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The rate of brain abnormalities on *in utero* MRI studies in fetuses with normal ultrasound examinations of the brain and calculation of indicators of diagnostic performance

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AIM: To estimate the rate of unexpected brain abnormalities detected by *in utero* magnetic resonance imaging (iuMRI) in fetuses without abnormalities at ultrasonography (USS).

MATERIALS AND METHODS: A prospective cohort study of pregnant women whose fetus had no structural brain (or body) abnormalities recognised on antenatal ultrasonography. Women were recruited from 12 centres across the UK and underwent iuMRI at 18 gestational weeks or more in the [blinded for review]. The imaging studies were reviewed by an experienced neuroradiologist. The positive and negative predictive values of both USS and iuMRI have been calculated by combining the results of this study with the results from the main [blinded for review] study.

RESULTS: One hundred and ninety-eight pregnant women were recruited and underwent iuMRI of 205 fetuses. Brain abnormalities were shown on iuMRI in two fetuses that were not recognised on USS (one case of a focal cortical abnormality and one case of mild ventriculomegaly). The negative predictive value for USS was 99.5% and 100% for iuMRI.

CONCLUSIONS: To the authors' knowledge, this is the first study comparing USS and iuMRI in low-risk pregnancies. USS has a comparatively high rule-out for fetal brain abnormalities and should remain the screening tool of choice.

Introduction

Recent systematic reviews[1–3] and the results from previous work from the MERIDIAN study[4] have shown that *in utero* magnetic resonance imaging (iuMRI) significantly improves the detection of fetal brain abnormalities when compared with antenatal ultrasonography (USS). Specifically, iuMRI improves diagnostic accuracy[4] and diagnostic certainty[5] when a brain abnormality is shown or suspected on USS, and those findings are likely to have substantial implications for clinical practice.[4] An important limitation of those studies is they have not evaluated the impact of iuMRI in cases in which no brain abnormality was detected or suspected on USS. The intrinsic value of a diagnostic test relies not only its ability to identify an abnormality correctly when one is

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present, but also to exclude abnormalities correctly when they are not present. To date, studies of iuMRI for fetal brain abnormality have been undertaken among fetuses in which a brain abnormality was suspected (predominantly on the basis of abnormal USS) and, although these strongly support the use of iuMRI in such cases, the benefit, if any, of iuMRI in ostensibly normal pregnancies is unknown.

In the present study, the results of an extension to the MERIDIAN study in which women with low-risk pregnancies and normal fetuses on USS were recruited in order to have iuMRI of the fetal brain (full protocol available at https://www.sheffield.ac.uk/meridian/studysummary) was undertaken. This enabled the calculation of negative predictive value (NPV) for both iuMRI and USS imaging in order to complement the positive predictive value (PPV) derived from the main MERIDIAN cohort. To the authors' knowledge, no previous study has evaluated the impact of iuMRI in this population. In addition, the problems of measuring diagnostic performance for iuMRI and antenatal USS are discussed with particular reference to the inherent difficulties in estimating sensitivity and specificity.

Materials and methods

Participants and recruitment

This work was funded by the NIHR-HTA by way of an extension to the main MERIDIAN study (ISRCTN 27626961) and conducted under the same ethics approval. The aim was to recruit approximately 200 women carrying a fetus in whom no brain (or somatic) abnormality was detected on the 20-week anomaly USS, which is routinely offered to women in the UK. Any subsequent USS examinations (if performed) also had to show normal fetal anatomy. All of the pregnancies were otherwise considered "low-risk" with no known serological or chromosomal/genetic concerns. Potential participants were informed about the study by way of posters and leaflets in 12 of the original 16 fetal medicine referral centres involved in the original MERIDIAN and by press coverage in those regions. Interested pregnant women contacted the central site (Academic Unit of Radiology, University of Sheffield) and were sent a patient information leaflet by email or post, which gave full details of the study. A follow-up telephone call enabled queries to be answered, initial screening questions to be assessed and eligibility for the study confirmed. A copy of the most recent antenatal USS report was then obtained to confirm the normal development of the pregnancy. Other inclusion criteria were: the woman was at least 16 years old and the fetus a minimum of 18 gestational weeks (gw) at the time of iuMRI was to be performed. Exclusion criteria were inability to give informed consent, contraindications to MRI, or inability/unwillingness to travel to Sheffield for iuMRI. There were no set requirements for the interval between considered eligible for the study and having the iuMRI.

