology
Academic Unit of Radiology
University of Sheffield
C floor, Royal Hallamshire Hospital
Sheffield S10 2JF
Email: p.griffiths@sheffield.ac.uk
Tel: 0114 271 2587

Local contact person
Address
Email
Tel

Appendix 2

MERIDIAN STUDY CONSENT FORM 26 June 2014, Version 4.1

Centre Number: Form C
Study Number: HTA Project 09/06/01 (MERIDIAN)
Patient Identification Number for this trial (if known):
Ethics reference: 11/YH/0006

Please initial box

1. I confirm that I have read and understood the information sheet dated 26 June 2014 (version 4.1) for the above study. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily. ☐

2. I understand that I will have the opportunity to ask further questions about the MRI scan itself before this takes place. ☐

3. I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected. ☐

4. I confirm that relevant sections of my medical notes and other data collected during the study, and after the birth of my child, may be looked at by responsible individuals from the Universities of Sheffield and Newcastle, regulatory authorities and by staff at the NHS Trust where I receive my clinical care, where it is relevant to my taking part in this research. I give permission for these individuals to have access to my medical records and those of my child. ☐

5. I agree that anonymous images from my ultrasound scan, MRI scan and any relevant tests performed postnatally may be used in the medical literature and for teaching purposes. ☐

6. I agree to take part in the above study. ☐

7. I agree to be approached by members of the research team at a later date to ask me if I wish to participate in future studies looking at my child's development. ☐

Name of Patient	Date	Signature
Name of Person taking consent	Date	Signature

When completed, 1 copy for participant, 1 copy for researcher site file, 1 (original) to be kept in medical/maternity notes

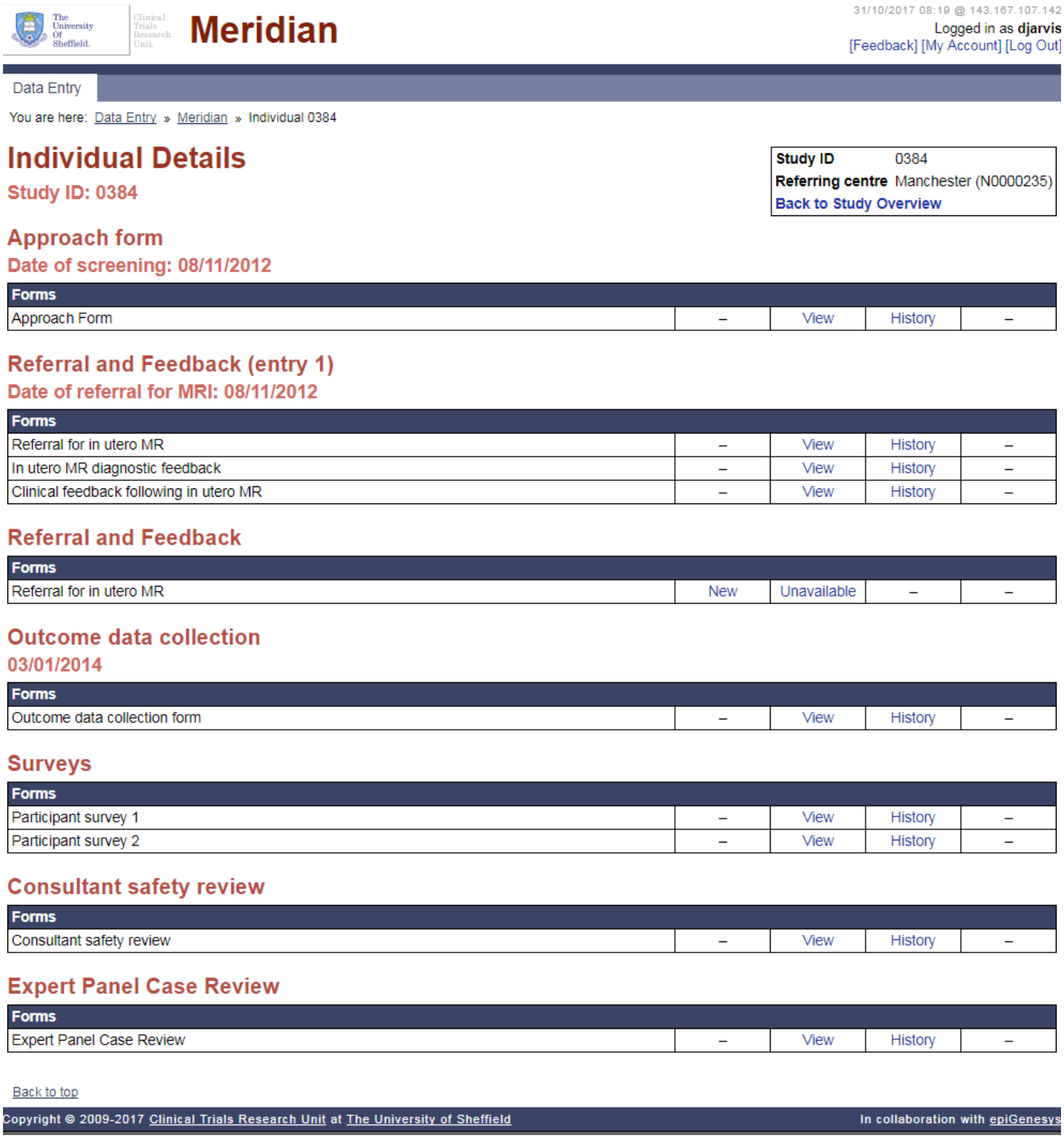
Appendix 3

The collection and management of the data for the MERIDIAN and MERIDIAN Add-on studies were overseen by the study management team at ScHARR (School of Health and Related Research). The databases for each of the studies, were developed by the Clinical Trials Research Unit's using the in-house clincial data management system, Prospect, in collaboration with epiGenesys a software company owned by the University of Sheffield (https://www.epigenesys.org.uk/). Each database was tailored to each study to capture all the data necessary.

Data was stored in a PostgreSQL database on virtual servers hosted by Corporate Information and Computing Services (CiCS) at the University of Sheffield. Security was ensured using industry standard techniques, including password authentication and encryption using SSL/TLS. The system logged activity by users, had a full data audit trail and was regularly backed up. Access to Prospect was controlled by usernames and encrypted passwords. A privilege management feature of Prospect meant that only the minimum amount of data required was available to each individual in order to complete their tasks allocated by the study management team at ScHARR. This ensured access to personal details was restricted to users with appropriate privileges.

The design of the databases for the MERIDIAN and Add-on studies provided an overview page for each participant, as shown below in figures A and B, with access to the forms for each stage of data collection as shown in Appendices 4, 5 and 6.

Figure A. Screen capture of the online database showing the initial data entry page for an individual participant of the MERIDIAN Study.



The University Of Sheffield. Clinical Trials Research Unit.

Meridian

31/10/2017 08:19 @ 143.167.107.142
Logged in as **djarvis**
[Feedback] [My Account] [Log Out]

Data Entry

You are here: Data Entry » Meridian » Individual 0384

Individual Details

Study ID: 0384

Study ID	0384
Referring centre	Manchester (N0000235)
Back to Study Overview	

Approach form

Date of screening: 08/11/2012

Forms				
Approach Form	–	View	History	–

Referral and Feedback (entry 1)

Date of referral for MRI: 08/11/2012

Forms				
Referral for in utero MR	–	View	History	–
In utero MR diagnostic feedback	–	View	History	–
Clinical feedback following in utero MR	–	View	History	–

Referral and Feedback

Forms				
Referral for in utero MR	New	Unavailable	–	–

Outcome data collection

03/01/2014

Forms				
Outcome data collection form	–	View	History	–

Surveys

Forms				
Participant survey 1	–	View	History	–
Participant survey 2	–	View	History	–

