A Prospective Study of Fetuses with Isolated Ventriculomegaly Investigated by Antenatal Sonography and In Utero MR Imaging


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A Prospective Study of Fetuses with Isolated Ventriculomegaly Investigated by Antenatal Sonography and In Utero MR Imaging

BACKGROUND AND PURPOSE: Fetal ventriculomegaly (VM) is important because of its high prevalence and high risk of association with other brain abnormalities. The purpose of this article was to investigate the hypotheses that including in utero MR imaging (iuMR) in the diagnostic pathway for fetuses with isolated VM on antenatal imaging will show other brain abnormalities in a high proportion of cases and that these will have a significant effect on clinical management.

MATERIALS AND METHODS: One hundred forty-seven pregnant women were recruited prospectively from 8 fetomaternal centers in Britain. All of the fetuses had VM diagnosed on sonography but no other abnormality. iuMR was performed, and the results of the examinations were compared with those of sonography. Two fetomaternal experts made independent assessments of the effects of any new diagnoses on clinical management.

RESULTS: Categoric assessments of ventricular size were the same in approximately 90% of fetuses. Other abnormalities were shown in 17% of fetuses. The most frequent additional brain abnormality shown on iuMR was agenesis of the corpus callosum. Severe VM was associated with an approximately 10-fold increase in the risk of another brain abnormality being present when compared with fetuses with mild VM. The most profound effects on clinical management, however, were found in cases of mild VM.

CONCLUSIONS: This work supports our hypotheses by showing a high detection rate of other brain pathology when iuMR was used to supplement antenatal sonography (17%). In a high proportion of cases, the detection of the extra pathology would have led to significant changes in clinical management.

Structural abnormalities of the fetus are investigated in many countries by using sonography, first by way of screening programs and then by detailed anomaly scanning if necessary. It is desirable to have as much anatomic information available as possible for the parents for 2 main reasons: First, finding no abnormality is of great comfort to parents, particularly if the fetus is at increased risk of malformation. Second, if abnormalities are found, the parents need as much accurate information as possible to assist in making decisions about the future of the pregnancy.

Abnormalities of the brain and spine are among the most common causes for concern in fetal imaging, and ventriculomegaly (VM) is one of the most frequent abnormal brain findings. The widely used definition of fetal VM is a transtrigone measurement of ≥10 mm at any stage of pregnancy. With that definition, VM is found in ≥2.5 per 1000 pregnancies. In some cases, VM is the only abnormal finding, leading to the term “isolated VM,” which is found in approximately 20% of all cases of fetal VM diagnosed on sonography (eg, 22% from 267 cases and 16% from 51 cases). Fetuses with isolated VM are at an increased risk of aneuploidy, particularly trisomy 21, and amniocentesis is often offered for this reason.

It is important to recognize VM antenatally because it may be an indicator and/or manifestation of other serious central nervous system (CNS) abnormalities with values of 88% sensitivity in 1 study. Fetal VM is associated with poor outcome in terms of both mortality and morbidity if projected outcome data from termination of pregnancy cases are included. Once VM has been demonstrated on a screening sonography examination, women are referred to specialist fetal/maternal centers for further sonographic assessment, which includes detailed neurosonography by an expert in fetal imaging. The implications of detecting fetal VM are complicated because there are many underlying etiologies. Most authorities believe that if other structural CNS abnormalities are found in conjunction with VM, there is a high risk of a poor neurologic and/or developmental outcome. When VM is the only abnormal finding and the fetus is known to be euploid, counseling parents is partly based on the severity of the VM because increasing size of the ventricles is associated with a higher risk of poor outcome. The most recent data on outcome have used the results of in utero MR imaging (iuMR) to define isolated VM.

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that including iuMR in the diagnostic pathway for fetuses with isolated VM on antenatal imaging will show other brain abnormalities in a high proportion of cases and that these will have a significant effect on clinical management. We have attempted to quantify these potential benefits to management.

Materials and Methods

The study was approved by the South Sheffield Research Ethics Committee and sponsored by the Wellcome Trust, United Kingdom. None of the cases have been previously reported in our earlier publications on diagnostic accuracy assessment on iuMR.