Written informed consent was taken on the day of the study after further explanation of the iuMRI procedure, including potential risks and the right to withdraw from the study at any time. The consent procedure also confirmed willingness of the woman to inform her general practitioner that she had been involved in the study and to send them a copy of the iuMRI report if no unexpected findings were shown. If a brain abnormality was detected at iuMRI, the woman agreed that the findings would be discussed verbally with her obstetrician who would subsequently receive a full clinical-style report in accordance with the guidance from the Ethics Committee. Participants were not paid for volunteering for the study, but a £10 gift voucher was given, along with travel expenses, for the participant and an accompanying person.

Sample size and reference diagnoses

Starting from the assumption that no USS false negatives will be found, the study aimed to recruit 200 fetuses on the basis of the 3/n rule,[6] a large sample approximation of the upper 95% confidence interval for very rare events. This allowed the negative predictive value of USS to be estimated to an upper confidence limit of 1.5% in the absence of any abnormal scans, and to within a standard error of $\leq$2% for an incidence of $<$10%.

The brain of the fetus was assumed to be normal if both USS and iuMRI were normal, an approach supported by the low rate of false positive findings for iuMRI in the main [blinded for review] study (1/570 = 0.18%). These became the true negatives for USS and iuMRI used in this study. Additional tests were undertaken in the event of a brain abnormality reported on iuMRI, and these were intended to be the reference against which USS and iuMRI were compared, although this approach was found to be too simplistic for practical cases as discussed below.

iuMRI procedures and protocols

All of the iuMRI examinations were performed at the Academic Unit of Radiology, University of Sheffield on either a 1.5 T whole-body scanner (HDx, GE Healthcare, Milwaukee, WI, USA) or a 3 T whole-body scanner (Ingenia, Philips, Netherlands). The 3 T scanner was used only when the 1.5 T was not available (e.g., breakdowns) and this occurred in two cases only. The iuMRI targeted the fetal brain only and the woman was on the scanner for maximum of 30 minutes. The imaging protocol performed at 1.5 T consisted of ultrafast imaging in the three orthogonal planes (T2 weighted single-shot fast spin-echo [SSFSE] and two dimensional (2D)-free induction echo stimulated acquisition [FIESTA]), T1 weighted, fluid-attenuated inversion recovery (FLAIR), diffusion-weighted imaging in the axial plane and T2-weighted volume acquisitions and MR cine using 3D-FIESTA. After the scan the woman and her companion(s) were shown some of the iuMRI images and given the opportunity to take some images on their phone or camera. The formal report on the study was issued the following day after review by a paediatric neuroradiologist with extensive experience of fetal neuroimaging.

Statistical methods for assessing diagnostic performance

The accuracy of a negative USS was quantified by the NPV, the percentage of fetuses in whom no abnormality was subsequently detected. For iuMRI, NPV agreement was derived separately for fetuses whose initial USS was normal and abnormal USS (i.e., USS+, iuMRI− and USS−, iuMRI−).The PPV of USS and iuMRI were derived analogously. PPVs and NPVs were presented alongside 95% binomial confidence intervals (CI). No attempt was made to combine the PPV and NPV of iuMRI with those from the main [blinded for review] study, or to estimate the sensitivity and specificity for reasons explained in the discussion.