Consultant safety review

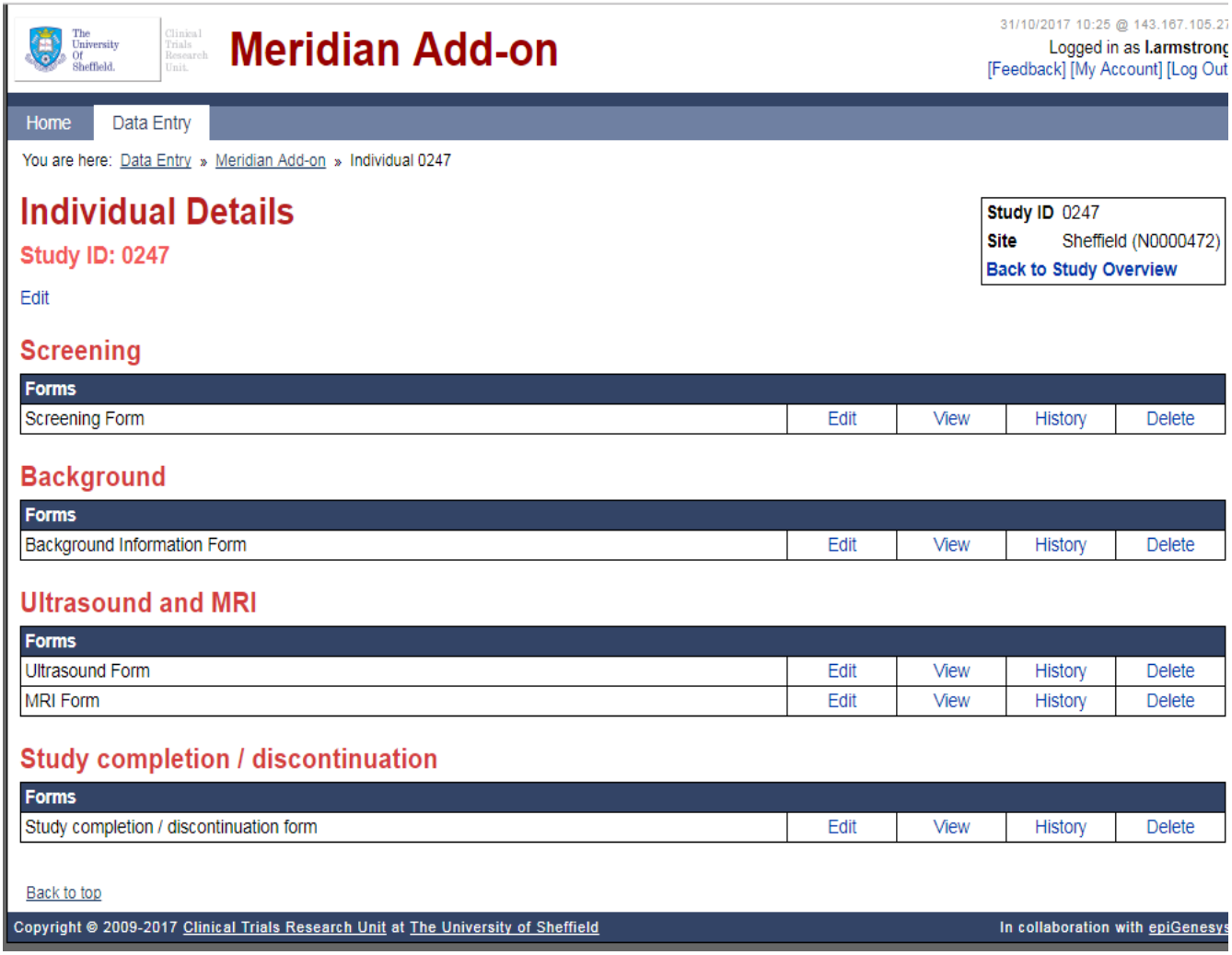
Forms				
Consultant safety review	–	View	History	–

Expert Panel Case Review

Forms				
Expert Panel Case Review	–	View	History	–

Back to top

Figure B. Screen capture of the online database showing the initial data entry page for an individual participant of the Add-on study



Appendix 4

MERIDIAN Study – Form D
NIHR HTA 09-06-01
Initial Fetal Medicine Consultation
Referral for in utero MR

Patient name
Patient DOB
Study ID (if known)

Background information

Date of Clinic
Referring Clinician
Clinic phone no:
NHS number
Patient phone no:
Gestational age ☐☐ weeks ☐☐ days ☐ Singleton pregnancy ☐ Multiple pregnancy

Structural diagnoses

List multiple abnormalities where necessary (brain only); please use "ViewPoint" diagnostic classification wherever possible. Please provide other relevant details, e.g. Location / side of abnormality). For multifetal pregnancies please specify fetus number.
Please attach or fax a copy of the most recent fetal medicine clinic letter or summary sheet.

Please complete for each diagnosis identified	Fetus #	Other details if relevant	Confidence of diagnosis: very unsure (10%)	unsure (30%)	equivocal (50%)	confident (70%)	highly confident (90%)
Ventriculomegaly*	☐		☐	☐	☐	☐	☐
Agenesis of the corpus callosum	☐		☐	☐	☐	☐	☐
Other (please specify):							
	☐		☐	☐	☐	☐	☐
	☐		☐	☐	☐	☐	☐
	☐		☐	☐	☐	☐	☐

*Ventriculomegaly cases

Normal situs? ☐ Yes ☐ No
If no, please give details:

	Trigone size (mm)	Please tick (√) near field measurement
Left side	☐☐.☐	☐
Right side	☐☐.☐	☐

Version: 3.1
Effective date: 5 February 2013

MERIDIAN Study – Form D (continued)
NIHR HTA 09-06-01
Initial Fetal Medicine Consultation
Referral for in utero MR

Patient name
Patient DOB
Study ID (if known)

Prognosis

What are the chances of normal neuro-developmental outcome?

☐ Not Known ☐ Intermediate (50-90%) ☐ Normal

☐ Poor (<50%) ☐ Favourable (>90%)

Management

Was TOP discussed? ☐ Yes ☐ No i.e. Was there any discussion at all about termination of pregnancy, whether raised by you or the woman herself?

Was TOP offered? ☐ Yes* ☐ No i.e. Did you discuss TOP as a potential management choice which would be available to the woman if she wishes?

*If yes, was this based on a substantial risk of handicap? ☐ Yes ☐ No i.e. Do you consider that the CNS abnormality alone is of sufficient severity to justify termination under clause E (significant risk of serious mental or physical handicap)?

Other comments:

Technical factors

Were there any technical factors that contributed to a low confidence structural diagnosis? ☐ Yes ☐ No

If yes: (please indicate all that apply)

☐ High body mass index ☐ Fetal position ☐ Oligohydramnios

☐ Other, please specify

Which ultrasound technique was used to make the diagnosis (one or both)? ☐ 2D ☐ 3D*
*Please save 3D US volume for retrospective analysis where possible

Date of Referral:

Version: 3.1
Effective date: 5 February 2013

Appendix 5

Form E used for the MERIDIAN study to record details of the iuMR examination

MERIDIAN Study – Form E
NIHR HTA 09-06-01
Attendance for MRI scan
In utero MR diagnostic feedback

Patient name
Patient DOB
Study ID (if known)

Background information

Date of MR

Referring Clinician

Patient hospital no:

Gestational age ____ weeks ____ days ☐ Singleton pregnancy ☐ Multiple pregnancy

Reporting radiologist

Contact no:

Adverse events / problems

Were any adverse events or problems encountered relating to the MRI examination? ☐ Yes ☐ No
(e.g. Patient injury, claustrophobia, incomplete or suboptimal examination, radiographer or patient-reported MR phenomena)

If yes: (please indicate all that apply)

- ☐ Loose metallic object/projectile
- ☐ Medical implant / prosthesis
- ☐ Anxiety/claustrophobia – Was the examination completed? ☐ Yes ☐ No
  If no: Was any useful diagnostic information provided? ☐ Yes ☐ No
- ☐ Skin heating/other sensory effects
- ☐ Persistent fetal movement causing incomplete / suboptimal examination
- ☐ MR equipment or software failure causing incomplete / suboptimal examination
- ☐ Other, please specify

Other relevant details / comments including incident reference number:

Version: 2.0

MERIDIAN Study – Form E (continued)
NIHR HTA 09-06-01
Attendance for MRI scan
In utero MR diagnostic feedback

Patient name
Patient DOB
Study ID (if known)

Structural diagnoses

List multiple abnormalities where necessary (brain only); please use "ViewPoint" diagnostic classification wherever possible.
Please also comment on each diagnosis identified at referral.
For multifetal pregnancies please specify fetus number.

Please complete for each diagnosis identified	Fetus #	Other details if relevant (e.g. Location / side of abnormality)	very unsure (10%)	unsure (30%)	equivocal (50%)	confident (70%)	highly confident (90%)	Diagnosis excluded
Ventriculomegaly*	☐		☐	☐	☐	☐	☐	☐
Agenesis of the corpus callosum	☐		☐	☐	☐	☐	☐	☐
Other (please specify):								
	☐		☐	☐	☐	☐	☐	☐
	☐		☐	☐	☐	☐	☐	☐
	☐		☐	☐	☐	☐	☐	☐

*Ventriculomegaly cases

	Trigone size (mm)
On the same side as the heart / stomach	☐☐.☐
Opposite side to the heart / stomach	☐☐.☐

Version: 2.0
Effective date: 25 May 2011

Appendix 6

Form G used for the MERIDIAN study to record details of the clinical feedback following iuMR examination.

MERIDIAN Study – Form G
NIHR HTA 09-06-01
Subsequent Fetal Medicine Consultation
Clinical feedback following in utero MR

Patient name
Patient DOB
Study ID (if known)

Please attach or fax a copy of the most recent fetal medicine clinic letter or summary sheet.

