

Anatomical subgroup analysis of the MERIDIAN cohort: Ventriculomegaly

Short title: iuMR for Ventriculomegaly

Paul D Griffiths PhD FRCR¹, Karen Brackley FRCOG DM², Michael Bradburn MSc³,
Daniel JA Connolly BSc MRCP FRCR⁴, Mary L Gawne-Cain MRCP, FRCR, MD²,
Daniel I Griffiths BSc⁵, Mark D Kilby DSc MD FRCOG, FRCPI⁶, Laura Mandefield
MSc³, Cara Mooney MSc³, Stephen C Robson MD MRCOG FRCP(Ed)⁷, Brigitte
Vollmer MD PhD⁸, Gerald Mason MD FRCOG⁹

¹Academic Unit of Radiology, University of Sheffield, Glossop Road, Sheffield, S10
2JF, England ii) INSIGNEO Institute for in silico Medicine, University of Sheffield,
UK, S10 2JF, ² University Hospital Southampton NHS Foundation Trust, UK SO16
6YD, ³Clinical Trials Research Unit, School of Health and Related Research, University
of Sheffield, S1 4DA, ⁴Department of Radiology, Sheffield Children's Hospital, S10
2TH and the Royal Hallamshire Hospital, Sheffield Teaching Hospitals NHS
Foundation Trust, S10 2JF, ⁵Academic Unit of Radiology, University of Sheffield, S10
2JF, ⁶i) Centre for Women's & Newborn Health, Institute of Metabolism & Systems
Research, University of Birmingham, B15 2TT. ii) Fetal Medicine Centre, Birmingham
Women's Foundation Trust (Birmingham Health Partners), Birmingham, B15 2TG,
⁷Newcastle University, Newcastle upon Tyne NE2 4HH, ⁸Clinical and Experimental
Sciences University of Southampton and Southampton Children's Hospital, University
Hospital Southampton NHS Foundation Trust SO16 6YD, ⁹Leeds Teaching Hospitals
NHS trust, LS9 7TF

This article has been accepted for publication and undergone full peer review but has not
been through the copyediting, typesetting, pagination and proofreading process, which
may lead to differences between this version and the Version of Record. Please cite this
article as doi: 10.1002/uog.17475

Corresponding author

Professor Paul Griffiths

Academic Unit of Radiology,

University of Sheffield,

Floor C, Royal Hallamshire Hospital

Glossop Road,

Sheffield, S10 2JF

England

Tel. +44 114 215 9604

Fax +44 114 271 1714

Email p.griffiths@sheffield.ac.uk

KEYWORDS: fetus; ventriculomegaly; ultrasonography; magnetic resonance imaging, diagnostic accuracy

ABSTRACT

Objective *To assess the contribution of in utero magnetic resonance (iuMR) imaging in fetuses diagnosed with ventriculomegaly as the only abnormal intracranial finding on antenatal ultrasonography (USS) in the MERIDIAN cohort.*

Methods *We report a sub-group analysis from the MERIDIAN study, of cases of fetal ventriculomegaly diagnosed on USS who then had iuMR imaging within 2 weeks of USS and for whom outcome reference data were available. The diagnostic accuracy of USS and iuMR are reported in relation to the severity of ventriculomegaly. We also study the*

difference in measurements of trigone size on the two imaging methods and present the clinical impact of adding iuMR to the diagnostic pathway.

Results *USS failed to detect 31 additional brain abnormalities other than ‘ventriculomegaly’ in the subgroup of 306 fetuses, giving an overall diagnostic accuracy of 89.9% for USS, whilst iuMR correctly detected 27 giving a diagnostic accuracy of 98.4% (statistically significant $p < 0.0001$). There were other brain abnormalities in 14/244 of fetuses with mild ventriculomegaly on USS (diagnostic accuracy 94.3%), and iuMR correctly diagnosed 12 of those (diagnostic accuracy 98.8%). All of those results reached statistical significance in favour of iuMR. There was a close agreement between the size of trigones measured on USS and on iuMR, with categorical differences in only 16% of cases. iuMR did not systematically over-estimate trigone size, as suspected before the study commenced. Complete prognosis data were available in 295/306 fetuses and the prognosis category changed after iuMR in 69/295 (23.4%) cases. The overall effect of iuMR on clinical management was considered to be either ‘significant’, ‘major’ or ‘decisive’ in 76/295 (25.8%) cases.*

Conclusion *Our data suggest that any woman whose fetus has ventriculomegaly as the only intracranial finding on USS should be offered an adjuvant investigation of iuMR for further evaluation.*

INTRODUCTION

Women in the UK are offered ‘mid-trimester anomaly scanning’ using ultrasonography (USS) at approximately 20 weeks gestational age with the aims set out by the national fetal anomaly screening program. These include the identification of serious abnormalities incompatible with life or associated with morbidity. Some abnormalities, however, are recognised for the first time later in pregnancy when further USS might be performed for reasons such as monitoring fetal growth or investigating reduced fetal movements. Fetal brain abnormalities are amongst the commonest lesions recognised on antenatal USS and are important because of the high risk of detrimental long-term neurodevelopmental outcomes. Enlargement of the lateral cerebral ventricles (or ventriculomegaly - VM) is by far the commonest intracranial abnormality recognised on antenatal USS (approximately 2.5/1000 pregnancies¹) but the clinical significance of this finding is complex. VM can be associated with other structural abnormalities (in which case the prognosis is often poor) but most often it is the only abnormal intracranial finding. In this situation, prognosis is related to the degree of VM, fetuses with larger ventricles generally have a higher risk of poor neurodevelopmental outcome.

The ‘Magnetic Resonance imaging to enhance the diagnosis of fetal developmental brain abnormalities *in utero*’ (MERIDIAN) study² is a multicentre prospective cohort study based in the UK designed to evaluate the diagnostic and clinical benefits of *in utero* Magnetic Resonance (iuMR) imaging in diagnosing fetal brain pathology antenatally. A description of the overall findings from the cohort has been reported previously³ and has confirmed major diagnostic and management impact when iuMR is included in the diagnostic pathway. At the planning stage of the study, focus groups of

fetal medicine consultants were asked what information MERIDIAN should attempt to provide in order to improve clinical practice and the most frequent response called for a sub-group analysis of apparently isolated VM on USS. In this paper, we detail the diagnostic and clinical impact brought about by including iuMR in the diagnostic pathway in 306 fetuses with VM as the only abnormality shown on antenatal USS.

METHODS

The fetuses reported in this paper came from the MERIDIAN cohort and the overarching methodology of that study is reported elsewhere^{2,3} but the parts relevant to this paper are summarised here. MERIDIAN was undertaken in accordance with the Medicines for Human Use (Clinical Trials) Regulations 2004 and ethics approval was obtained for a multi-centre study through the Integrated Research Application System (62734). Inclusion criteria were – pregnant women aged ≥ 16 years whose fetus had a brain abnormality detected by USS at a gestational age of 18 weeks or more, with no contraindications to iuMR and gave written, fully informed consent to enter the study. Recruitment was from 16 fetal medicine units in the UK.

Ultrasonography and iuMR imaging

All of the USS studies were performed by appropriately trained NHS consultants in fetal medicine and they recorded each brain abnormality using nomenclature from the “*ViewPoint*” antenatal ultrasound reporting software (GE Healthcare, Chalfont St Giles UK). Each woman then had an iuMR examination performed on a 1.5T superconducting clinical MR system at one of six centres. The base requirement for the iuMR study was T2-weighted images of the fetal brain in the three orthogonal planes and a T1-weighted ultrafast sequence in at least one plane (usually axial). The reporting radiologist was aware of the diagnoses made on USS from the study paperwork and also had access to the full clinical USS report. The radiologist was required to comment on each brain abnormality recognised on USS (using ‘diagnosis excluded’ if the finding was not present on iuMR) and added extra anatomical diagnoses where appropriate onto a similar form as used for USS.