Results

Recruitment and scanning took place between November 2013 and May 2017 during which time 225 pregnant women enquired about the study, but three women did not meet the inclusion criteria because of pregnancy complications. Appointments for iuMRI were made for the other 222 women who did meet the entrance criteria, but of those 23 did not attend. One woman underwent the iuMRI study, but the procedure was abandoned due to the participant feeling unwell before any relevant data were obtained and three women withdrew from the study after iuMRI was performed. In total, therefore, 198 participants with 205 fetuses (14 twin pregnancies) were scanned successfully as shown in Fig 1. The pregnant women recruited were from a wide geographical area, with 68 (34%) participants living within 18 miles of the [blinded for review] MRI unit and the remaining 137 from further afield (maximum 189 miles). The age range of the pregnant women was 20–46 years (mean 31.5 years) and the gestational age at the time of iuMRI is shown in Fig 2 (26% between 18 and 23 gw, 74% ≥24 gw). There were no reportable adverse events during the iuMRI of these pregnant women. iuMRI studies were reported as normal for 203 cases and brain abnormalities were reported in two fetuses (from separate pregnancies) as described below.

Case 1

iuMRI for this study was performed at 35 gw following normal USS examinations in the second trimester (Fig 3a–c). There was focal abnormal high signal on T2-weighted images in the right inferior/sub-central gyri with broadening of the gyri. The diagnostic confidence of abnormality was quoted as 70% (certain) and pathology such as a focal cortical dysplasia or cortical tuber was suggested, although the possibility of an artefact was considered. Post-natal MRI performed at 3 weeks (Fig 3d–f) confirmed the antenatal findings, but its nature remained uncertain. Developmental assessment at 6 months showed plagiocephaly and reduced central tone but otherwise a normal repertoire of movements. The Bayley Infant Neurodevelopmental Screener (a developmental tool across four domains) put the baby in the “middle risk” group. Genetic testing for tuberous sclerosis complex was negative. The infant remains under clinical review and a further MRI examination is planned at 3 years.

Case 2

Routine anomaly USS was performed at 20 gw and showed no abnormalities. iuMRI for this study was undertaken at 26 gw and showed mild ventriculomegaly (trigones measurements between 10–11 mm (Fig 4). The rest of the brain was normal, although the fetus had macrocephaly (bi-parietal diameter >97th centile and occipitofrontal on the 97th centile). Normal-sized ventricles were confirmed on review of the USS performed at 20 gw, but follow-up USS confirmed non-progressive ventriculomegaly at 30 gw. The child was developing normally in all domains at 14 months.

Analysis

Case 1 is treated as a true brain abnormality, although the nature of the abnormality is still not known, so is considered to be a false negative for USS and a true positive for iuMRI. In contrast, the appearance of ventriculomegaly on iuMRI in case 2 after retrospective confirmation of normality at 20 weeks is interpreted as an evolving feature that could not be recognised at 20 weeks because it was not present; however, the confirmation of ventriculomegaly on the third-trimester USS confirmed the iuMRI finding. This is taken as a true negative for USS and a true positive for iuMRI. Table 1 shows the number and characteristics of correct and incorrect diagnoses made by USS and iuMRI using data from both this study and the MERIDIAN study. Both USS and iuMRI have high NPV for the normal risk pregnancies, being 99.5% (95% CI: 97.3–100%) for USS and 100% (95% CI: 98.2–100%).

In the main MERIDIAN cohort, 388/570 fetuses were correctly diagnosed by USS giving a PPV of 68.1% (95% CI: 64.1–71.9%). Of these, iuMRI found abnormalities in 513 fetuses of whom 39 were incorrect diagnoses giving a PPV of 92.4% (95% CI: 90–94.5%). The remaining 57 were recorded as normal on iuMRI, one of whom was subsequently found to have a brain abnormality matching the original USS diagnosis, giving an NPV in this population of 98.2% (95% CI: 90.6–100%).

