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ORIGINAL RESEARCH

The Use of In Utero MR Imaging to Delineate Developmental Brain Abnormalities in Multifetal Pregnancies

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FELLOWS' JOURNAL CLUB

BACKGROUND AND PURPOSE: iuMR has been shown to increase the detection rate of developmental abnormalities of the CNS, though most reports are limited to singleton pregnancies. The hypothesis tested in this study was that iuMR performed in multifetal pregnancies will show additional information about fetal CNS abnormalities in a similar proportion of cases when compared with singleton pregnancies.

MATERIALS AND METHODS: Fifty women with multifetal pregnancies were recruited consecutively carrying at least 1 fetus with a suspected developmental fetal CNS abnormality on sonography. All had iuMR at the same center by using the same MR imaging protocol. When the sonography and MR imaging reports were discrepant, 1 fetomaternal expert assessed the reports independently to predict in what percentage a change in prognosis/counseling would have occurred if iuMR was included in the diagnostic pathway.

RESULTS: There was agreement between the sonography and iuMR reports in 66% and disagreement in 34% of cases. The major cause for discrepancy was the presence or absence of the corpus callosum, which accounted for 10/17 of the disagreements. In 12/17 of the discrepant cases, the effect on management was judged to be significant.

CONCLUSIONS: We conclude that iuMR has a similar rate of discrepancy to sonography in multifetal pregnancies compared with the published data concerning singleton pregnancies. Our analysis of the effect on management shows that changes in the decision to consider termination of pregnancy would have occurred in 12/17 of the discrepant cases (ie, in 24% of our cases overall).

ABBREVIATIONS: ACC = agenesis (or severe hypogenesis) of the corpus callosum; iuMR = in utero MR imaging; VM = ventriculomegaly, subclassified as mild, moderate, or severe

Multifetal pregnancies present a number of diagnostic challenges. There is an increased risk of both developmental and acquired CNS pathology; however, the multifetal pregnancy itself may reduce the chance of detecting abnormalities before delivery because of unfavorable viewing conditions on sonography. There are also significant problems in clinical management in situations in which 1 fetus has a major CNS abnormality but the cofetus appears normal. In these cases, there are 3 possible options to consider: the woman continues with the pregnancy, terminates the entire pregnancy, or opts for a selective termination of the abnormal fetus.[1]

iuMR is being used increasingly to detect CNS abnormalities in the fetus. One of the major applications is the complementary use of iuMR alongside antenatal sonography to detect and classify developmental CNS abnormalities, many of which are first suspected in the second trimester. There is a series of publications that indicate the clinical advantages of including iuMR within the diagnostic pathway to define fetal neuropathology, mostly in singleton pregnancies.[2-7] These studies show that there is a high probability of detecting additional findings (most studies reporting in the range of 17%–48%, for example[2,3]) that may alter clinical management and decision-making. Some publications have already looked at the value of iuMR in twin pregnancies but mostly in acquired complications.[8,9]

The hypothesis tested in this study is that iuMR performed in multifetal pregnancies will show additional information about developmental fetal CNS abnormalities in a similar proportion of cases compared with singleton pregnancies. In addition, we have studied the potential changes of management that are likely to have resulted from the inclusion of iuMR in the diagnostic pathway of multifetal pregnancies.

Materials and Methods

Subjects and Inclusion Criteria

Fifty pregnant women were included as consecutive cases referred to our institution from hospitals in England and Scotland. Entrance criteria were: multi-fetal pregnancy, suspected developmental abnormality of the CNS of 1 or more fetuses on ultrasound, referral to our center at 18 weeks gestational age or later. The women did not have any known or suspected contraindications to MR imaging. No case reported in this study has been used in our group's earlier publications on diagnostic accuracy assessment on iuMR, which described singleton pregnancies.[2,3] We stress that fetuses suspected of having acquired pathology (on the basis of twin/twin transfusion or death of a co-twin, for example) were not included.

The ultrasound examinations were performed by a consultant with a responsibility for looking after fetal medicine problems within

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the referring hospital. Unlike our previous studies of singleton pregnancies, all of whom were referred from regional feto-maternal units, we accepted referrals from both feto-maternal units and general hospitals in this study. Forty-three were referred from tertiary centers and 7 from general hospitals. Most of the women involved in this study were recruited as research cases under the guidance of the South Sheffield Research Ethics Committee and provided written consent after full explanation, in line with the requirement at the time of recruitment. The women were not paid for their involvement in the study, but travel expenses were offered for themselves and a companion. From 2004, iuMR examinations were also offered as a clinical service to the referring hospitals and a minority of cases in the study came from that source. Relevant review and approval was sought and obtained from the Institutional Clinical Effectiveness Unit to include those cases in this report.