Background information

Date of Clinic
Consultant
Clinic phone no:
Patient hospital no:
Gestational age ☐☐ weeks ☐☐ days
☐ Singleton pregnancy
☐ Multiple pregnancy

Diagnosis

Did the MRI provide additional information in this case? ☐ Yes ☐ No
If yes, was this information also visible on your follow up US? ☐ Yes ☐ No

Prognosis

What are the chances of normal neuro-developmental outcome?
☐ Not Known ☐ Intermediate (50-90%) ☐ Normal
☐ Poor (<50%) ☐ Favourable (>90%)
Did the MRI change your prognosis in this case? ☐ Yes ☐ No

Management

Was TOP discussed? ☐ Yes ☐ No i.e. Was there any discussion at all about termination of pregnancy, whether raised by you or the woman herself?

Was TOP offered? ☐ Yes* ☐ No i.e. Did you discuss TOP as a potential management choice which would be available to the woman if she wishes?

*If yes, was this based on a substantial risk of handicap? ☐ Yes ☐ No i.e. Do you consider that the CNS abnormality alone is of sufficient severity to justify termination under clause E (significant risk of serious mental or physical handicap)?

Did MRI change your counselling in this case?
☐ Not at all ☐ Minor influence (reassurance or confirmation only)
☐ Major change (changed discussion of management options)

Version: 3.0
Effective date: 21 September 2011

MERIDIAN Study – Form G (continued)
NIHR HTA 09-06-01
Subsequent Fetal Medicine Consultation
Clinical feedback following in utero MR

Patient name
Patient DOB
Study ID (if known)

Please attach or fax a copy of the most recent fetal medicine clinic letter or summary sheet.

Management

Chosen management plan:

- ☐ Continued pregnancy – discharged from fetal medicine clinic
- ☐ Continued pregnancy – with fetal medicine follow-up
  - ☐ Further imaging planned to monitor progress? ☐ Yes ☐ No
  - **If yes:** ☐ US ☐ MRI
- ☐ Termination of pregnancy With feticide: ☐ Yes ☐ No

How do you rate the contribution of MRI to the final choice of management?

☐ None ☐ Minor ☐ Significant ☐ Major ☐ Decisive

Other investigations

Were other investigations performed? ☐ Yes ☐ No

If yes: (indicate all those performed and whether they were contributory)

		Changed the prognosis and counselling?	Major factor in choice of management?
☐ Karyotype	☐ Normal ☐ Abnormal	☐	☐
☐ Echo	☐ Normal ☐ Abnormal	☐	☐
☐ Infection screen	☐ Normal ☐ Abnormal	☐	☐
☐ 3D US*		☐	☐
☐ Other, please specify		☐	☐

*Was 3D imaging performed at initial fetal medicine assessment – prior to MRI ? ☐ Yes ☐ No
*Did 3D US modify your initial diagnosis prior to MRI? ☐ Yes ☐ No
*Was the volume saved and interpreted off-line by an expert? ☐ Yes ☐ No
*Did 3D US provide the same diagnostic information as MRI? ☐ Yes ☐ No
*Did 3D US modify your confidence in the 2D US diagnosis? ☐ No change ☐ Increased ☐ Decreased

***Please save the 3D volume for subsequent analysis wherever possible.**

Other comments, including results of karyotyping or virology

Version: 3.0
Effective date: 21 September 2011

Appendix 7

The University of Sheffield
Unit of Academic Radiology
School of Medicine, Royal Hallamshire Hospital
Researcher: Prof Paul Griffiths

Patient Information Sheet

Magnetic resonance imaging to enhance the diagnosis of fetal developmental brain abnormalities in utero. **MERIDIAN Add on study**

Thank you for your interest in this research. We would like to ask you to take part in a research project which uses new methods of looking at a baby's brain while still in the womb. The project involves magnetic resonance imaging (MRI), which is a type of scan already used in many hospitals for other reasons both in and out of pregnancy. Please read this information sheet carefully and if there is anything that is not clear or you need more information, please do not hesitate to ask us. Even if we cannot speak to you immediately, one of our team will get back to you.

Why is the project happening?

Ultrasound scanning is universally used during pregnancy. Although ultrasound is good, no medical test is perfect and in some cases ultrasound does not give all the information needed to make a full assessment of the unborn baby's brain development. MRI has been demonstrated to be better at looking at some aspects of the developing brain. We are currently trying to identify how much better MRI is than ultrasound.

The aim of the project is to find out how and when MRI should be used to improve the information available to parents before birth about the health of their baby. In this part of the project we are looking at babies whose brains are developing normally. We are going to see if a detailed ultrasound and MRI give the same information about brain development. The research is set up to look at brain development only and any investigations used by us focus on this area alone.

Would I be able to take part?

You will be able to take part if you are over the age of 16 years, at least 18 weeks pregnant and have had an antenatal ultrasound which showed your baby's brain was developing normally.

Do I have to take part?

No, your taking part in this study is voluntary. You may decide not to take part. If you decide to take part, you will be given this information sheet to keep, and you will be asked to sign a written consent form.

You can still withdraw at any time. You do not have to give a reason if you withdraw from the study, this will not affect your medical care.

What will happen to me if I take part?

If you decide to take part, we will contact you to ask some routine questions to make sure that MRI is a safe procedure for you. If you have a heart pacemaker, you have had previous brain or heart surgery, or you have suffered an injury to your eye (such as a metal splinter) you should inform us so we may check this before the MRI takes place. We will arrange a date for your scans. When you come in for the scans we will also take your written consent to take part.

The Ultrasound scan and MRI will take place at the Academic Unit of Radiology in the Royal Hallamshire Hospital in Sheffield. You will have a detailed ultrasound scan, this will be very similar to previous ultrasound scans that you have had, except it will be performed by a consultant who will only be looking at you baby's brain development. You will then be seen by a member of staff in the MRI department who will explain to you what will happen during the MRI scan. You will also be able to ask questions before and after the scan takes place. The MRI scan normally takes around 30 minutes in total, although this may be longer if you are carrying twins or if your baby is particularly active during the scan. You will be asked to lie very still. During the scan you will hear the loud noise made by the MRI scanner while it is working. You will be given earplugs or headphones before the scan starts to reduce this noise. Some people may feel enclosed inside the scanner, and possibly experience feelings of "claustrophobia", so you may wish to have another person present in the scanner room with you (for instance your partner, a close relative or friend). This is OK as long as they complete a visitor safety questionnaire so that we know they are safe to enter the scanner room.

Extra Options

If you agree we would like to be able to use some of the pictures, or “images”, from your scan for teaching purposes or where appropriate in other publications relevant to this research. None of your personal details would ever be printed on these images. We may also wish (which is included on the consent form) to contact you regarding future studies into your child’s development.

It is entirely your choice whether you agree to the use of images for teaching purposes, or take part in any future studies as your child grows. It will not affect your care you receive if you decide not to take any of these options.

What are the possible disadvantages and risks of taking part?

There are no known problems regarding the use of MRI scanning in pregnant women. Some people can find being in the MRI scanner uncomfortable or unpleasant. It is important to point out though that most people experience little or no problem at all when they are having their MRI scan.

It is possible that the information from your detailed ultrasound scan and MRI scan might be different from the information shown on your previous ultrasound scan. This can happen because no single medical test is perfect, and sometimes information provided by tests such as ultrasound and MRI may be incomplete or difficult to interpret. We know this could be worrying for you. We will make sure your GP and consultant at your hospital have the information so they can talk to you about what it might mean.

What are the possible benefits of taking part?

Researchers, doctors and other health care professionals who are involved in scanning babies before birth could benefit from this research by gaining a better understanding of how and when to perform MRI scans for pregnant women. In the future, pregnant women who have been told their baby might have a problem could benefit from the results of this research.

You will also be offered an MRI picture of your baby to keep and a £10 voucher.

Will my taking part in this project be kept confidential?

All data obtained in the study will be kept confidential. All information provided by you or recorded by the research team will be kept under code number. Data will be made available only to the research team staff, your GP and consultant (if you have one). All

information will be kept in a locked room at the Academic Unit of Radiology in the University of Sheffield, within the hospital clinic or radiology department where your MRI scan takes place. Copies will also be stored in a locked room and on a secure electronic database at the University of Sheffield School for Health and Related Research (ScHARR).

Will I get travel expenses?

We will be able to pay reasonable travel expenses for your travel to Sheffield for your MRI scan. If you bring a partner, relative or friend their travel costs will also be covered.

What will happen to the results of the research project?

Researchers may present the results of this project in research conferences, or they may publish in scientific or medical journals. None of your personal details will be identifiable.

What if something goes wrong?