Discussion

The MERIDIAN study, along with published systematic reviews, demonstrate a significant improvement in diagnostic accuracy when iuMRI is used in the diagnostic pathway.[1–4] One important implication of this finding is USS might fail to detect some brain abnormalities during screening. This study shows that this does not occur at high frequency and supports USS being the primary screening method for brain imaging. iuMRI should be used as an adjunct to USS only when brain abnormalities are suspected on USS in low-risk pregnancies. There were two abnormalities noted on iuMRI following a normal USS in 205 fetuses, one of which was a case of mild ventriculomegaly that was confidently described as an evolving pathology

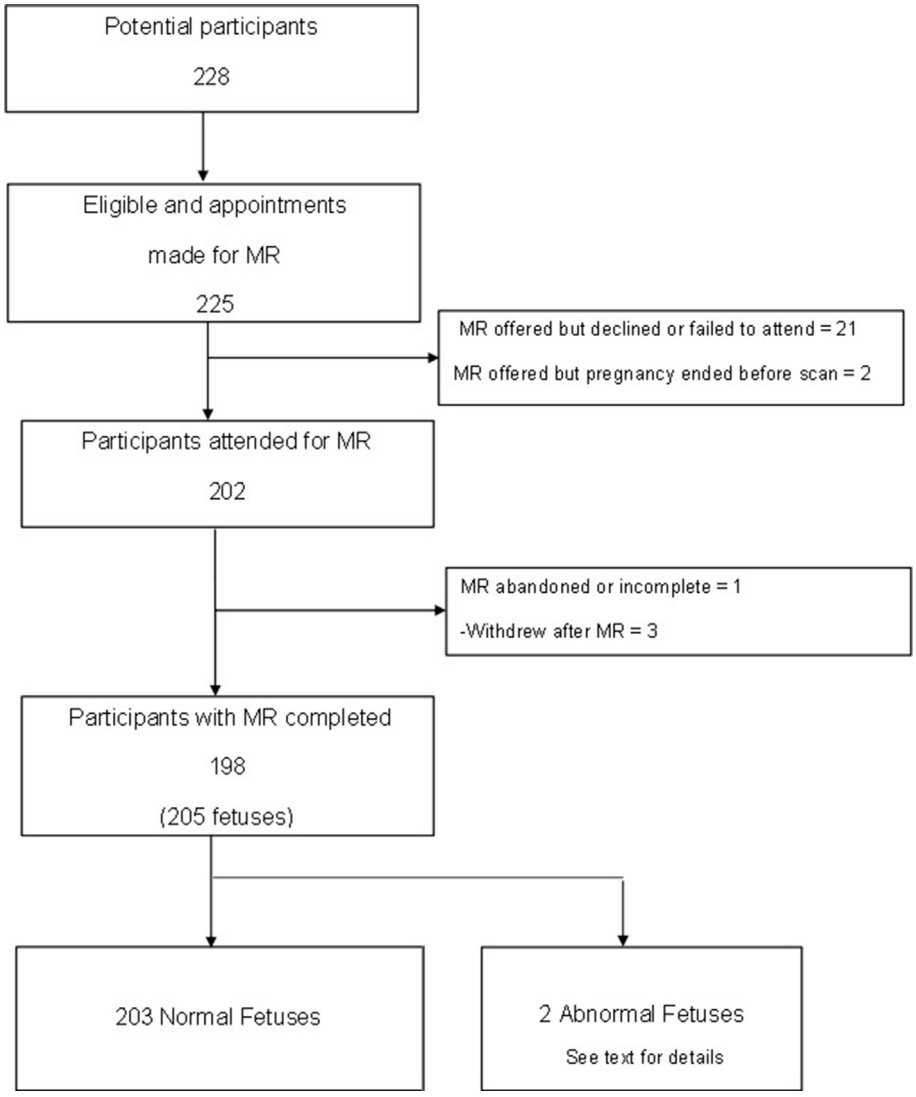

Figure 1 Flow of participants through the study.

and the original USS report was correct at the time of scanning. As such, USS has a NPV of 99.5% (95% CI: 97.3–100%), supporting the contention that a normal USS can safely be assumed to rule out fetal brain abnormality with very high certainty in fetuses with no other risk factor.