In cases where the pregnancy continued and the child survived, outcome reference data (ORD) was obtained from the clinical notes based on diagnoses made on postnatal neuroimaging studies up to the age of six months, with the exception of those fetuses described in b) below. In cases of Termination of pregnancy (TOP), stillbirth or neonatal deaths the ORD was based on autopsy and/or post-mortem MR imaging. An independent paediatric neuroradiologist determined whether a full review by a Multidisciplinary Independent Expert Panel (MIEP) was required. Review was required in every case unless;

- a) There was complete and unequivocal agreement between the abnormal findings on USS, iuMR and the ORD; or
- b) VM was the only finding described on both USS and iuMR examinations but the size of the ventricles had returned to normal as shown on USS later in pregnancy or on neonatal imaging. The latter was counted as agreement in recognition that VM commonly resolves spontaneously during later pregnancy.

The MIEP consisted of three consultants working in the NHS (neuroradiologist, fetal medicine consultant, and paediatric neurologist) from a centre that did not recruit into MERIDIAN. They were asked to judge if the USS-based diagnoses and iuMR-based diagnoses were in complete agreement with the ORD. The primary analysis in MERIDIAN centred on participants who underwent iuMR within 14 days of USS and for whom ORD was available and consisted of a calculation of diagnostic accuracy for USS and iuMR studies defined as;

$$[\text{True positives} + \text{True negatives}] / \text{Total number of cases}$$

Potential differences in the diagnostic accuracies of USS and iuMR were assessed by McNemar's paired binomial test. The subgroup reported in this paper consists of women who were recruited into MERIDIAN carrying a fetus with VM as the only finding on USS. Fetal VM was categorised into three groups based on the size of the largest trigone measured on USS as used clinically in the referring centres namely;

- mild (10, 11 and 12mm)
- moderate (13, 14 and 15mm)
- severe (16mm and over).

Presence of other brain abnormalities

The main analysis consists of calculations of diagnostic accuracy of USS and iuMR by comparing of the ORD with the imaging-based diagnoses in the entire sub-group and then in relation to the severity of VM diagnosed on USS.

Assessment of ventricular size

The fetal medicine consultant performing the USS was asked to record the ventricular measurements as left or right trigone and to specify which one was the near-field measurement. There are frequently problems in visualising the near-field ventricle on USS and hence measurements may be difficult for that hemisphere. The trigone measurements made on iuMR imaging were recorded and compared with the USS-derived measurements. We first compared the category of VM made on USS and iuMR by taking the size of the largest trigone and classified it as mild, moderate or severe using the definitions given above. We then compared the absolute measurements of the left and right trigones made on USS and iuMR and describe the difference in order to

judge the degree of agreement. We also compared the degree of agreement in relation to which measurement was near-field and which was far-field on USS.

We also assessed the risk of other brain abnormalities in relation to unilateral or asymmetric VM as judged by iuMR imaging. In accordance with our previous publications, unilateral VM is defined in a fetus with one trigone measurement of $\geq 10\text{mm}$ and the other within the normal range. Asymmetric VM is defined in a fetus where both trigone measurements are $\geq 10\text{mm}$ but there is a difference between the two sides of $\geq 3\text{mm}$. Fisher's Exact test was used to test for a statistically significant difference in other brain abnormalities between unilateral and asymmetric VM.

Effects on clinical management

MERIDIAN captured data from the fetal medicine specialists about changes in prognosis and clinical management brought about by iuMR as described in detail elsewhere³ and we have included that data in the assessment of value of iuMR data. The fetal medicine specialist was asked to record the predicted prognosis on each case before the iuMR study was performed i.e. based on USS information only. Five categories were used:

- 1) Normal - no worse than the risk to a fetus without a demonstrable brain abnormality
- 2) Favourable - Normal neurological outcome expected in $>90\%$ of cases
- 3) Intermediate - Normal neurological outcome expected in 50 to 90% of cases
- 4) Poor - Normal neurological outcome expected in $<50\%$ of cases
- 5) Unknown

At the next consultation with the woman, at which time the iuMR report was available, the clinician was asked if iuMR had provided any extra diagnostic information. They

also recorded the updated prognostic information using the same five categories. For the purposes of description in this report we describe if the prognosis remained the same worsened or improved after iuMR. This approach is straightforward when prognoses were in groups 1) to 4) or if the prognosis was ‘Unknown’ on both USS and iuMR. Problems arise when the prognosis on one imaging method was ‘Unknown’ but specified on the other. We elected to assign:

- USS prognosis ‘Unknown’, iuMR prognosis ‘Normal’ or ‘Favourable’ = improved prognosis
- USS prognosis ‘Unknown’, iuMR prognosis ‘Intermediate’ = no change in prognosis
- USS prognosis ‘Unknown’, iuMR prognosis ‘Poor’ = worse prognosis
- USS prognosis ‘Normal’ or ‘Favourable’, MR prognosis ‘Unknown’ = worse prognosis
- USS prognosis ‘Intermediate’, MR prognosis ‘Unknown’ = no change in prognosis
- USS prognosis ‘Poor’, MR prognosis ‘Unknown’ = no change in prognosis

Clinicians were asked if TOP was offered because the abnormalities on USS only were sufficient to consider that option under Ground E of the Abortion Act (section 1(1)(d) – substantial risk of serious mental or physical handicap).⁴ They were subsequently asked if they would now offer TOP with the combined results. Finally, the fetal medicine specialists were asked to rate the overall contribution iuMR to the final clinical management choice using a five point descriptive scale; a) No effect, b) Minor effect, c) Significant effect, d) Major effect, and e) Decisive effect.

RESULTS

The primary MERIDIAN cohort consisted of 570 fetuses with ORD and in whom the iuMR study was done within 2 weeks of the referring USS study. 421 (73.9%) of those fetuses had VM as part of the USS diagnosis and in 306/570 (53.7%) VM was the only intracranial abnormality shown on USS. Those 306 cases form the basis of this report and the gestational age at which iuMR was performed in that group is shown in figure 1. 199/306 fetuses (65%) had their iuMR studies between 18 and 23 weeks and 107/306 (35%) at or after 24 weeks. 244/306 (80%) fetuses had mild VM, 36/306 (12%) moderate VM and 26/306 (8%) severe VM according to the largest of the trigone measurements on USS. 14/306 (5%) had known non-brain abnormalities, including 5 cardiac abnormalities, 3 thoracic, 3 head and neck, 2 abdominal and 1 genitourinary. 11/306 (4%) had chromosomal or genetic abnormalities, shown in table 1.

Presence of other brain abnormalities

Additional brain abnormalities other than VM were found on ORD in 31/306 fetuses (10.1%), 17/199 (8.5%) in the 18-23 week group and 14/107 (13.1%) in the ≥ 24 week group. Other brain abnormalities were shown in 5.7% (14/244) of fetuses with mild VM, 19.4% (7/36) of fetuses with moderate VM rising to 38.5% (10/26) of fetuses with severe VM (table 2). Those brain abnormalities consisted of:

- Failed commissuration (agenesis and hypogenesis of the corpus callosum) in 17/31 (55%). Three cases had other significant brain/eye abnormalities
- Encephalomalacia and/or intracranial haemorrhage in 8/31 (26%)
- Cortical formation abnormalities in 4/31 (13%)

- Absent cavum septum pellucidum due to septo-optic dysplasia in 2/31 (6%)

‘Acquired brain pathologies’ (i.e. encephalomalacia or intracranial haemorrhage) accounted for 1/17 (7%) cases of brain abnormalities in the 18 to 23 week group and 7/14 (50%) cases in the ≥ 24 weeks group. ‘Acquired brain pathologies’ were most frequently found in conjunction with moderate or severe VM. When the results of iuMR studies were compared with the ORD results there was complete agreement in 302/306 fetuses, of which 27 cases had additional pathologies and 275 cases were confirmed to have VM alone. The four fetuses incorrectly diagnosed on iuMR consisted of three cases of failed commissuration (all hypogenesis of the corpus callosum) and one case of absent cavum septum pellucidum. Representative cases are shown in figures 2-6.