MR Imaging Protocol

Most iuMR examinations were performed within 5 working days of the referral; exceptions included periods of equipment failure or when the referral was made before 18 weeks' gestational age (in which case the examination was delayed to 20 weeks' gestational age). The iuMR technique used in this study has been described in detail elsewhere[3] but is summarized here. All images were acquired on a 1.5T scanner (either Infinion, Philips Healthcare, 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 1 of the fetal heads was located, single-shot fast spin-echo sequences were run by using the following typical parameters: TR, 20,000 ms; TE_{eff}, 75 ms; echo-train length, 132; FOV, 25 cm; matrix size, 248 × 256; NEX, 1; flip angle, 120°. Twenty 5-mm-thick sections of the fetal brain were obtained (approximately 20-second acquisitions) in the 3 natural orthogonal planes. After those were judged to be of diagnostic quality, similar acquisitions were performed by using 3-mm-thick sections with TR, 31,416 ms; TE_{eff}, 92 ms; echo-train length, 136; FOV, 25 cm; matrix size, 183 × 256; NEX, 1; refocusing angle, 120°. In cases in which a fetal spinal abnormality was known or suspected, the 3- and 5-mm single-shot fast spin-echo sequences were repeated for the whole spine. The procedure was then repeated for the other fetuses of the pregnancy.

The iuMR examinations were reported for clinical purposes by radiologists with experience in fetal MR imaging. A clinical style report was made shortly after the time of the examination, and any discrepancy between iuMR and sonography was reported to the referring clinician and handled within the regional multidisciplinary team environment. For the purpose of this study, all iuMR cases were reviewed by an experienced pediatric/fetal neuroradiologist (P.D.G.) who had access to the earlier sonographic and clinical iuMR reports. Results for diagnostic agreement between sonography and iuMR and the proportion of cases in which discrepant diagnostic information was found are expressed as percentages, with 95% confidence intervals estimated by using the binomial exact method. We stress that reference standard information from, for example, postnatal imaging was not collected in this study.

Clinical Assessments

The detailed assessment of the effect on management reported in this article was made retrospectively by presenting the discrepant cases to a fetomaternal expert (G.M.) for independent discussion at his regional multidisciplinary meeting in an anonymized hypothetic fashion. Any changes in management were discussed, and effects on management were classified in 1 of 5 categories as described previously[2,3] but modified here: Group 1, iuMR provided information that did not change the management or the information given to the woman; group 2, iuMR provided additional information about the fetal brain that was discussed with the woman but did not alter management; group 3, iuMR gave additional information that affected either management/treatment and/or prognosis, but not to a degree warranting offering termination of pregnancy; group 4a, iuMR gave additional information that significantly altered prognosis to a degree that termination of pregnancy was offered (ie, where termination of pregnancy was not considered on the basis of the sonographic findings); and group 4b, iuMR gave additional information that significantly altered prognosis to a degree that termination of pregnancy was not offered (ie, where termination of pregnancy would have been discussed on the basis of the sonographic findings but not when the iuMR results were known).

Results

The median maternal age at the time of iuMR was 31 years (range, 22–41 years), and the median gestational age at the time of iuMR was 23 weeks (range, 18–30 weeks).

The results of the sonographic and iuMR examinations were not materially different in 33/50 cases (66%; 95% confidence intervals, 51%–79%), and those cases are summarized in On-line Table 1. In 5 of those cases, there was involvement of >1 fetus: 3 cases with isolated VM of both twins; 1 case with microcephaly of both twins; and 1 case of a triplet pregnancy complicated by anencephaly in 1, VM in another, and a healthy third fetus (Fig 1).

Disagreements between sonography and iuMR occurred in 17/50 (34%; 95% confidence interval, 21%–49%) women carrying a total of 34 fetuses (ie, all were twin pregnancies), and those results are presented in On-line Table 2. In 10/17 of these cases, the fundamental disagreement between sonography and iuMR centered on the presence or absence of the corpus callosum (Figs 2 and 3). In 6 cases, sonography had diagnosed isolated VM in 1 twin, while iuMR showed ACC. In 1 case, VM was found in conjunction with an absent cavum septum pellucidum on sonography, but ACC was shown on iuMR. In 3 cases, ACC was diagnosed on sonography but was not confirmed on iuMR (healthy findings in 1, isolated VM in the second, and VM and absent cavum septum pellucidum in the third). Of the other discrepancies, 3/17 cases consisted of various suspected brain malformations, including isolated unilateral VM diagnosed on sonography, which was shown to be hemimegalencephaly on iuMR; a fetus with suspected semilobar holoprosencephaly on sonography, in whom no abnormality was shown on iuMR; and a small-for-dates fetus identified on sonography with lissencephaly shown on iuMR.