Participants

One hundred forty-seven pregnant women were recruited from 8 tertiary fetal assessment units in England and Scotland. Entrance criteria for the study were the following: singleton pregnancy with fetal VM diagnosed on sonography (trigone measurement of ≥10 mm) referred to the study center at 20 weeks' gestational age or later and no other abnormality of the fetus shown by sonography (brain or somatic) under good sonographic conditions (eg, no obscuration because of maternal body mass index problems, fetal position, or oligohydramnios). None of the fetuses had a known abnormality on karyotyping at the time of referral. The women did not have any known or suspected contraindications to MR imaging and agreed to provide written consent after full explanation by 1 of the authors. The women were not paid for their involvement in the study, but travel expenses were offered for themselves and a companion. Most iuMR examinations were performed within 4 days of the referral; exceptions included periods of machine breakdown and the referral being made before 20 weeks' gestational age (in which case the examination was delayed to 20–21 weeks' gestation). The study extended from 2005 to 2009.

Procedures

Our iuMR technique has been described in detail elsewhere but is summarized here. All images were acquired on a 1.5T scanner (either Infineon, Philips Medical Systems, Best, the Netherlands; or HDx, GE Healthcare, Milwaukee, Wisconsin). A flexible phased array body coil was attached around the lower abdomen, and a series of 3-plane scout views was obtained. Once the fetal head was located, single-shot fast spin-echo sequences were run by using the following typical parameters: TR, 20,000 ms; TE, 75 ms; echo-train length, 132; FOV, 25 cm; matrix size, 248 × 256; NEX, 1; FA, 120°. Twenty 5-mm-thick sections of the fetal brain were obtained (20-second acquisitions) in the 3 natural orthogonal planes. After these were judged to be of diagnostic quality, similar acquisitions were performed by using the 3 natural orthogonal planes. The parameters for the T1 sequence acquired in 30-second acquisition time, either with or without sus-

Twenty to 24 Weeks’ Group

The median gestational age at the time of iuMR in this group was 22 weeks. Additional brain pathology was identified in 9/99 (9%; 95% CI, 4%–17%) fetuses imaged between 20 and 24 weeks' gestational age. The categories of enlarged trigones (on the most severely affected side) in the 90 confirmed isolated VMs in fetuses of 20–24 weeks’ gestational age, according to iuMR, were the following: normal, 2/90; mild, 66/90; moderate, 15/90; and severe, 7/90. The additional brain ab-
normalities shown in the 9 fetuses of this subgroup are described in on-line Table 1 and consisted of developmental abnormalities in 8/9 fetuses. Failed commissuration (agenesis of the corpus callosum) was the most frequently found abnormality in fetuses with VM in the 20–24 weeks’ group (5/9). An example is shown in Fig 1. The sizes of the enlarged trigones on the most severely affected side in the 9 fetuses with abnormal brains are shown in on-line Table 1, with most cases having mild VM.

Twenty-five-weeks’ and Over Group
The median gestational age range at the time of iuMR for this group was 25–27 weeks. Forty-eight fetuses were referred with isolated VM on sonography at 25 weeks’ gestational age or later, most between 30 and 34 weeks. Sixteen of 48 (33%; 95% CI, 20%–48%) fetuses had additional brain pathology. The categoric assessment of the largest trigone in the 32 cases of confirmed isolated VM according to iuMR was the following: mild, 17/32; moderate, 10/32; and severe, 5/32. The details of the 16 cases with other brain abnormalities shown on iuMR are presented in on-line Table 2 and consisted of 11 developmental abnormalities and 5 acquired pathologies. As in the 20–24 weeks’ group, failed commissuration was the most frequently associated developmental abnormality of the 25+ weeks’ group (6/16, 3 associated with a neocortical abnormality). Examples are shown in Figs 2 and 3. The categories of enlarged trigones (on the most severely affected side) in the fetuses with other brain abnormalities are shown in on-line Table 2. Most fetuses had severe VM.

Table 1 shows that there is a 6% risk for fetuses with mild VM to have a further brain abnormality in both gestational age groups. The overall increase in relative risk in fetuses with severe VM was 10.3 when compared with fetuses with mild VM, and this elevated risk did reach statistical significance.

There was excellent independent agreement between the 2 reviewers who performed the analysis on the effect on management in cases of other brain pathology being shown. There was complete agreement in 20/25 (80%; 95% CI, 59%–93%) cases, 1 grade of disagreement in 3, and 2 grades of disagreement in 2 (on-line Tables 1 and 2). In 4/9 cases with abnormal findings in the 20–24 weeks’ group, the effect of iuMR on management was judged as “iuMR gave additional information that significantly altered prognosis to a degree that termination of pregnancy was
offered” as judged by both reviewers. Those circumstances occurred in 2/16 cases in the 25+/w group.