Assessment of ventricular size

VM was the only intracranial finding on USS, iuMR and ORD in 275 fetuses - mild VM in 230/275 (84%), moderate VM in 29/275 (10%) and severe VM in 16/275 (6%) based on USS measurements. The trigone measurements of the 275 iuMR studies were compared with the equivalent USS measurements, and agreement by category (i.e. mild, moderate or severe) was found in 230/275 (84%) and disagreement by category in 45/275 (16%). In all but one case the degree of disagreement was only one category (table 3), including 4 cases in which the iuMR measurements of the trigones were within the normal range.

In 42/275 cases (15%) only one trigone could be measured on USS because of near-field effects, so it was only possible to compare the absolute measurements of 508 trigones on USS and iuMR (both trigones in 233 cases and one trigone in 42 cases – figure 7). In 142/508 (28%) the trigone measurements made on USS and iuMR agreed

to the nearest millimetre, 326/508 (64%) measurements were within $\pm 1\text{mm}$ and 409/508 (81%) were within $\pm 2\text{mm}$. The distribution of the differences was symmetrical, indicating that there is no tendency for iuMR to systematically either under-estimate or over-estimate the trigone size compared with USS.

It was possible to make a direct comparison of trigone measurements made on USS and iuMR with the knowledge of which USS measurement was near-field and which was the far-field in 197 fetuses with 394 trigones. In 36 cases the near-field/far-field information was not recorded and in 42 cases it was only possible to measure the far-field trigone on USS. In the 197 cases that could be assessed there was no significant difference in the level of agreement between the measurements made on near-field and the far-field measurements trigones - difference (modulus) for near field measurements ($1.6 \pm 1.8\text{mm}$) and for far field ($1.5 \pm 1.9\text{mm}$) indicating close correlation in those ventricles that could be visualised on USS.

109/306 (35.6%) fetuses had unilateral VM and 44/306 (14.4%) fetuses had asymmetric VM on iuMR imaging. Other brain abnormalities were found in 2/109 (1.8%) fetuses with unilateral VM (both with cortical formation abnormalities) and 5/44 (11.4%) fetuses with asymmetric VM (four cases of failed commissuration [with a cortical formation abnormality in one] and one case of intracranial haemorrhage) with a statistically significant difference of 9.6% ($p=0.0213$). This is compared with a rate of brain abnormalities of 23/149 (15.4%) in fetuses with symmetric VM. NB there were 4 fetuses in which VM was excluded on iuMR imaging.

Effects on clinical management

There was incomplete prognosis/management data in 11/306 (3%) cases hence it was possible to study effects on prognosis/management brought about by the iuMR in 295 fetuses; this included 29/31 fetuses with other brain abnormalities (table 4). In 106/295 (35.9%) cases fetal medicine consultants recorded that iuMR provided additional information over that available on USS. The prognosis category changed after iuMR in 69/295 (23.4%) cases, in 22 cases the prognosis was worse after iuMR and in 47 the prognosis was improved after iuMR. TOP was offered to 42/295 (14.2%) women on the basis of the USS alone and in eight of those cases the offer of TOP was reversed on the basis of iuMR imaging. In addition, TOP was offered to a further 14 women after iuMR on the basis of brain abnormalities other than VM being diagnosed (see below and table 4). As a consequence, the decision to offer TOP was changed after iuMR in 22/295 (7.5%) fetuses. Termination was performed in 14/295 (4.7%) cases. The effect of iuMR on clinical management on the whole group of 295 fetuses according to the fetal maternal expert was described as none (14%), minor (61%), significant (21%), major (4%) and decisive (0.3%).

A detailed summary of the effects on prognosis and management on the 29/295 fetuses that had brain pathology other than VM and complete prognosis/management data is presented in table 4. Prognosis was considered worse after iuMR in 13/29 (44.8%) cases and the effect of iuMR on overall clinical management was 'significant', 'major' or 'decisive' in 15/29 (51.7%).

DISCUSSION

VM refers to enlargement of the ventricular system and can involve some, or all, of the cerebral ventricles but the clinical assessment of ventricular size on antenatal USS is centred on the trigones of the lateral ventricles. To reduce the subjective nature of assessing 'enlarged ventricles', ultrasonographers have devised a reproducible method for assessing the trigone size of the lateral ventricles⁵. A measurement of $\geq 10\text{mm}$ is considered to be abnormal at any stage of pregnancy as this is approximately 4 standard deviations above the mean. This definition is generally accepted for fetal VM in the UK and used in MERIDIAN. It should be appreciated that it is possible to have VM involving other parts of the ventricular system (e.g. frontal horns) with trigone measurements $< 10\text{mm}$, these cases are relatively rare and have not been included herein.

VM can be categorised further based on the largest trigone size. The MERIDIAN recruiting centres use three categories, mild ($10\text{--}12\text{mm}$), moderate ($13\text{--}15\text{mm}$) and severe ($\geq 16\text{mm}$). The extra level of detail allows correlation with long-term neuro-developmental outcomes in cases where VM is the only abnormality. All referring centres in MERIDIAN regard 'isolated' mild VM as low risk and place such fetuses in the 'Favourable - Normal neurological outcome expected in $\geq 90\%$ of cases' group. Specifically, half quote $\geq 90\%$ chance of normal outcomes and the other half quote $\geq 95\%$. There was considerable variation in the prognosis given to fetuses with moderate VM. Of the 36 cases of moderate VM on USS, full prognosis/management data was available in 34. The referring fetal medicine consultants gave a 'favourable' prognosis to 7/34, 'intermediate' prognosis to 21/34, 'poor' prognosis to 5/34 and 1/34 'not known' before iuMR imaging. This is in spite of robust information in published

literature that mostly describes ‘intermediate’ prognosis. Similarly, there is robust published literature about the ‘poor’ prognosis for fetuses with severe⁶ but the 24 fetuses with severe VM in this study with full prognosis/management data were given an ‘Intermediate’ prognosis in 8/24 and ‘Poor’ in 16/24 after USS alone. This indicates a degree of clinical uncertainty in the UK. Future follow-up studies of the MERIDIAN cohort may provide results in order to clarify this uncertainty.

The overall rates of unilateral and asymmetric VM are in line with our previous publications^{7,8}. In this study we have shown that the risk of another brain abnormality is reduced in fetuses with unilateral VM when compared to those with bilateral VM (9.6% difference, $p=0.0213$). This is in comparison with asymmetric VM cases, in whom the risk is no different from the bilateral group.

There is now considerable evidence supporting the value of iuMR in diagnosing fetal brain abnormalities, based on systematic reviews⁹⁻¹² and our prospective study³. Whilst designing MERIDIAN we formed fetal medicine focus groups to identify important issues to be addressed. One major recommendation was the need to perform separate analyses on anatomical sub-groups of fetal brain abnormalities, including isolated VM. Some questions related to differences in the technical measurements of the ventricles on USS and iuMR, specifically there was an impression that iuMR over-estimated ventricle size compared with USS. The depth of problems arising from near-field effects on USS was also identified for investigation. We have attempted to address those issues herein but the leading issue raised by the focus groups was the widely held belief that when mild VM is the only intracranial finding on USS the diagnosis is invariably correct and

does not require iuMR imaging. This is of importance to healthcare funders because, if that opinion is correct, the resources required to provide a clinical service are significantly reduced.