Since there are no known health risks specifically associated with this study, it is very unlikely that you will be harmed as a result of taking part. In the event that something does go wrong and you are harmed during the research, and this is due to someone's negligence, then you may have grounds for legal action for compensation against the University of Sheffield. You may however have to pay your own legal costs. The normal National Health Service complaints procedure will still be available to you.

What if I wish to make a complaint?

If you wish to raise a complaint about the way you have been dealt with, or about any harm you feel you have suffered, you can contact Professor Paul Griffiths (see contact details below).

Alternatively, you can contact the Patient Service Team at the Royal Hallamshire Hospital at; Patient Partnership Department, B Floor, Royal Hallamshire Hospital, Glossop Road, Sheffield, South Yorkshire, S10 2JF, tel: 0114 2712400 or via e-mail: PST@sth.nhs.uk.

Involvement of general practitioner (GP)

We will write to your GP to let them know that you are taking part in this study.

Who is organising and funding and reviewing the research?

This research is being carried out by the University of Sheffield and is funded by the National Institute for Health Research (NIHR), which is a part of the NHS involved in medical

research. The research has been approved by South Yorkshire Research Ethics committee (reference: 11/YH/0006).

The doctor who oversees the ultrasound scan or MRI scan will not be paid specifically to perform the scan and therefore he/she has no conflict of interest in your care.

Contact for further information

If you would like further information about the study, please contact Professor Paul Griffiths:

Paul D Griffiths
p.griffiths@sheffield.ac.uk
Professor of Radiology
Academic Unit of Radiology
University of Sheffield
C floor, Royal Hallamshire Hospital
Sheffield S10 2JF

Email:

Tel: 0114 215 9605

Thank you for taking the time to read this information sheet

Appendix 8

Participant screening form for the Add-on study

MERIDIAN Study – Form 1
NIHR HTA 09-06-01
Screening form

Date participant contacted ☐☐/☐☐/☐☐☐☐

How did you find out about the study?

- ☐ Hospital
- ☐ GP
- ☐ Community midwife
- ☐ Other, give details

Are you still interested in the study and willing to answer some screening questions?

☐ Yes ☐ No

- ☐ Declined to give reason
- ☐ No longer interested
- ☐ Does not want any further information about pregnancy
- ☐ Does not want to take part in research
- ☐ Did not want to take part because MRI scan is of the brain only
- ☐ Too difficult to arrange time for MRI visit
- ☐ Unwilling to travel
- ☐ Does not want MRI
- ☐ Other, specify

Screening questions

We need to check that women coming into the study have babies whose brains are developing normally.

As far as you are aware is your baby's brain developing normally? ☐ Yes ☐ No

Based on

- ☐ Ultrasound by fetal maternal expert
- ☐ Dating ultrasound
- ☐ Anomaly scan performed by sonographer
- ☐ No scans performed to date but no reason to suspect any problems
- ☐ Other, give details

Version 1 16/01/2014 1 of 2

Screening questions (continued)

For the research we also need to know if there are any other medical concerns about babies who will be scanned. Women in this group can still be scanned but we need to give them some additional information.

Are there any medical concerns about your baby's development? ☐ Yes ☐ No

Give supplementary information sheet

Details

Are you willing to travel for Sheffield for specialist MR imaging? ☐ Yes ☐ No

Are you 16 years or older? ☐ Yes ☐ No

Are you willing for your GP to be told about the study and given copies of scan reports? ☐ Yes ☐ No

Have you a cardiac pacemaker, intra-orbital metallic foreign body, or recent surgery with metallic sutures or implant? ☐ Yes ☐ No

Have you previously experienced or are likely to suffer severe anxiety or claustrophobia during the MR imaging examination? ☐ Yes ☐ No

Have you in a previous pregnancy had a baby who was suspected or did have a brain abnormality? ☐ Yes ☐ No

Gestational age ☐☐ weeks ☐ days

OR

Expected date of delivery ☐☐ ☐☐ ☐☐☐☐

Single or multiple pregnancy ☐ Single ☐ Multiple

Appendix 9

Participant background information form for the Add-on study.

MERIDIAN Study – Form 2
NIHR HTA 09-06-01
Background information form

Academic unit of radiology visit

Date of visit ☐☐/☐☐/☐☐☐☐

Did the participant agree to take part in the study?

☐ Yes

Date of consent ☐☐/☐☐/☐☐☐☐

☐ No

- ☐ Declined to give reason
- ☐ Does not want to take part in research
- ☐ Does not want any further information about pregnancy
- ☐ Did not want to take part because MRI scan is of the brain only
- ☐ Does not want MRI
- ☐ Other, specify _____

Contact details

Forename / Surname _____ / _____

Address 1 _____

Address 2 _____

Address 3 _____

Postcode _____ _____

Phone number _____ _____ _____ _____

Is the participant willing to be contacted about future studies? ☐ Yes ☐ No

NHS number _____ _____ _____

Age _____

Version 1 16/01/2014 1 of 3

MERIDIAN Study – Form 2
NIHR HTA 09-06-01
Background information form

Academic unit of radiology visit (continued)

GP details

GP name

Practice name

Practice address 1

Practice address 2

Practice address 3

Practice postcode

Practice telephone number

Is this the participant's first pregnancy? ☐ Yes ☐ No

Were there any complications in a previous pregnancy ☐ Yes ☐ No

☐ Fetus had an abnormality diagnosis, give details

☐ Other, give details

MERIDIAN Study – Form 2
NIHR HTA 09-06-01
Background information form

Academic unit of radiology visit (continued)

Date of detailed ultrasound scan by feto maternal expert ☐☐☐☐☐☐☐☐

Where was the scan done?

- ☐ MERIDIAN Investigator site
- ☐ Academic unit of radiology
- ☐ Other, give details

Under care of consultant (name)

Why was the woman scanned by a fetal medicine consultant?

- ☐ Risk from previous pregnancy, give details
- ☐ Suspected non brain abnormality, give details
- ☐ Other, give details
- ☐ Scans performed for this study

Appendix 10 Consent Form for the Add-on Study

The University of Sheffield
Unit of Academic Radiology
School of Medicine, Royal Hallamshire Hospital
Researcher: Prof Paul Griffiths

MERIDIAN Add on study,
Ethics reference: 11/YH/0006

Patient Identification Number :

STUDY CONSENT FORM

Version 3.0 13th November 2014

Magnetic resonance imaging to enhance the diagnosis of fetal developmental brain abnormalities in utero. MERIDIAN Add on study

Please initial box

1. I confirm that I have read and understood the information sheet dated 22nd April 2014 (version 2.0) for the above study. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily. (This participant has/ has not been given supplementary information sheet 18th Nov 2013 v1.0/ congenital heart disease supplementary information sheet 13th Nov 2014 v1.0) ☐
2. I understand that it is my choice to participate and that I can leave the study at any time without giving any reason and this will not affect my care in any way. ☐
3. I confirm that relevant sections of my medical notes and other information collected during the study may be looked at staff involved in the study, where it is relevant to my taking part in this research. I give permission for these individuals to have access to my medical records. ☐
4. I understand that the MRI scan is of my baby's brain only. ☐
5. I agree that my GP can be told I am taking part in this study and receive a copy of my MRI scan report. ☐
6. I agree that anonymous images from my MRI scan may be used in the medical literature and for teaching purposes. ☐
7. I agree to take part in the above study. ☐
8. I agree to be approached by members of the research team at a later date to ask me if I wish to participate in future studies looking at my child's development. ☐

Name of Patient	Date	Signature
Name of Person taking consent	Date	Signature

When completed, 1 copy for participant, 1 copy for researcher site file, 1 (original) to be kept in medical/maternity notes

Appendix 11

Data captured for each participant for the Add-on study following MR examination

MERIDIAN Study – Form 4
NIHR HTA 09-06-01
MRI form

Date of MR ☐☐☐☐☐☐☐☐

Reporting radiologist

Was scan performed on ☐ 1.5 Tesla MR ☐ 3 Tesla MR

Adverse events / problems

Were any adverse events or problems encountered relating to the MRI examination? ☐ Yes ☐ No
(e.g. Patient injury, claustrophobia, incomplete or suboptimal examination, radiographer or patient-reported MR phenomena)

(please indicate all that apply)

- ☐ Loose metallic object/projectile
- ☐ Medical implant / prosthesis
- ☐ Anxiety/claustrophobia – Was the examination completed? ☐ Yes ☐ No
  - Was any useful diagnostic information provided? ☐ Yes ☐ No
- ☐ Skin heating/other sensory effects
- ☐ Persistent fetal movement causing incomplete / suboptimal examination
- ☐ MR equipment or software failure causing incomplete / suboptimal examination
- ☐ Other, please specify

Other relevant details / comments including incident reference number:

Version 1 16/01/2014 1 of 2

MERIDIAN Study – Form 4
NIHR HTA 09-06-01
MRI form

Diagnosis

Is the brain normal? ☐ Yes ☐ No

What is the structural diagnosis and its certainty?