A review of the literature has not shown any other studies of iuMRI in normal pregnancies as identified by USS, so there are no other comparative estimates of NPV and PPV for these techniques. The present study has addressed that knowledge gap by recruiting 205 fetuses considered to be developing normally on USS; these were combined with the MERIDIAN results to estimate NPV and PPV. 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), and are arguably more relevant to clinicians when making decisions on the basis of diagnostic tests.[7,8] Traditionally, sensitivity and specificity have been the preferred measures of diagnostic performance, as the PPV and NPV depend on prevalence,[9] indeed, the STARD checklist for diagnostic accuracy studies made only cursory mention of predictive values until the 2015 update.[10,11] In the present study no attempt was made to estimate the sensitivity and specificity, as the two studies have (deliberately) not recruited random samples of pregnant women. The main MERIDIAN study evaluated iuMRI in pregnancies where an abnormality was found on USS, with 570 fetuses included in the primary analysis. As abnormal brain USS occurs in <1% of fetuses, a prospective study of all pregnancies would have needed more than 57,000 participants in order to recruit this number of brain abnormalities. By conducting two parallel studies, fetuses with normal and abnormal USS could be studied, but combining the two into one data set is inappropriate as doing so vastly over-represents by comparison to the general population, resulting in a biased estimate of both sensitivity and specificity. Although the sensitivity could, in theory, be derived by re-weighting the two studies to match population incidence, this would entail allocating a weight of <1% to the original MERIDIAN study with the remainder being

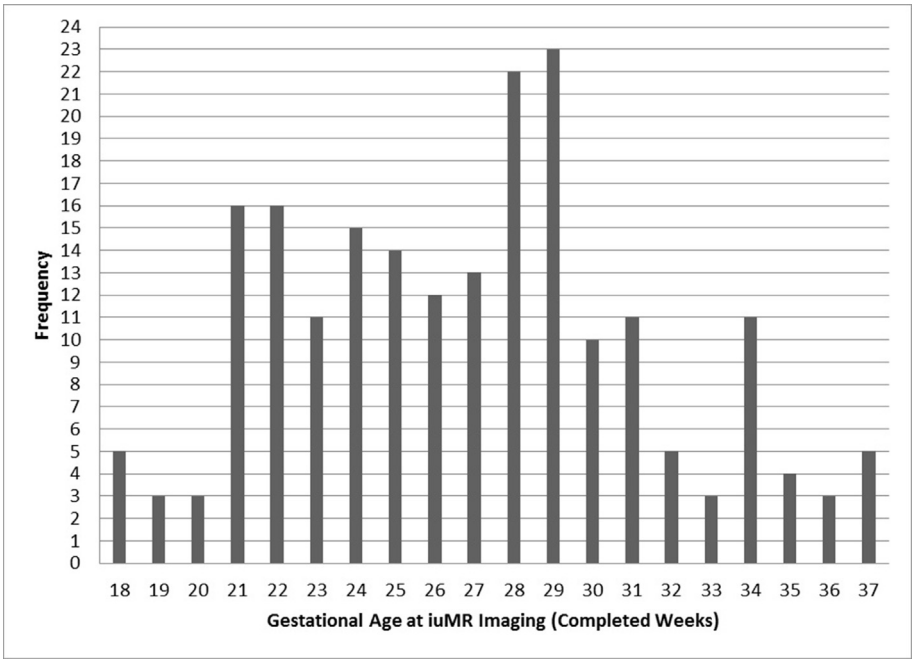

Figure 2 Chart showing the number of fetuses scanned by gestational age.