The sub-group analysis of VM cases from MERIDIAN presented here shows additional brain abnormalities were present in 31/306 (10.1%) of fetuses overall and there was a higher rate of brain abnormalities in the more severe VM categories, which is comparable with our previous report, although ORD was not available in that study^{7,8}. Other brain abnormalities were shown in 5.7% (14/244) of fetuses with mild VM, 19.4% (7/36) of fetuses with moderate VM rising to 38.5% (10/26) of fetuses with severe VM, compared with 6%, 14% and 57% respectively in our previous work. iuMR demonstrated 27/31 of the other brain abnormalities and improved diagnostic accuracy in all VM categories. A factor that has the potential to reduce the diagnostic accuracy of USS is the deleterious results of the near-field effect. Although there is good correlation of trigone sizes between USS and iuMR when trigones can be visualised on USS, we have shown that in 15% of the cases reported one cerebral hemisphere was not visualised to a degree that the trigone of the lateral ventricle could not be measured. This is likely to be an important diagnostic limitation generally but particularly in cases of unilateral pathology if it involves the ‘near-field’ hemisphere. This can interfere with the detection of both developmental brain pathology (cortical formation abnormalities are frequently unilateral) and acquired pathology (e.g. haemorrhage and encephalomalacia).

iuMR had a major clinical impact in cases of USS-diagnosed VM. The prognosis was changed in 23.4% and the overall effect on clinical management was considered to be ‘Significant’, ‘Major’ or ‘Decisive in over 25% of cases. The decision to discuss TOP

was changed in 7.5% of foetuses, this included reversing a decision to offer TOP based on USS (8 fetuses) and offering TOP after iuMR that was made after USS alone (14 fetuses).

In conclusion, based on our current data we believe that iuMR imaging should be offered to all women in whom a diagnosis of VM as the sole intracranial abnormality is made on USS. As a minimum, women should be advised that even in cases of mild VM there is a 1 in 20 chance that additional brain abnormalities have been overlooked on USS and this increases with higher categories of VM. The absolute measurements of the size of the trigones of the lateral ventricles are very similar on USS and iuMR, in particular iuMR does not appear to systematically over-estimate the size.

ACKNOWLEDGMENTS

This project was funded by the National Institute for Health Research Health Technology Assessment Programme (project number 09/06/01). The views and opinions expressed therein are those of the authors and do not necessarily reflect those of the Health Technology Assessment Programme, NIHR, NHS or the Department of Health.

REFERENCES

1. European Surveillance of Congenital Anomalies EUROCAT (2012) Prevalence Tables for Nervous system anomalies (per 10,000 births). EUROCAT. Available via <http://www.eurocat-network.eu/accessprevalencedata/prevalencetables>. [29 November 2016]
2. Griffiths PD, the MERIDIAN study group. Protocol 11PRT/2491: Magnetic Resonance Imaging to Enhance the Diagnosis of Fetal Developmental Brain Abnormalities in Utero (MERIDIAN) (ISRCTN27626961) *The Lancet* <http://www.thelancet.com/protocol-reviews/11PRT-2491>
3. Griffiths PD, Bradburn M, Campbell MJ, Cooper CL, Graham R, Jarvis D, Kilby MD, Mason G, Mooney C, Robson SC, Wailoo A. Use of MRI in the diagnosis of fetal brain abnormalities in utero (MERIDIAN): a multicentre, prospective cohort study. *The Lancet* 2016; doi: 10.1016/S0140-6736(16)31723-8
4. Abortion Act 1967 section 1
5. 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):711-714.
6. Hannon T, Tennant PWG, Rankin J, Robson SC. Epidemiology, Natural History, Progression, and Postnatal Outcome of Severe Fetal Ventriculomegaly. *Obstetrics & Gynecology* 2012; **120**(6) : 1345-1353

7. Griffiths PD, Reeves MJ, Morris JE, Mason G, Russell SA, Paley MNJ, Whitby EH. A prospective study of fetuses with isolated ventriculomegaly investigated by ante-natal ultrasound and in utero MR. *Am J Neuroradiol* 2010; **31**(1) : 106-111
8. Griffiths PD, Morris JE, Mason G, Russell SA, Paley MNJ, Whitby EH, Reeves MJ. Fetuses with ventriculomegaly diagnosed in the second trimester of pregnancy by in utero MR imaging: What happens in the third trimester? *Am J Neuroradiol* 2011; **2**(3) : 474-480.
9. Mundy L, Hiller J, Braunack-Mayer A, Merlin T. MRI for the detection of foetal abnormalities. *Adelaide: Adelaide Health Technology Assessment (AHTA)* 2007; **15**(6)
10. Rossi AC, and Prefumo F. Additional value of fetal magnetic resonance imaging in the prenatal diagnosis of central nervous system anomalies: a systematic review of the literature. *Ultrasound Obstet Gynecol* 2014; **44**(4) : 388–393
11. Van Doorn M, Oude Rengerink K, Newsum EA, Reneman L, Majoie CB, Pajkrt E. Added value of fetal MRI in foetuses with suspected brain abnormalities on neurosonography: a systematic review and meta-analysis. *J Matern Fetal Neonatal Med* 2015; **29**(18) : 2949-2961
12. Jarvis D, Mooney C, Cohen J, Papaioannou D, Bradburn M, Sutton A, and Griffiths PD. A systematic review and meta-analysis to determine the contribution of mr imaging to the diagnosis of foetal brain abnormalities In Utero. *Eur Radiol* 2016; DOI 10.1007/s00330-016-4563-4

CONFLICT OF INTEREST

The authors confirm that there are no conflicts of interest.

FIGURE LEGENDS

Figure 1. Gestational ages of 306 fetuses with ‘ventriculomegaly only’ on ante-natal USS at the time of iuMR imaging.

Figure 2. Severe VM was detected in this fetus on USS but no other intracranial abnormalities were shown. Severe VM was confirmed on iuMR (axial images 2a and 2b) along with features consistent with communicating hydrocephalus; enlargement of all cerebral ventricles, large head, reduced extra-axial CSF spaces. Intraventricular clot is shown (mainly in the trigone and occipital horns of the left lateral ventricle) on the axial images (2a and 2b), coronal (2c) and sagittal (2d) images. All of those features were confirmed on post-natal imaging (not shown).

Figure 3. A fetus with severe VM diagnosed on USS and iuMR performed at 36 weeks gestational age. VM was confirmed on axial (3a) coronal (3b) and images and is markedly asymmetric, right worse than left. There is also marked loss of white matter volume adjacent to right lateral ventricle and there is abnormal high signal in the adjacent periventricular/deep white matter diagnosed as encephalomalacia. Those features were confirmed on post-natal MR imaging (3c and 3d).

Figure 4. A fetus with severe VM diagnosed on USS. iuMR was performed at 28 weeks gestation which showed colpocephaly on axial iuMR images (4a) along with agenesis of the corpus callosum on sagittal (4b) and coronal (4c and 4d) images. Those features were confirmed on post-natal imaging (not shown).

Figure 5. A fetus with mild VM on USS. iuMR was performed at 22 weeks gestation and showed colpocephaly on the axial iuMR image (5a) and agenesis of the corpus callosum on the coronal (5b) images. In addition, there is marked irregularity of and

reduced volume of the right frontal lobe (5c-5d) consistent with a cortical formation abnormality, probably polymicrogyria, which was confirmed on autopsy.

Figure 6. A fetus with mild VM diagnosed on USS. iuMR was performed at 21 weeks gestation, which confirmed mild VM/colpocephaly on the axial image (6a) but also showed agenesis of the corpus callosum (6a and 6b). Axial image at the level of the cerebellum (6c) and coronal image through the face (6d) shows poor development of the right globe leading to a diagnosis of Aicardi syndrome. All of those features were confirmed on autopsy.

Figure 7. Differences in 506 trigone measurements made on ultrasonography and iuMR imaging in fetuses with ‘ventriculomegaly only’ on ante-natal ultrasonography, *in utero* MR imaging and confirmed on the outcome reference data.