Please complete for each diagnosis identified	Fetus #	Other details if relevant	Confidence of diagnosis: very unsure (10%)	unsure (30%)	equivocal (50%)	confident (70%)	highly confident (90%)
Ventriculomegaly*	☐		☐	☐	☐	☐	☐
Agenesis of the corpus callosum	☐		☐	☐	☐	☐	☐
Other (please specify):							
	☐		☐	☐	☐	☐	☐
	☐		☐	☐	☐	☐	☐
	☐		☐	☐	☐	☐	☐

*Ventriculomegaly cases

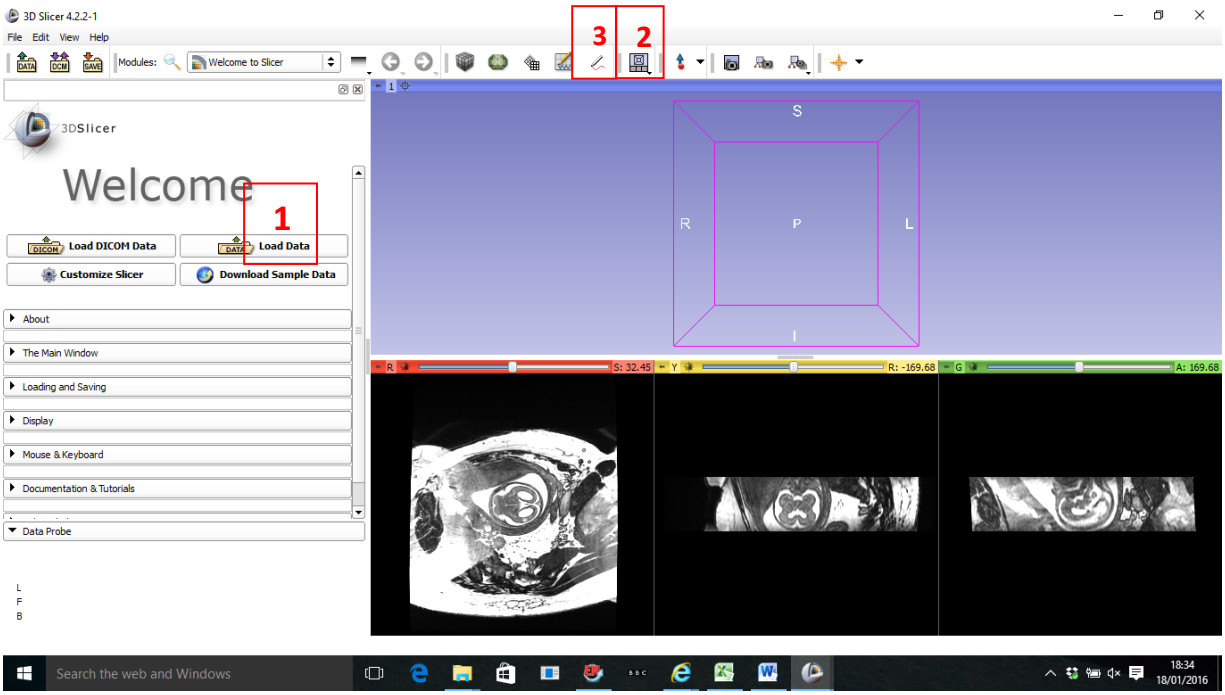
On the same side as the heart / stomach ☐☐.☐ Trigone size (mm)

Opposite side to the heart or stomach ☐☐.☐ Trigone size (mm)

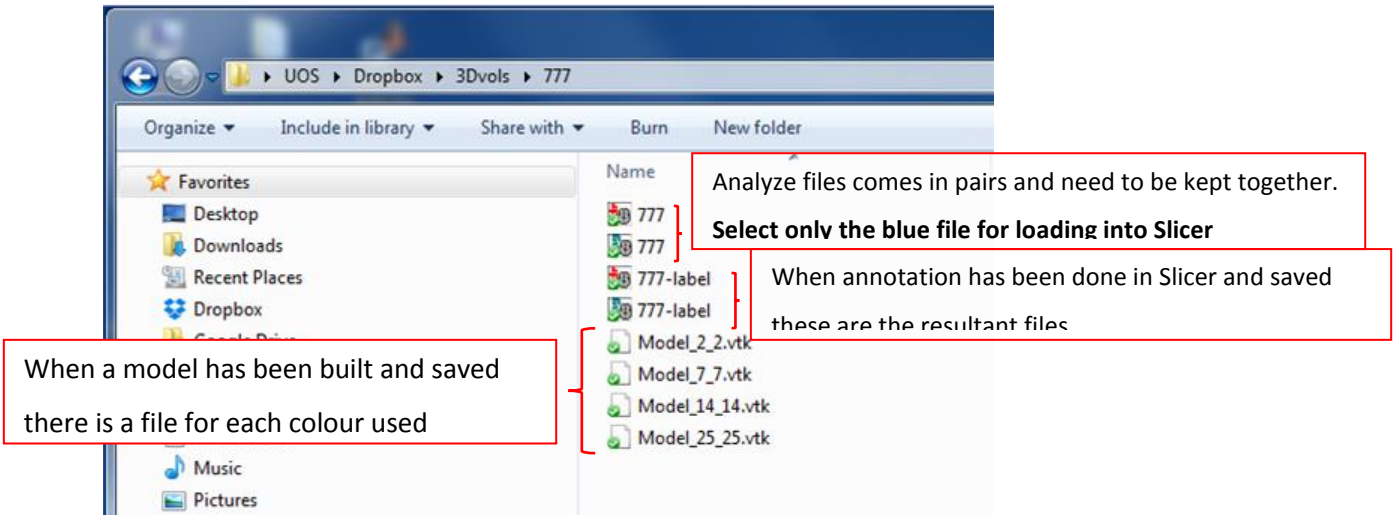
Appendix 12

3D SLICER USER INSTRUCTIONS: A Beginners Guide For Brain Segmentation.

1. Select Load Data from the start up page of Slicer
2. From the pop up box click ‘choose files to add’ (**1**)
3. Find and select the image file you want to annotate
4. The file should now appear listed in the box- Click ok
5. The images will now appear in slicer.



6. In order to annotate the images select the appropriate colour pane from the drop down menu (**2**)– i.e. choose red if you want to select axial
7. Using the mouse LEFT click mouse to zoom images to the size you want
8. Use RIGHT mouse to alter windowing to appropriate levels.
9. Middle scroll to move through images and press and hold to grab and centre the images
10. To start drawing click on the pencil on the tool bar (**3**)
11. 11. This will now change the welcome panel on the left to give you the functions to annotate (see below)
12. 12. A pop up box will appear. The default directory is usually Generic Anatomy colours- if it isn't use the drop down arrow to find this choice. Select Apply



13. The menu shown below will now appear on the left.
14. Choose the label colour by clicking (**4**) Standard colours used are:-

Blue- no 25 for ventricular system
Yellow- no 2 for one hemisphere
Cream- no 14 for second hemisphere
Green- no 7 for cerebellum/brain stem
Red- no 5 for remaining intracranial volume

For annotation it is important to note that you need to work from the <u>inside out</u> as Slicer 'fills in' any drawing you do.