## Discussion

Fetal VM can arise from a number of causes, including obstruction to CSF flow (leading to hydrocephalus), focal or generalized loss of brain volume (ex-vacuo dilation), and secondary to malformation of the CNS (dysmorphic). In many cases, however, no cause is found either before or after delivery. The 2 clinical considerations in a fetus with VM are the degree of ventricular enlargement and the presence or absence of other abnormalities, of which CNS abnormalities are common. It is widely accepted that severe categories of VM are associated with higher risks of poor clinical outcome, and indeed recent studies have questioned whether mild VM (trigone measurements of 10–12 mm) is truly abnormal if it is an isolated finding. For example, in a study of 176 cases, Gaglioti et al showed that a fetus with isolated VM had a 97.7% chance of being alive at 2 years if the VM was mild, an 80% chance with moderate VM, and a 33.3% chance with severe VM. Of those that were alive, neurodevelopmental outcome was normal in 93% of mild cases, 75% of moderate, and 62.5% of severe VM cases.

An earlier study by Gupta et al described 276 cases of apparent isolated VM, all of whom were delivered. They found a 70% survival rate, and 59% of the survivors were developmentally normal. Most centers referring cases into our study quote figures of <5% chance of adverse neurologic outcome in cases of mild VM if there are no other CNS abnormalities. This view has been supported in the recent paper of Falip et al, who incorporated iuMR study results into their ante-natal definition of isolated VM. They showed that the outcome of isolated VM was excellent in fetuses with 10–11.9-mm trigones in 94% of cases and in 85% of cases with trigone measurements of 12–15 mm.

There have been improvements in sonographic image quality which, together with an increased understanding of the importance of failed commissuration (eg, agenesis of the corpus callosum) in prognosis, have contributed to improved detection of isolated VM. The presence of other CNS abnormalities is important because it is the brain abnormality that is responsible for the postnatal morbidity and mortality in most cases rather than VM per se. It is of major importance, therefore, to have sought other pathology with the best imaging method available.

The introduction of iuMR into clinical practice has provided a supplementary method of assessing the fetal brain. There could be no a priori reason to believe that iuMR would be more accurate than sonography in assessing the size of fetal ventricles. Early work by Garel and Alberti seemed to support that assumption, but a more recent publication, including the same author, showed the opposite conclusion. The retrospective analysis of Salomon et al included 185 third-trimester fetuses who had isolated mild VM (ie, 10–12-mm trigones) as measured on sonography. They found that the most frequent disagreement between sonography and iuMR was...

### Risk of detecting brain abnormalities on iuMR relative to the degree of VM of the fetus

<table>
<thead>
<tr>
<th></th>
<th>Mild VM</th>
<th>Moderate VM</th>
<th>Severe VM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall risk of another brain abnormality</td>
<td>6% (2%–12%)</td>
<td>14% (4%–2%)</td>
<td>57% (37%–76%)</td>
</tr>
<tr>
<td>Overall relative risk compared with mild VM</td>
<td>6/90</td>
<td>4/29</td>
<td>16/28</td>
</tr>
<tr>
<td>Risk of another brain abnormality in 20–24 w group</td>
<td>1% (2%–14%)</td>
<td>17% (4%–41%)</td>
<td>22% (3%–60%)</td>
</tr>
<tr>
<td>Relative risk compared with mild VM (20–24 w)</td>
<td>3.0 (0.7–12.2)</td>
<td>3/18</td>
<td>2/9</td>
</tr>
<tr>
<td>Risk of another brain abnormality in 25 w+ group</td>
<td>6% (0%–27%)</td>
<td>9% (0%–41%)</td>
<td>74% (49%–91%)</td>
</tr>
<tr>
<td>Relative risk compared with mild VM (25 w+)</td>
<td>1.6 (0.1–23.6)</td>
<td>1/11</td>
<td>14/19</td>
</tr>
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</table>

Note: VM indicates ventriculomegaly, w, week. Figures in brackets indicate 95% confidence intervals. Statistical significance at the <0.05 level.
was in the classification of the degree of VM. Forty-three fetuses (23.3%) had ventricles <10 mm on iuMR (ie, normal size), and 36 fetuses (19.4%) had trigone measurements of >12 mm on iuMR. All of those findings would have had significant effects on the information given to the parents.

The work described in our article supports the authors' original findings—that is, there is little disagreement between the dimensions of the trigones measured on sonography when compared with iuMR. In the 122 cases of isolated VM confirmed by iuMR in this study, there was complete categorical agreement about the degree of VM in approximately 90%. In all but 1 case of categorical disagreement, there was a difference in absolute measurements of no greater than 2 mm, which is in broad agreement with the work of Salomon et al.\textsuperscript{18} We found only 2 cases diagnosed on sonography as mild VM with trigone measurements of <10 mm on iuMR.