Table 1.

| Chromosomal / genetic abnormality | Number of fetuses |
|--|--------------------------|
| Trisomy 21 | 7 |
| Aicardi syndrome | 1 |
| Congenital myotonic dystrophy, pneumothorax | 1 |
| Karyotype 47XYY | 1 |
| Trisomy 7q | 1 |

Table 1. The tabulated results of the 11 known chromosomal or genetic abnormalities within 306 fetuses.

Table 2.

| USS Diagnoses | | iuMR Diagnoses | | Comparison of diagnostic accuracy | | | |
|-----------------------------|-----|---|---------------------|---|---------------------|---------------------|-------------------|
| Subgroup | n | Other brain abnormalities on ORD [†] (n) | Diagnostic accuracy | Other brain abnormalities on ORD [†] correctly diagnosed on MR (n) | Diagnostic accuracy | Difference (95% CI) | p-value* |
| <i>All cases of VM only</i> | 306 | 31 | 89.9% | 27 | 98.4% | 8.5(4.9, 12.1%) | <0.0001 |
| Mild | 244 | 14 | 94.3% | 12 | 98.8% | 4.5(1.3, 7.8%) | 0.0034 |
| Moderate | 36 | 7 | 80.6% | 7 | 100% | 19.4(3.7, 35.2%) | 0.0156 |
| Severe | 26 | 10 | 61.5% | 8 | 92.3% | 30.8(9.2, 52.4%) | 0.008 |

Table 2. The results of cases of ‘ventriculomegaly only’ diagnosed by ultrasonography compared with outcome reference data and the results of *in utero* MR imaging in the same cases compared with outcome reference data. The group ‘all cases of VM only’ includes any severity of VM defined as at least one trigone ≥ 10 mm whereas the three other groups have the cases divided by severity of VM (mild = 10-12mm, moderate = 13-15mm and severe ≥ 16 mm). [†] Outcome Reference Diagnosis. * McNemar’s test between ultrasonography and *in utero* MR imaging correct diagnoses.

Table 3.

| Ventricle size based on iuMR | Ventricle size based on USS | | | |
|------------------------------|-----------------------------|---------|-------------|-----------|
| | | Mild VM | Moderate VM | Severe VM |
| | Normal size | 4 | - | - |
| | Mild VM (10-11.9mm) | 201 | 9 | - |
| | Moderate VM | 24 | 16 | 3 |
| | Severe VM | 1 | 4 | 13 |

Table 3. Differences in the category of ventriculomegaly described on ultrasonography and *in utero* MR imaging in 275 fetuses with VM as the only intracranial finding suspected on USS and iuMR and confirmed on outcome reference data.

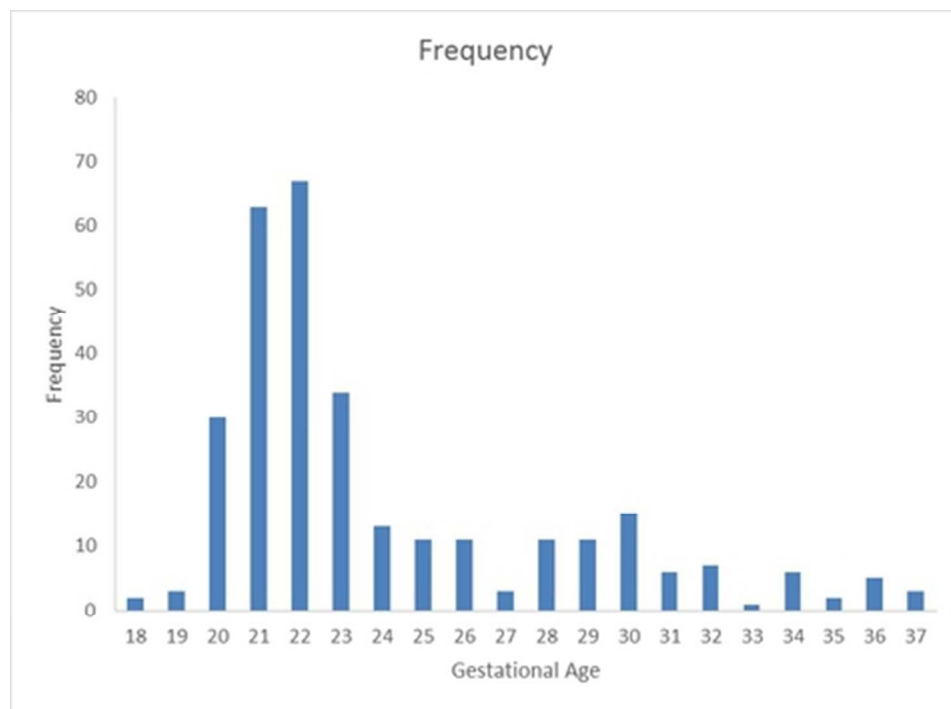
Table 4

| Case | GA at iuMR | USS findings | iuMR findings | ORD | Prognosis from USS | Prognosis from iuMR | TOP offer on USS | TOP offer on iuMR | TOP performed | Effect on management |
|--------------|------------|--------------|---|-------------------------------------|--------------------|---------------------|------------------|-------------------|---------------|----------------------|
| 40 | 21w | Moderate VM | Moderate VM Absent CSP | VM Absent CSP | Favourable | Favourable | No | Yes | No | Minor |
| 48 | 34w | Mild VM | Mild VM | VM Absent CSP | Favourable | Favourable | No | No | No | Minor |
| 79 | 22w | Mild VM | Mild unilateral VM CFA | VM CFA | Favourable | Not known | No | Yes | Yes | Major |
| 155 | 23w | Severe VM | Severe VM | VM Hypogenesis CC | Poor | Poor | Yes | Yes | No | Significant |
| 201 | 31w | Moderate VM | Severe VM ICH | VM ICH | Poor | Poor | Yes | Yes | No | Minor |
| 209 | 22w | Moderate VM | Moderate VM Hypoplasia CC and cerebellum | VM Hypogenesis CC and cerebellum | Intermediate | Not known | Yes | Yes | Yes | None |
| 219 | 22w | Moderate VM | Moderate asymmetric VM, Agensis CC | VM Agensis CC | Intermediate | Intermediate | No | Yes | No | Major |
| 264 | 37w | Severe VM | Severe asymmetric VM, Agensis CC | VM Agensis CC | Intermediate | Poor | No | Yes | No | Minor |
| 297 Fig 2 | 32w | Severe VM | Severe asymmetric VM, ICH | VM ICH | Poor | Poor | No | Yes | No | Major |
| 327 | 35w | Severe VM | Severe VM Agensis CC | VM Agensis CC | Intermediate | Poor | No | Yes | No | Major |
| 340 | 35w | Severe VM | Severe asymmetric VM, Agensis CC CFA | VM Agensis CC CFA | Intermediate | Poor | No | Yes | Yes | Major |
| 343 | 28w | Mild VM | Mild VM encephalomalacia | VM encephalomalacia | Not known | Poor | No | Yes | Yes | Major |
| 433 Fig 3 | 36w | Severe VM | Severe VM encephalomalacia | VM encephalomalacia | Intermediate | Intermediate | No | No | No | Significant |
| 482 | 23w | Severe VM | Severe asymmetric VM | VM Hypogenesis CC | Poor | Poor | Yes | Yes | No | Minor |
| 489 | 22w | Mild VM | Mild VM | VM Hypogenesis CC | Favourable | Favourable | No | No | No | Minor |
| 495 | 28w | Mild VM | Mild VM ICH | VM ICH | Favourable | Favourable | No | No | No | Minor |