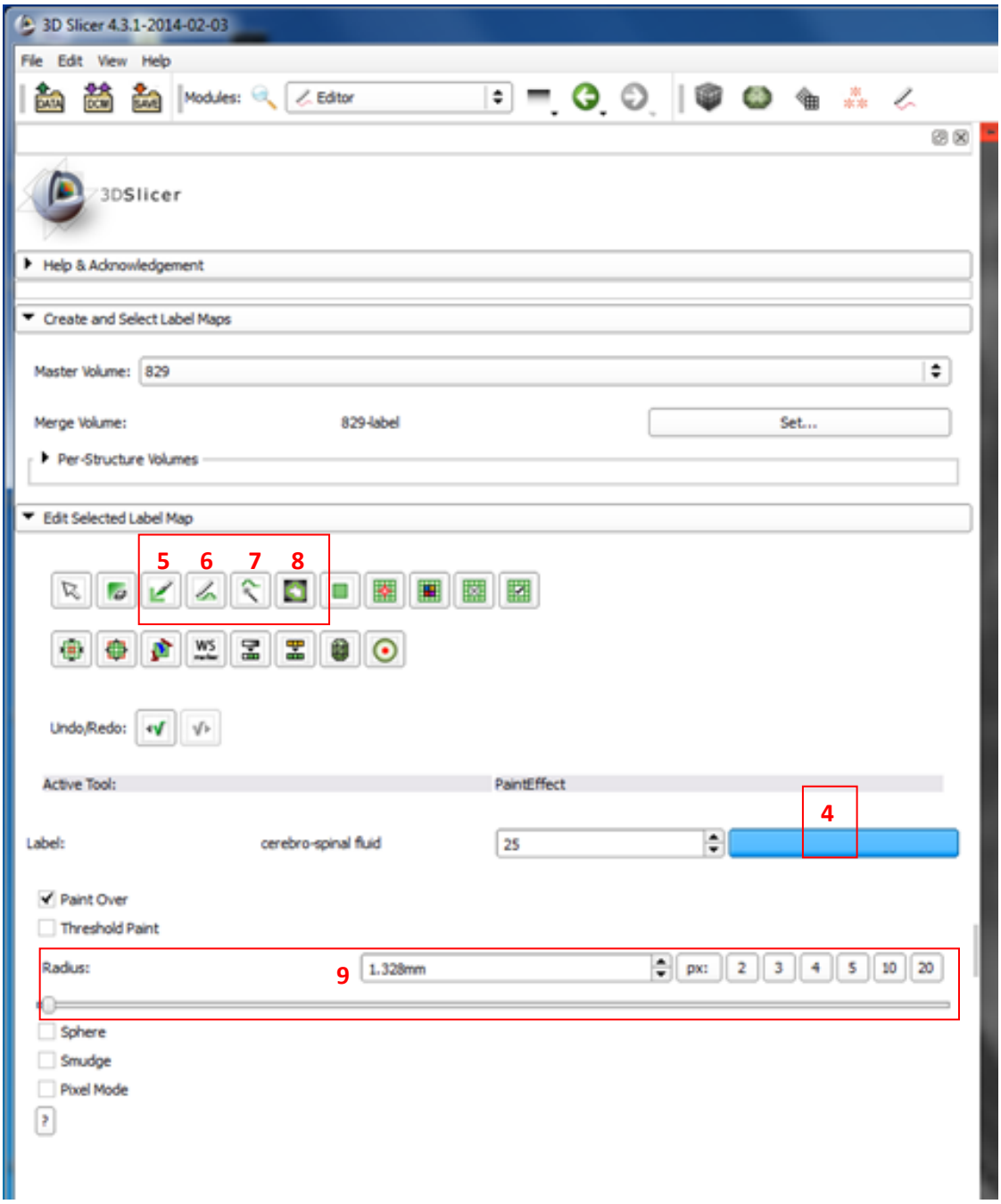
15. The tools available for drawing are:-

5- this gives a circle which you can use to fill in the area you choose. Simply left click and hold then release to apply the colour. You can increase the size of the circle by either choosing one of the pre-set sizes or by sliding the tool bar (**9**) below the colour selector

6- free hand line drawing- left mouse and hold to draw- right mouse click within drawn area to fill it

7- spot fill – click with left mouse to fill one pixel at a time

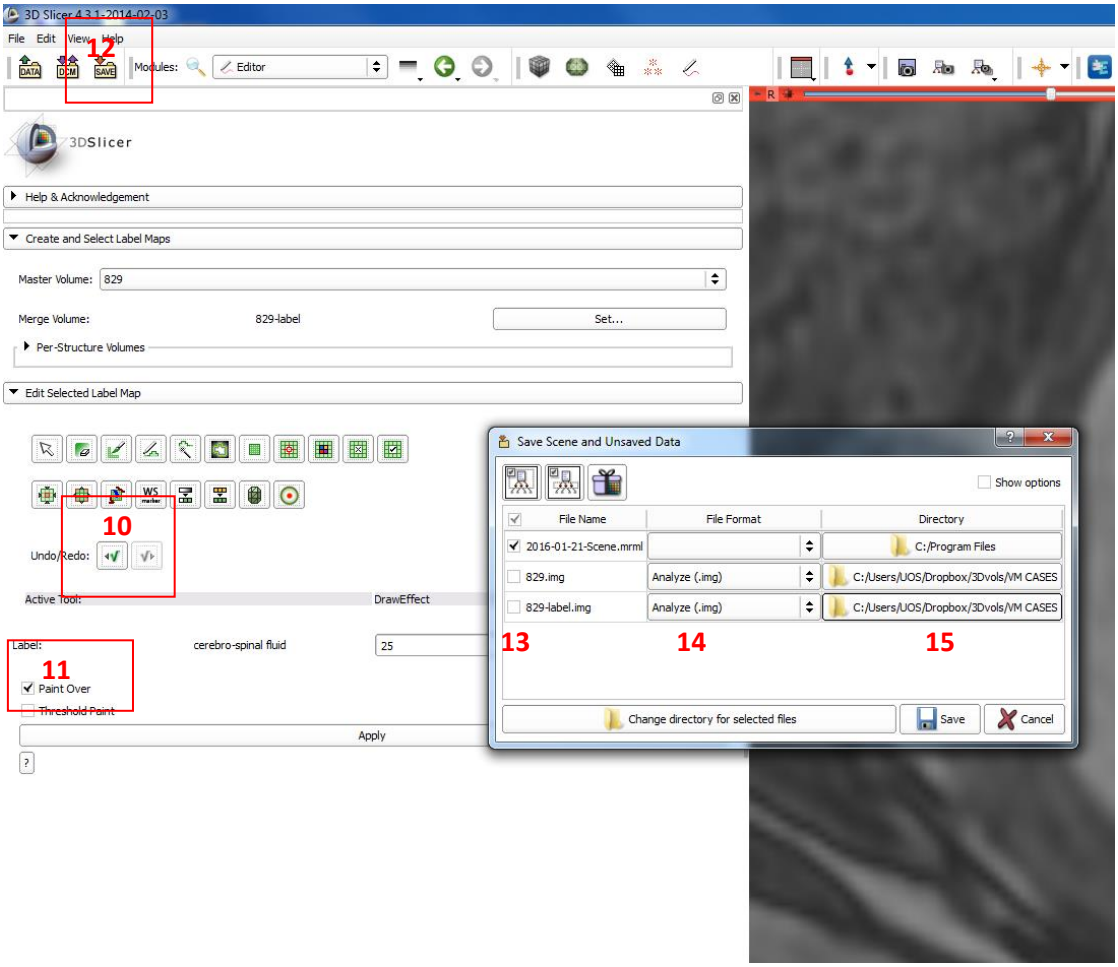
8- pixel intensity matching- this gives a box which will find pixels of similar intensity across the image



If you make a mistake you can use the undo/re apply button (**10**)

NB When moving on to applying subsequent colours it is important to make sure the 'paint over' (**11**) button is unchecked unless you do actually want to do this.

NB Remember to save your work at regular intervals. To do this select save (**12**) and in the pop up box tick what you want to save (the label is what you have drawn **13**) Change the file format to Analyze(.img) (**14**) using the drop down arrow. Select where you want to save the file to by clicking **15** and choosing file the location.