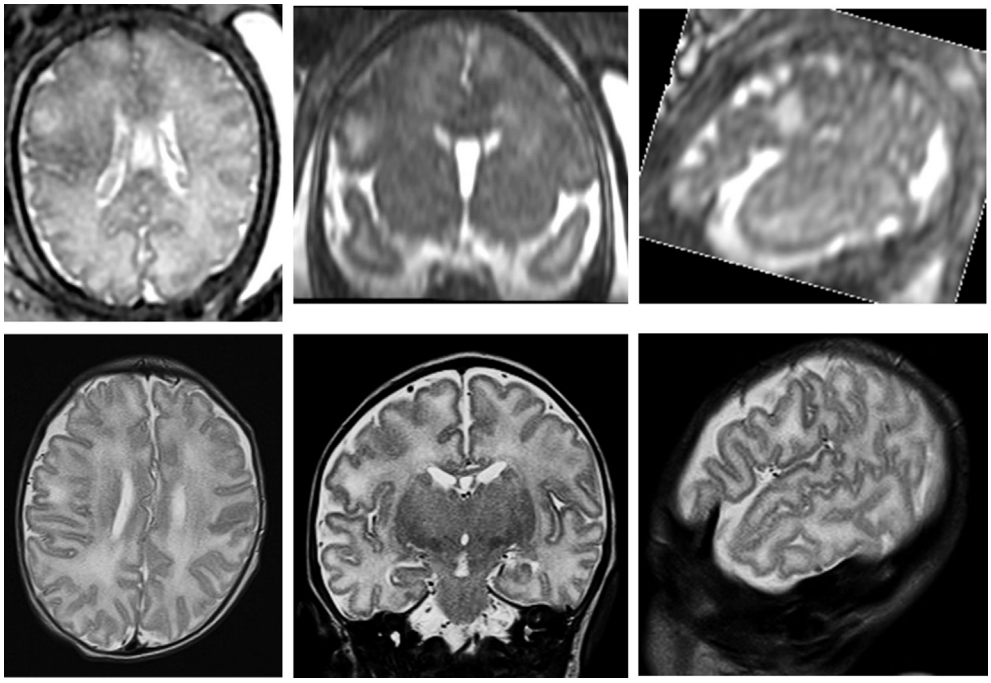

Figure 3 SSFSE image (a), coronal (b) and sagittal (c) reconstruction from T2-weighted 3D datasets show broadening of the right inferior frontal gyrus and abnormal white matter signal extending into the sub-central gyrus. These features were confirmed on post-natal imaging (d–f). See text for details.

allocated to the two cases identified in this study. A similar (though less extreme) situation applies to the specificity, and clearly this results in instable estimates, which are best avoided.

USS is offered to all women in the UK (and taken by >95%) so sensitivity and specificity of USS may be derived from routine patient notes.[12] 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)[13] described the findings from those studies, showing that although the sensitivity of USS was variable (15%–85%) the specificity was consistently very high (99.4%–

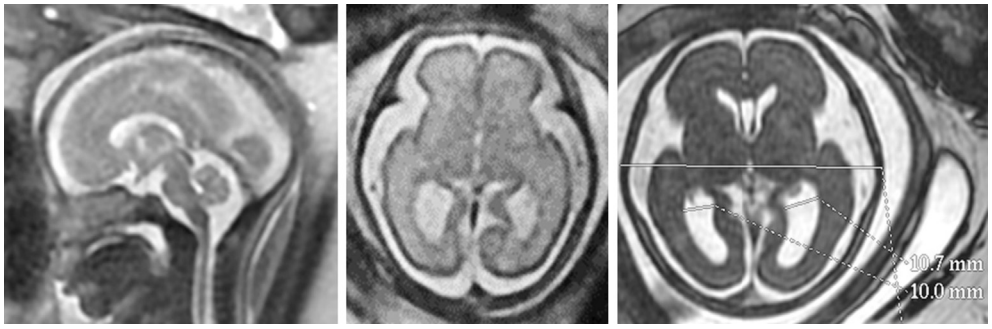

Figure 4 (a) Sagittal and (b) axial SSFSE images show mild ventriculomegaly and macrocephaly (trigones of the lateral ventricles measured an axial reconstruction from a 3D dataset (c). See text for details.

Table 1
Data showing the agreement between ultrasonography and *in utero* magnetic resonance imaging when compared with outcome reference data.