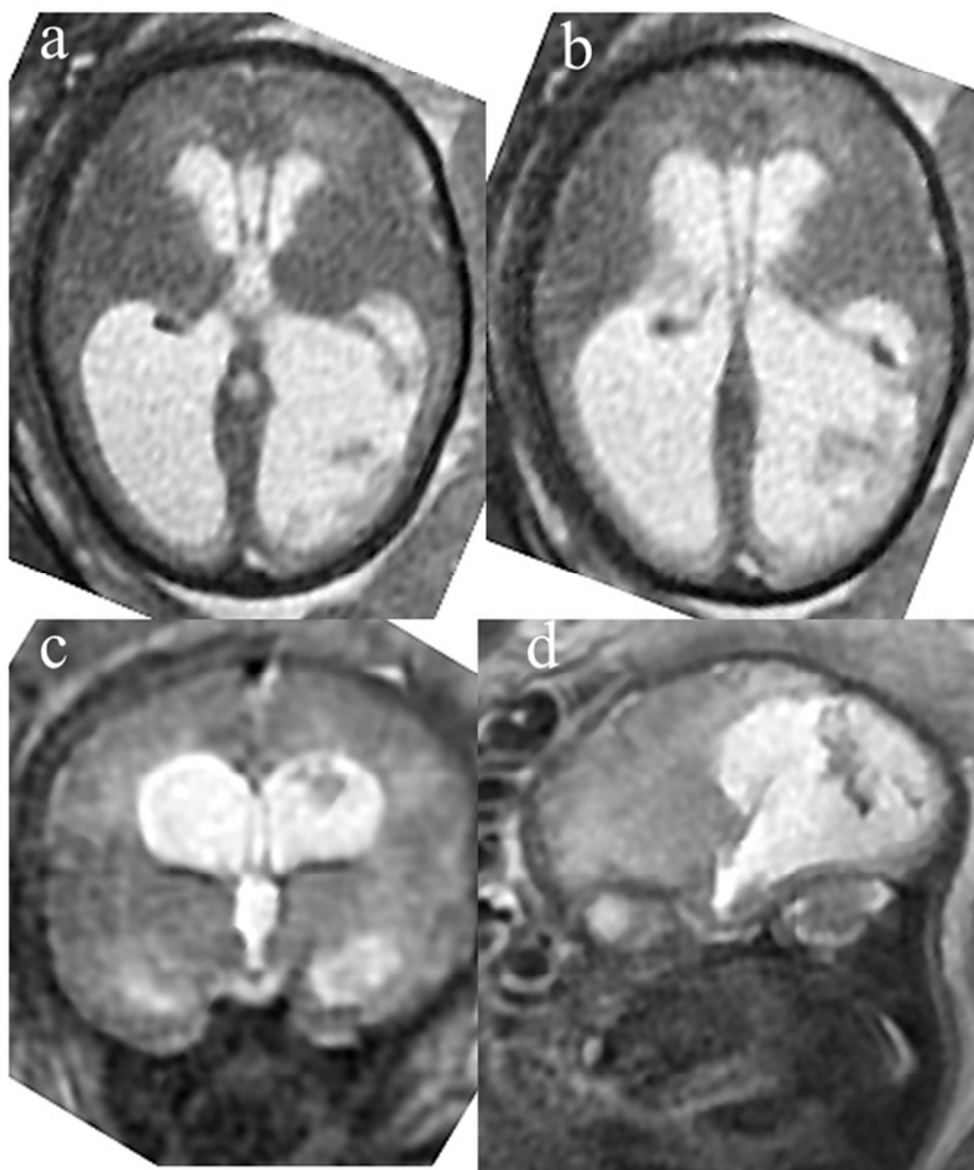
| | | | | | | | | | | |
|--------------|-----|-------------|--|---|--------------|--------------|-----|-----|-----|-------------|
| 509 | 24w | Moderate VM | Severe VM ICH | VM ICH | Poor | Poor | No | Yes | Yes | Significant |
| 528 | 22w | Mild VM | Mild VM Agenesis CC | VM Agenesis CC | Favourable | Intermediate | No | No | No | Minor |
| 543 | 36w | Severe VM | Severe VM Agenesis CC | VM Agenesis CC | Poor | Poor | Yes | Yes | No | None |
| 590 Fig 6 | 21w | Mild VM | Mild VM Agenesis CC Microphthalmia Aicardi syndrome | VM Agenesis CC Microphthalmia Aicardi syndrome | Favourable | Poor | No | Yes | Yes | Major |
| 704 | 22w | Mild VM | Mild VM CFA | VM CFA | Favourable | Not known | No | Yes | Yes | Significant |
| 732 | 23w | Mild VM | Mild VM CFA | VM CFA | Favourable | Intermediate | No | No | No | Minor |
| 735 | 21w | Mid VM | Mild unilateral VM CFA | VM CFA | Intermediate | Poor | No | Yes | No | Major |
| 753 | 22w | Mild VM | Mild VM ICH | VM ICH | Intermediate | Intermediate | No | No | No | Minor |
| 761 Fig 5 | 22w | Mild VM | Mild VM Agenesis CC CFA | VM Agenesis CC CFA | Favourable | Poor | No | Yes | Yes | Decisive |
| 767 Fig 4 | 28w | Severe VM | Severe VM Agenesis CC | Severe VM Agenesis CC | Poor | Poor | Yes | Yes | No | Minor |
| 943 | 34w | Mild VM | Mild VM Hypogenesis CC CFA | VM Hypogenesis CC CFA | Favourable | Poor | No | Yes | No | Major |
| 1041 | 19w | Mild VM | Mild VM Hypogenesis CC | VM Hypogenesis CC | Favourable | Not known | No | No | No | Significant |
| 1053 | 21w | Moderate VM | Mild VM Hypogenesis CC | VM Hypogenesis CC | Intermediate | Poor | No | No | No | None |

Table 4. Imaging information for the 29 cases in which a diagnosis of ‘ventriculomegaly only’ was made on ante-natal USS but other brain abnormalities were shown on the outcome reference diagnosis and there was complete prognostic/clinical management data available. See

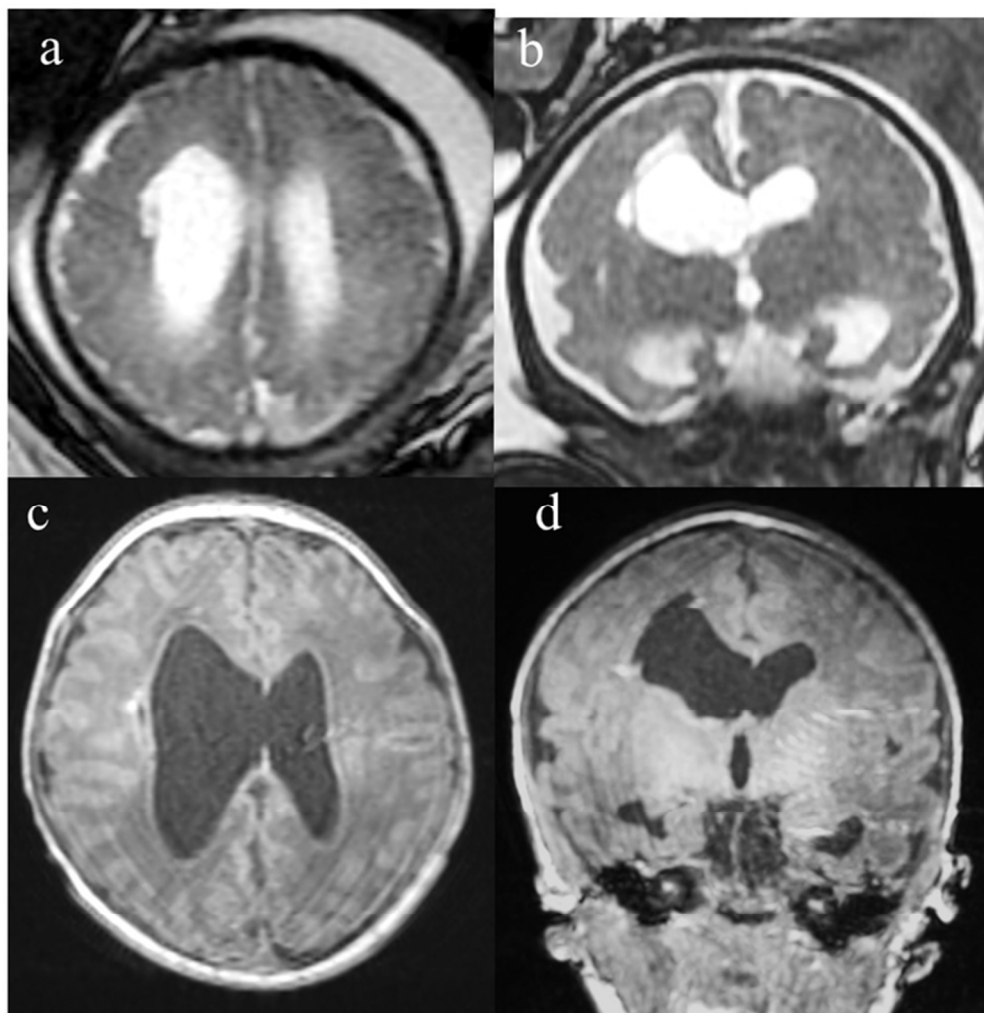
‘Results’ for details. *CSP = cavum septum pellucidum, CFA = Cortical formation abnormality, Hypogenesis CC = hypogenesis of the corpus callosum, Agenesis CC = agenesis of the corpus callosum, ICH = Intracranial haemorrhage.*