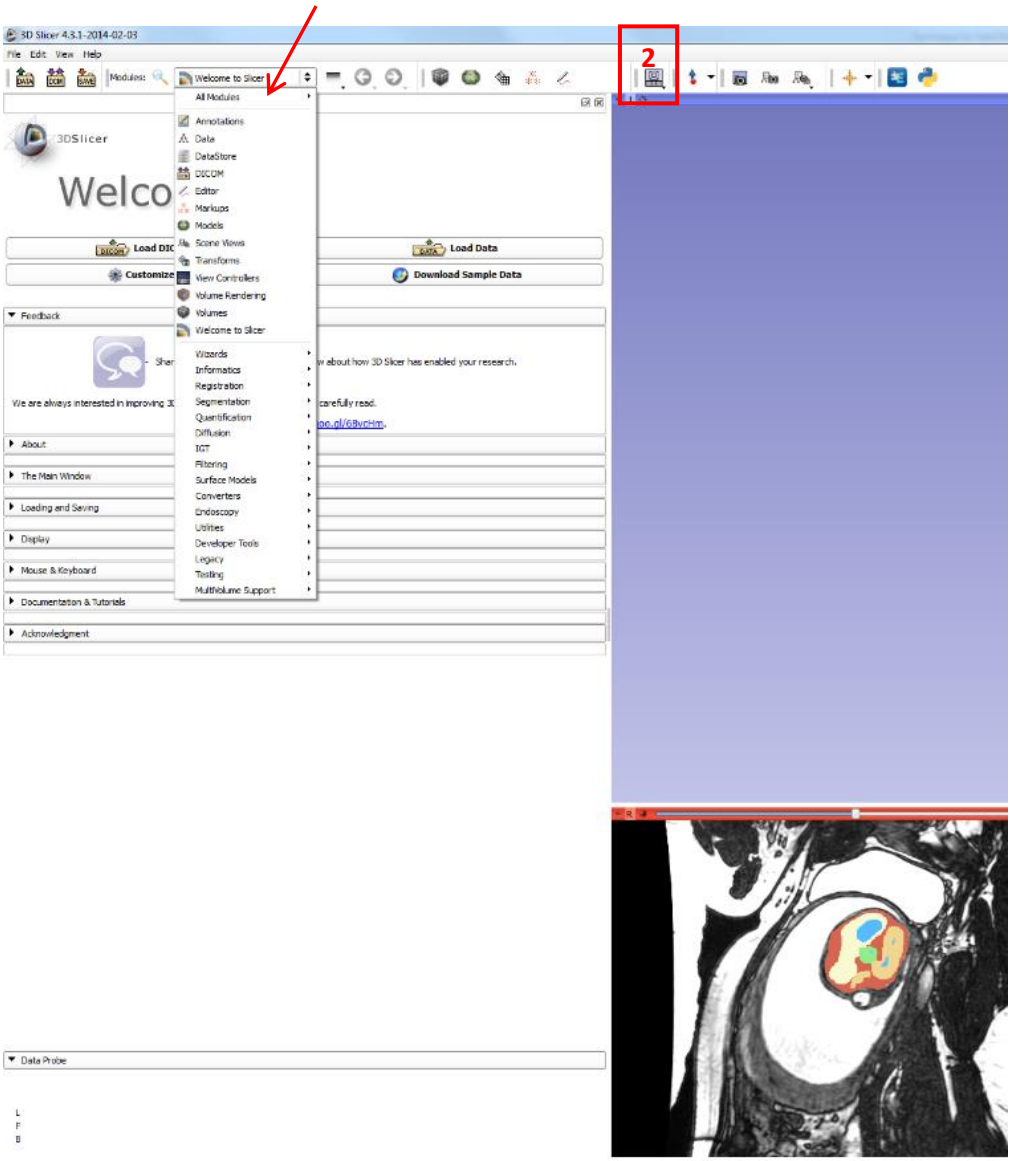


When all the anatomy has been annotated a 3D model can be built. This can be done at any time point i.e. just to see ventricles etc. but it is important to note – Slicer has a slight bug in that if models are continually built at different stages it can corrupt the data and this results in missing patches in the model.

Building the 3D Model.

a) Set the view to Conventional (**2**) in order to see the model when it is built

b) Select- All models -then Model Maker from the drop down menu (arrow)



c) In boxes **16** and **17** use the drop down arrows and choose ‘create new model hierarchy

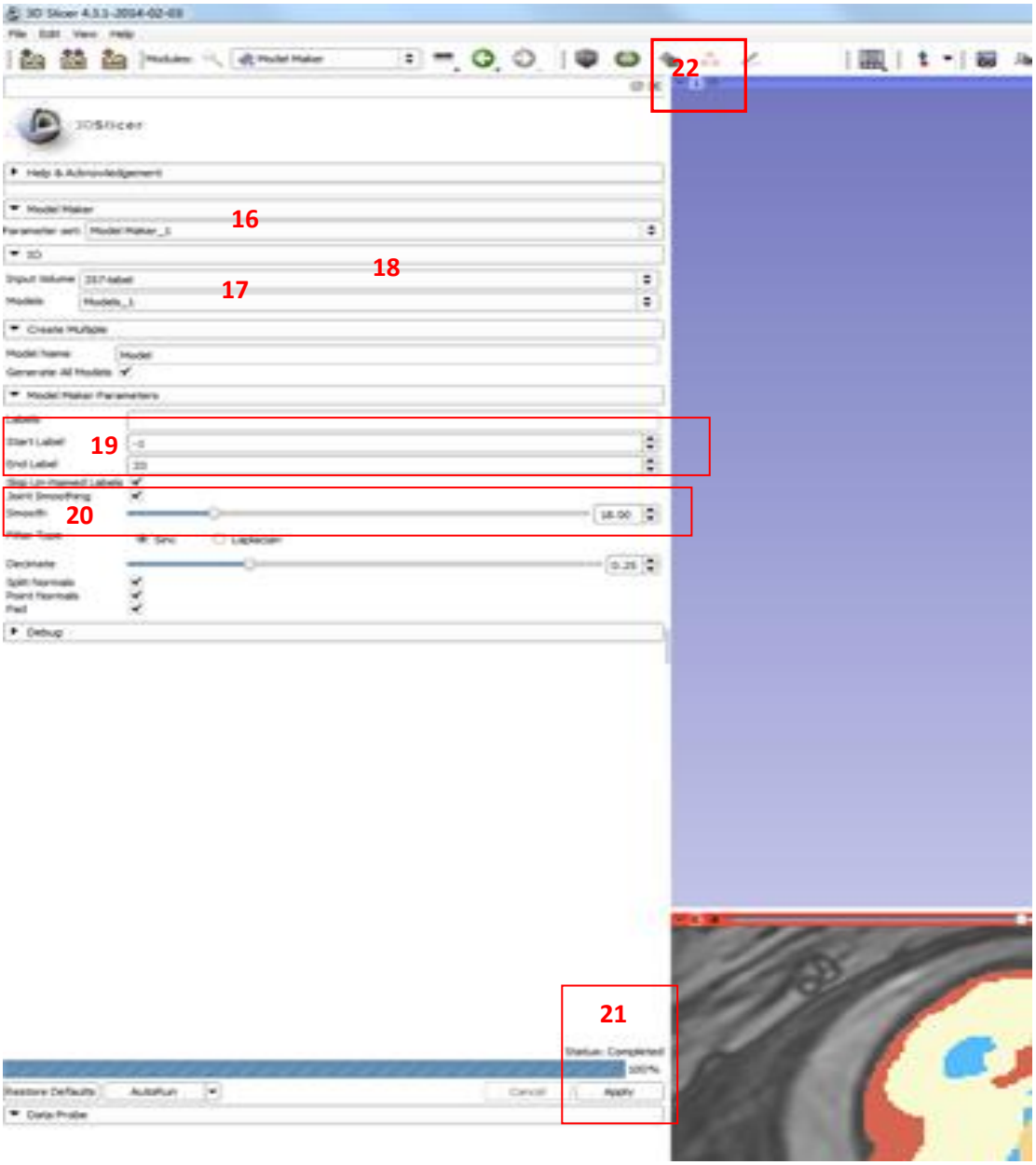
d) In box **18** select the label you have drawn from the drop down menu

e) In model Maker Parameters (**19**) choose the range of labels you want including eg 1-25

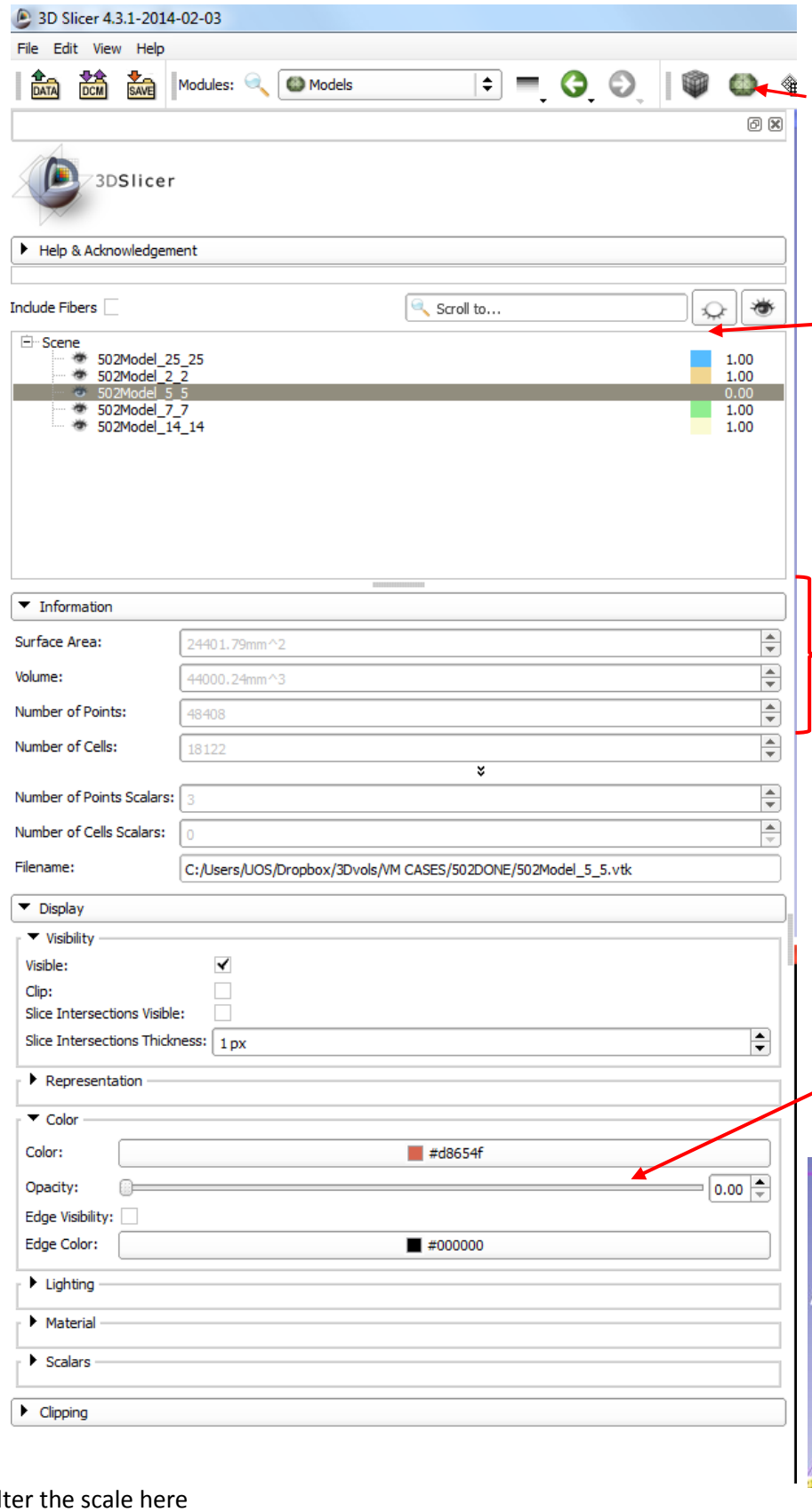
f) Check the Joint Smoothing box and move the slide to 18 (**20**)