On the basis of those findings, we conclude that iuMR does not have a role in assessing the size of the ventricular trigones over and above sonography, but with 2 caveats. There are sometimes problems in visualizing the entire ventricular system on sonography because of factors such as fetal position and problems caused by calvarial ossification.\textsuperscript{19} There is also a sometimes problems in visualizing the entire ventricular system, particularly retrospective reviews of clinical referrals, and our present prospective evaluation of fetuses with isolated VM provided an opportunity to control the referral bias as much as possible. In particular, we started with the assumption that the degree of VM and the risk of other brain abnormalities. In particular, we started with the assumption that the diagnoses of "abnormalities of cortical formation," for example, cannot be taken as read at present. It is our intention to perform clinical and radiologic studies later in life on the children born in this study. Due comment must also be made about the problems of obtaining postmortem information for studies performed in the United Kingdom because of the very low autopsy rate as discussed previously by Griffiths et al.\textsuperscript{27}

Our results show that there is a clear relationship between the degree of VM and the risk of other brain abnormalities. In the entire group of fetuses studied, severe VM was approximately 10 times more likely to be found in association with a brain abnormality than mild VM. iuMR was more likely to find a brain malformation in the 25+ weeks’ group when compared with the 20–24 weeks’ group, though this is probably explained by the higher frequency of severe VM cases in the later gestational age group. The small number of fetuses recruited into the severe VM group makes interpretation problematic, but as the data stand, the relative risk of a brain abnormality with severe VM in the 25+ weeks’ group was much higher (13.3) than in the 20–24 weeks’ group (4.0).

There was, however, a 6% chance of showing a brain abnormality in cases of mild VM at any gestational age older than 20 weeks. A wide range of brain pathology was shown by iuMR, both developmental and acquired. One malformation that was featured most frequently was failed commissuration (agenesis of the corpus callosum), which accounted for 11/25 (44%) cases either alone or in conjunction with further brain abnormalities. This suggests that failed commissuration can be a difficult diagnosis on sonography. Why that structure presents such difficulties is a subject of debate and warrants further investigation. In many cases, it is difficult or impossible to visualize the corpus callosum directly in the fetus with sonography, and the cavum septum pellucidum is often used as a surrogate indicator that the corpus callosum is present. It has also been raised recently whether there is a potential for misidentification of the septal leaves because of abnormally placed fornice.\textsuperscript{28–30} The role of advanced sonographic methods such as 3D/4D sonography with its ability to create reconstructed sonographic images in the midline is also under evaluation.

The detection of CNS abnormalities by iuMR has been shown to have a high impact on clinical management in other studies, but not specifically in isolated VM cases. Simon et al\textsuperscript{22} showed that 46% of 52 cases were managed differently after
iuMR, and a similar analysis made by Levine et al.31 showed an overall 13.5% rate of management change and a counseling change in 49.7%. Those authors have suggested that in fetuses with VM “MR can be helpful in visualizing associated abnormalities...,” but they did not say which cases should be selected for iuMR.9 Significant effects on clinical management in our study occurred most frequently in the 20–24 weeks’ group of pregnancies; the assessors judged that termination of pregnancy would have been considered in 4/9 cases. Similar changes in patient management were less likely in the 25+ weeks’ group, occurring in only 2/16. The most likely explanation for this is the severity of VM associated with the brain malformation. The negative effect on outcome for the more severe forms of VM has been re demonstrated by Ouahba et al.25 recently in a study that included iuMR investigations to confirm or refute isolated VM. Severe VM was much more common in the 25+ weeks’ group, and the assessors judged that women with fetuses with severe VM would have been advised of high risks of poor outcomes and perhaps offered termination of pregnancy irrespective of the information about brain malformation provided by iuMR.

This point is well illustrated in our 20–24 weeks’ group, in which 3/5 of the cases of failed commissuration were associated with mild or moderate VM, and termination of pregnancy would have been considered as a result of the iuMR. In contrast, in the 2 cases in the 20–24 weeks’ group with failed commissuration and severe VM, the effect on management brought about by the detection of the additional brain malformation was minor.

Conclusions
Our work demonstrates that there is a good case for including iuMR as part of the diagnostic process for fetuses thought to have isolated VM on sonography at any time after 20 weeks’ gestational age, with additional brain abnormalities shown in 17%. It could be argued that any resource to provide iuMR on a national basis is best directed at the 20–24 weeks’ group. Although the improvement in detection rate was only 6% in that group, there was a higher impact on clinical management as judged by the independent assessors. It should be noted, however, that some significant changes in clinical management were brought about by the inclusion of iuMR in the older gestational age fetuses.

References