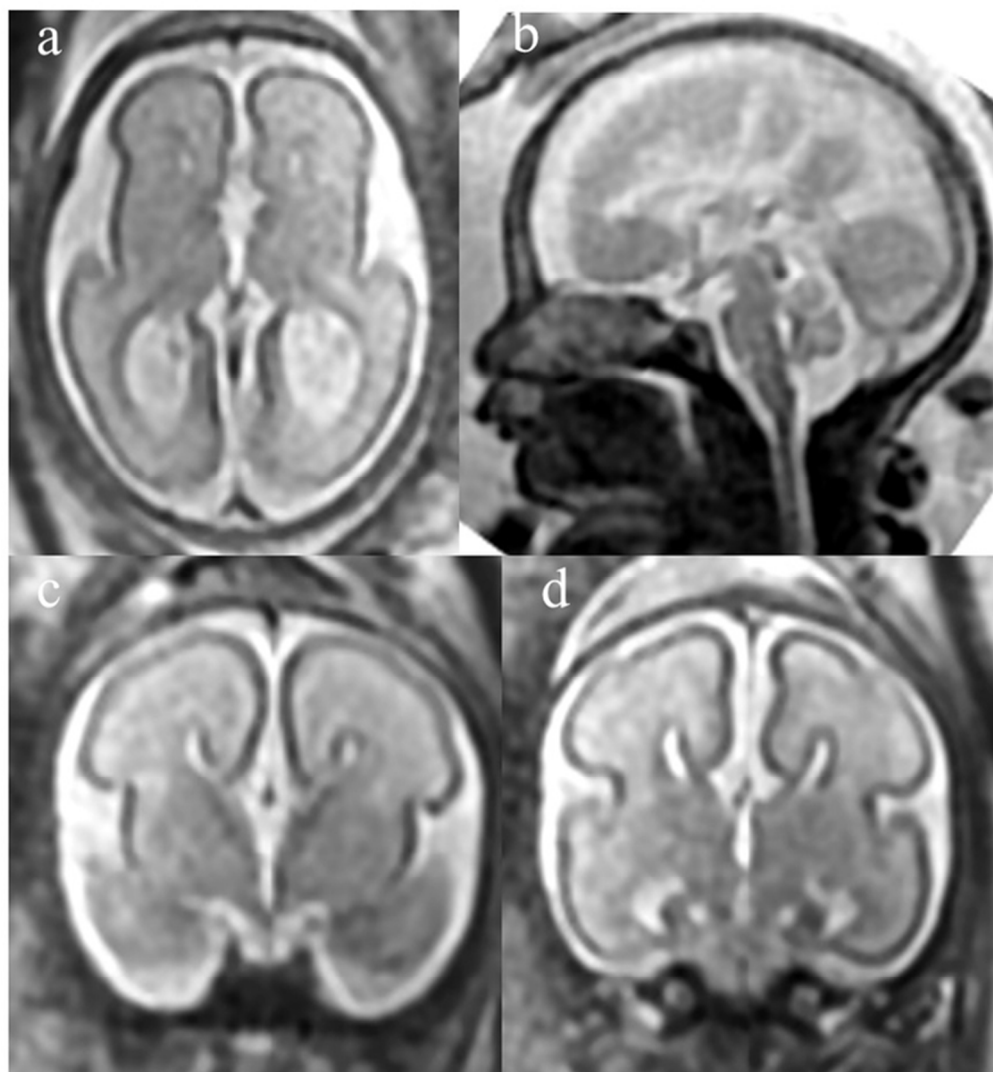
Gestational ages of 306 fetuses with 'ventriculomegaly only' on ante-natal USS at the time of iuMR imaging.



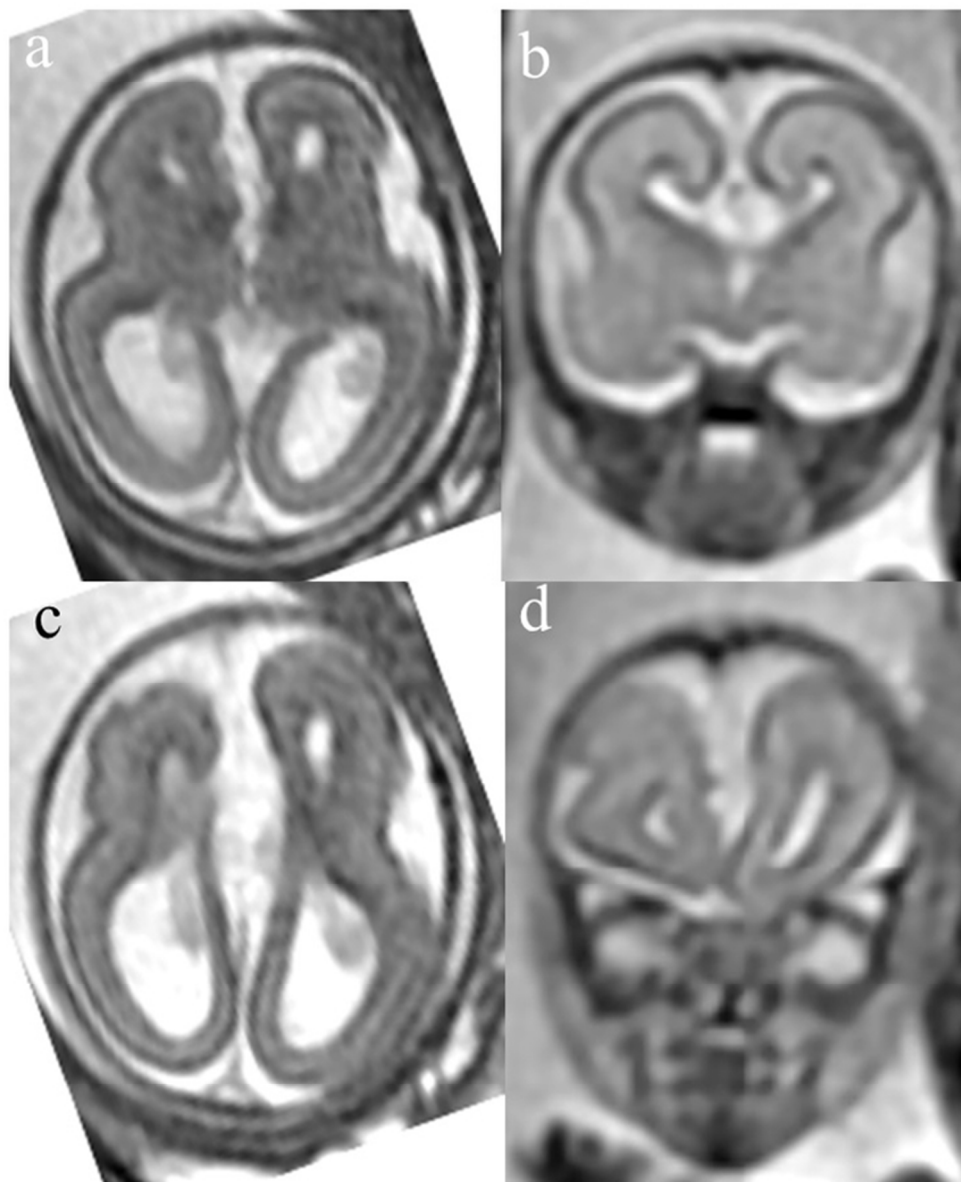
Severe VM was detected in this fetus on USS but no other intracranial abnormalities were shown. Severe VM was confirmed on iuMR (axial images 2a and 2b) along with features consistent with communicating hydrocephalus; enlargement of all cerebral ventricles, large head, reduced extra-axial CSF spaces. Intraventricular clot is shown (mainly in the trigone and occipital horns of the left lateral ventricle) on the axial images (2a and 2b), coronal (2c) and sagittal (2d) images. All of those features were confirmed on post-natal imaging (not shown).