g) Click Apply **21**

The facility to rotate, centre, change background colour etc. can be found behind the pin icon **22**



Viewing the model and Quantitative Data

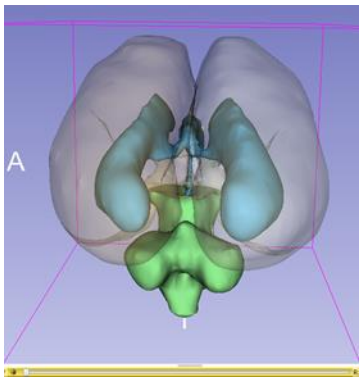


a) Click on icon

b) Click on one of the labels listed to adjust that label

Quantitative data is displayed here

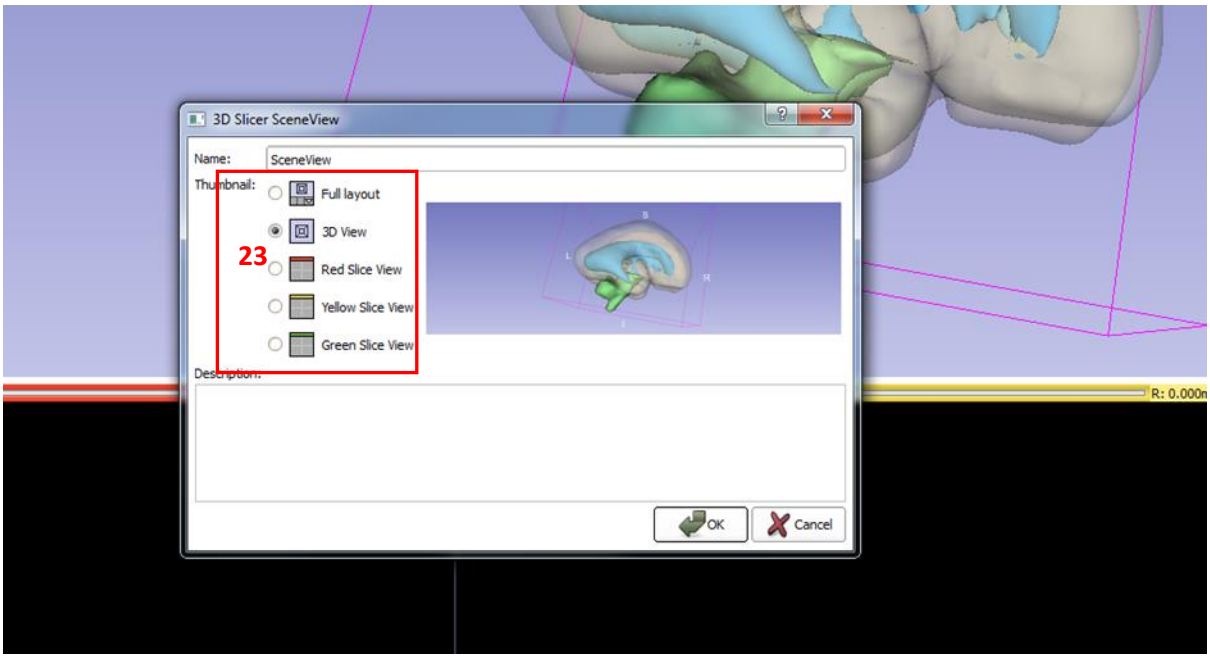
To change the opacity as below



alter the scale here

To save images of the model you build you can take screen shots. Click on the  icon on the tool bar.

Click on the view (**23**) you want to save and give the image a name in the box. Click ok. You will still need to save the image to a file location in the same way you save your labelling (**12**)

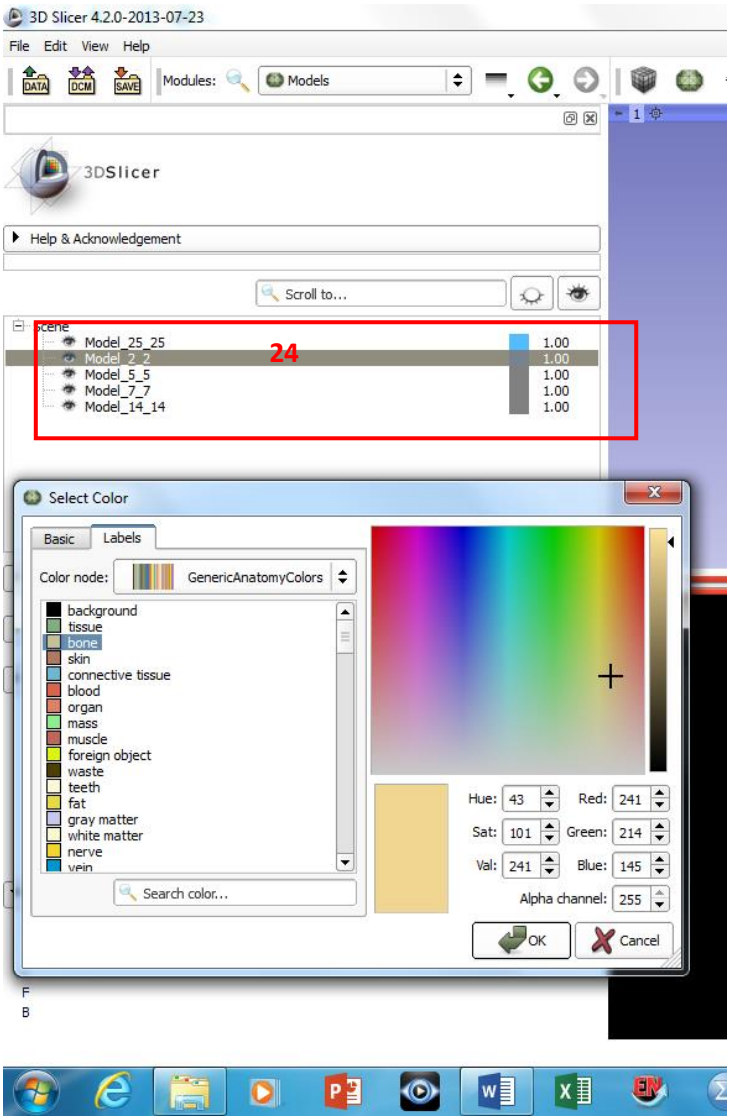


Re-loading previously annotated data.

Slicer will save annotated data as a label and can be saved at any timepoint- finished or not. To re-load previous label you do this in the same way as selecting the data initially with the exception that you not only have to select the original file but also the matching label file by using ctrl.

If you have already saved a model you will need to choose each of the model files. A reloaded model will be shown as a single colour (grey) but each of the files will be shown separately (**24**)

To reapply the colours to each label double click the grey box for each model label. This will bring up a box where you can select the colour you wish to apply.


3D Slicer 4.2.0-2013-07-23
File Edit View Help
Modules:
Models
3DSlicer
Help & Acknowledgement
Scroll to...
Scene
Model_25_25 1.00
Model_2_2 1.00
Model_5_5 1.00
Model_7_7 1.00
Model_14_14 1.00
24
Select Color
Basic
Labels
Color node:
GenericAnatomyColors
background
tissue
bone
skin
connective tissue
blood
organ
mass
muscle
foreign object
waste
teeth
fat
gray matter
white matter
nerve
vein
Search color...
Hue: 43
Red: 241
Sat: 101
Green: 214
Val: 241
Blue: 145
Alpha channel: 255
OK
Cancel
F
B