Test finding	Agreement with Outcome reference data (ORD)		Predictive value
	Test correct	Test incorrect	
Ultrasound			
Ultrasound abnormal[a]	388	182	PPV=68.1% (95% CI: 64.1–71.9%)
Ultrasound normal	204	1	NPV=99.5% (95% CI: 97.3–100%)
In utero magnetic resonance imaging (iuMRI)			
Following abnormal ultrasound[a]			
iuMRI abnormal	474	39	PPV=92.4% (95% CI: 90–94.5%)
iuMRI normal	56	1	NPV=98.2% (95% CI: 90.6–100%)
Following normal ultrasound			
iuMRI abnormal	2	0	PPV=100% (95% CI: 15.9–100%)
iuMRI normal	203	0	NPV=100% (95% CI: 98.2–100%)

PPV, positive predictive value; NPV, negative predictive value; CI, confidence interval.
[a] Taken from original MERIDIAN cohort of fetuses with brain abnormality on ultrasound.

100%). Rossi and Perfumo[2] attempted to define the diagnostic capability of iuMRI using similar sensitivity and specificity measures but, as the vast majority of fetuses were initially suspected of being abnormal by USS, the truly normal pregnancies were again greatly under-represented and their findings do not adequately generalise to the wider population of pregnancies. Perhaps more importantly, it is questionable whether the diagnostic ability of iuMRI needs to be evaluated among all pregnancies. Although neonatal screening relies heavily on USS, constraints on resources mean it is likely that iuMRI will be used more selectively as a second-line screen for high-risk pregnancies, most likely a suspected abnormality on USS—a position backed by the data from the study. There are more than 800,000 pregnancies in the UK each year,[14] the majority of which undergo at least one USS, and the resource implications (trained expertise and financial) of providing iuMRI routinely is prohibitive. It is interesting to note that the results of the adequately powered study reported by NICE[13] were comparable to the NPV reported here.

There are several possible limitations to the present 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 volunteers. It is unclear if the women in the sample were fully representative of the obstetric population as, although recruited from a wide geographical area within the UK, demographics, such as ethnicity, were not recorded. Secondly, it was not possible to restrict recruitment to women who could attend for iuMRI shortly after USS as the study was reliant on participants' availability. In theory, the longer time period between USS and iuMRI, the greater the possibility of abnormalities evolving and hence being visible on MRI, which would therefore biased the findings in favour of iuMRI; in reality, the two technique agreed in all bar two cases. The advantage to not restricting the time between USS and iuMRI was that a wider age range of fetuses were scanned, and allowed a greater range of gestational age to be assessed as pregnant women are offered an anomaly screening USS between 18 and 21 weeks' gestation in the UK. Thirdly, the diagnostic accuracy of USS for this study was based on routine USS screening rather than USS by a fetal–maternal expert, which was a requirement of MERIDIAN. The availability of suitably qualified staff and the cost implications made this unattainable. It is impossible to ascertain whether the two cases with abnormalities

detected by iuMRI were not present at USS or if they were missed. In the fetus with ventriculomegaly, there was 6 weeks between USS and iuMRI, and in the second abnormal case there was 16 weeks. It was therefore possible that the abnormality was not present at the time of the USS, and even if it was, it is impossible to say whether a fetal–maternal expert could have identified the abnormality.

The consequences of abnormalities being missed on antenatal USS are variable. Detecting abnormalities allows further investigations and additional monitoring of the pregnancy, or if the abnormality is severe and detrimental to long-term outcome, allows the option of termination of pregnancy. Isolated mild ventriculomegaly is a common finding during pregnancy and a very high proportion have a favourable outcome, but iuMRI is necessary to identify additional abnormalities.[15–17] This finding therefore is perhaps less significant than the cortical abnormality diagnosed by iuMRI in a fetus of 35 gw. Cortical dysplasia (or cortical tubers) is exceptionally difficult to identify by USS prenatally[18] and can have a range of causes and outcomes. Earlier identification of this abnormality 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 its management.

In conclusion, the present results confirm the ability of both USS and iuMRI to confirm when brain development of the fetus is normal. This highlights the validity of USS remaining as the primary screening imaging method for pregnancy, and further supports the need for additional iuMRI when abnormalities are detected on USS; however, further research on fetuses at an increased risk of brain abnormality may be appropriate.[19]

Conflicts of interest

The authors declare no conflict of interest.

Acknowledgements

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