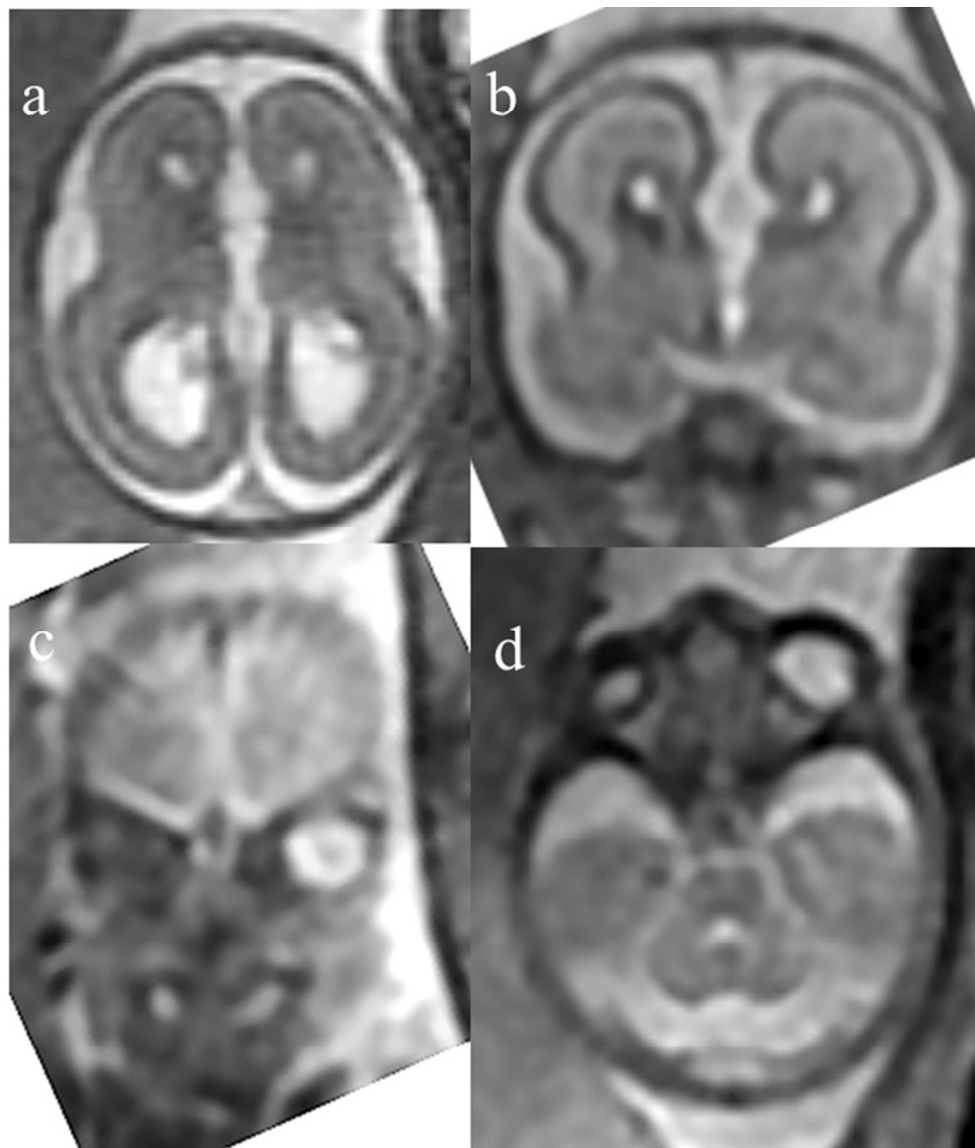
A fetus with severe VM diagnosed on USS and iuMR performed at 36 weeks gestational age. VM was confirmed on axial (3a) coronal (3b) and images and is markedly asymmetric, right worse than left. There is also marked loss of white matter volume adjacent to right lateral ventricle and there is abnormal high signal in the adjacent periventricular/deep white matter diagnosed as encephalomalacia. Those features were confirmed on post-natal MR imaging (3c and 3d).



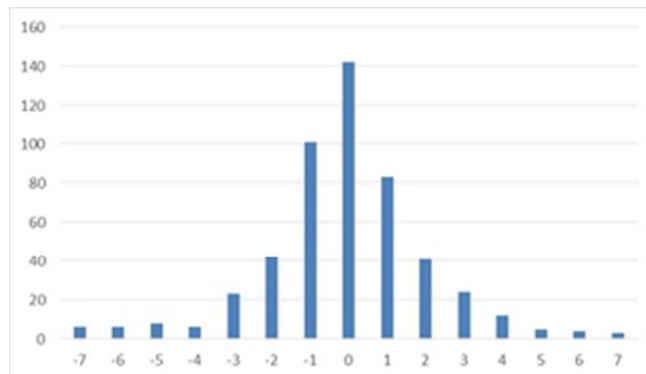
A fetus with severe VM diagnosed on USS. iuMR was performed at 28 weeks gestation which showed colpocephaly on axial iuMR images (4a) along with agenesis of the corpus callosum on sagittal (4b) and coronal (4c and 4d) images. Those features were confirmed on post-natal imaging (not shown).



A fetus with mild VM on USS. iuMR was performed at 22 weeks gestation and showed colpocephaly on the axial iuMR image (5a) and agenesis of the corpus callosum on the coronal (5b) images. In addition, there is marked irregularity of and reduced volume of the right frontal lobe (5c-5d) consistent with a cortical formation abnormality, probably polymicrogyria, which was confirmed on autopsy.



A fetus with mild VM diagnosed on USS. iuMR was performed at 21 weeks gestation, which confirmed mild VM/colpocephaly on the axial image (6a) but also showed agenesis of the corpus callosum (6a and 6b). Axial image at the level of the cerebellum (6c) and coronal image through the face (6d) shows poor development of the right globe leading to a diagnosis of Aicardi syndrome. All of those features were confirmed on autopsy.



Differences in 506 trigone measurements made on ultrasonography and iuMR imaging in fetuses with 'ventriculomegaly only' on ante-natal ultrasonography, in utero MR imaging and confirmed on the outcome reference data.