The discrepant diagnoses involved primary spinal malformations in the remaining 4/17 cases. One case was a fetus with the typical findings of a Chiari 2 malformation on sonography, but the low lumbrosacral myelomeningocele was shown only on iuMR. In another, sonography had shown a lumbrosacral myelomeningocele and a Chiari 2 malformation but did not show the diastematomyelia subsequently identified on iuMR. In the third case, sonography showed a lumbrosacral myelomeningocele and Chiari 2 malformation, but iuMR showed a lipomyelomeningocele with a normal brain (Fig 4). In the fourth, the lower spine was recognized as being nonspecifically abnormal on

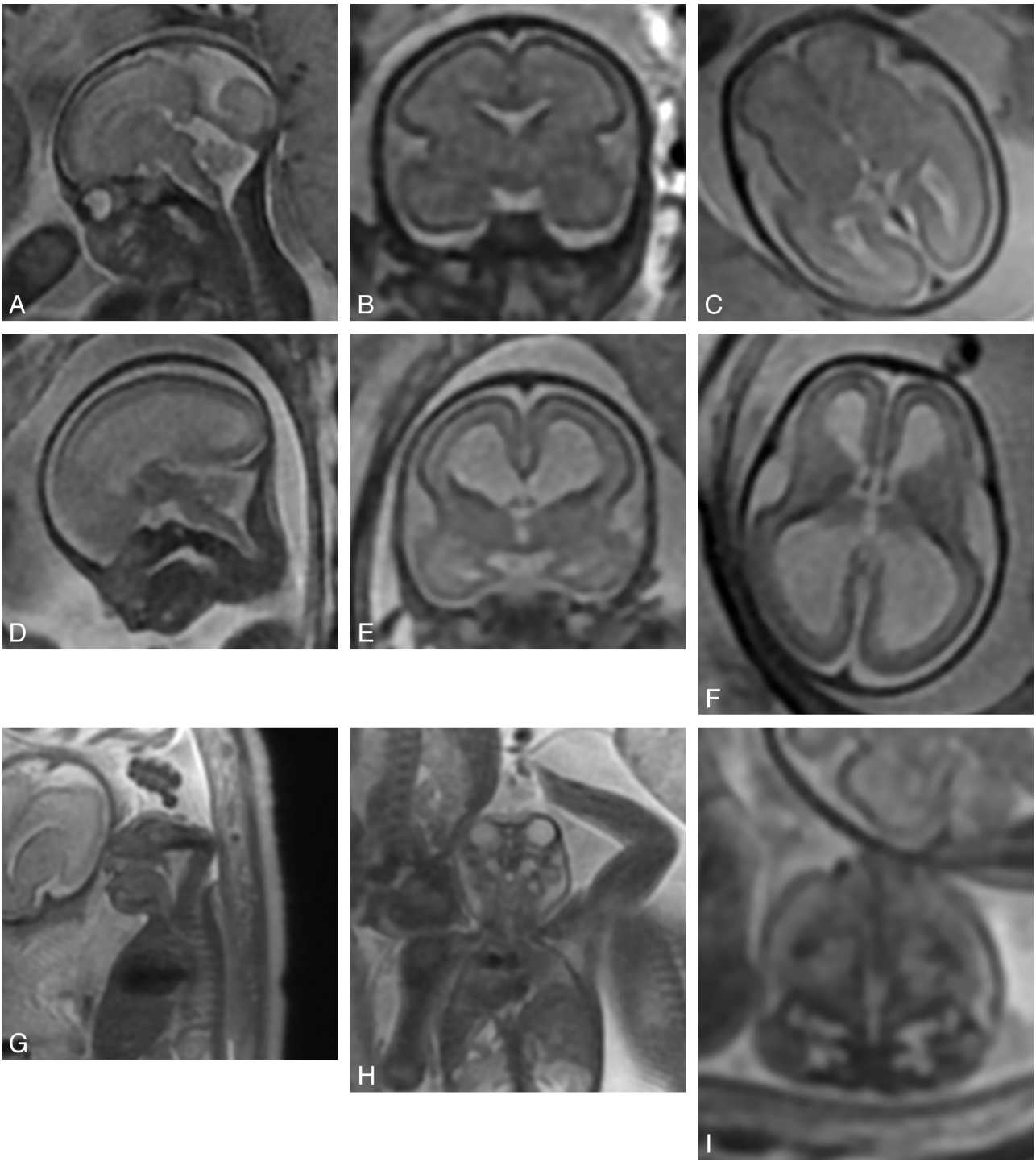

Fig 1. Example of a triplet pregnancy in which all 3 fetuses had different brain findings, but sonography and iuMR findings were the same (study number 28). The fetuses underwent the original iuMR at 22 weeks, and this was repeated at 27 weeks. The results of the 2 studies were the same, but we show the 27-week study here. *A*–*C*, Sagittal, coronal, and axial images of the normal fetus. *D*–*F*, The fetus with severe VM. *G*–*I*, The anencephalic fetus.

sonography, and this fetus was thought to have caudal regression syndrome on iuMR.

In 12/17 of the discrepant cases (ie, 24% of all cases included in the study; 95% confidence interval, 13%–38%), the findings of the iuMR were judged to have made a significant impact on clinical management (group 4a or 4b). In 9 cases, the iuMR results changed the diagnosis to a degree that termination of pregnancy would have been offered; and in 3 cases, termination of pregnancy would have been offered on the strength of the sonographic examination but would not have been warranted on the basis of the iuMR. Group 2 findings (extra abnormalities shown on iuMR but no effect on clinical management) were present in 4 cases, and group 1 (no change in management or information given to the woman) was present in 1 pregnancy.

Discussion

At present, most articles describe added value of including iuMR in the diagnostic pathway for possible fetal neuropa-

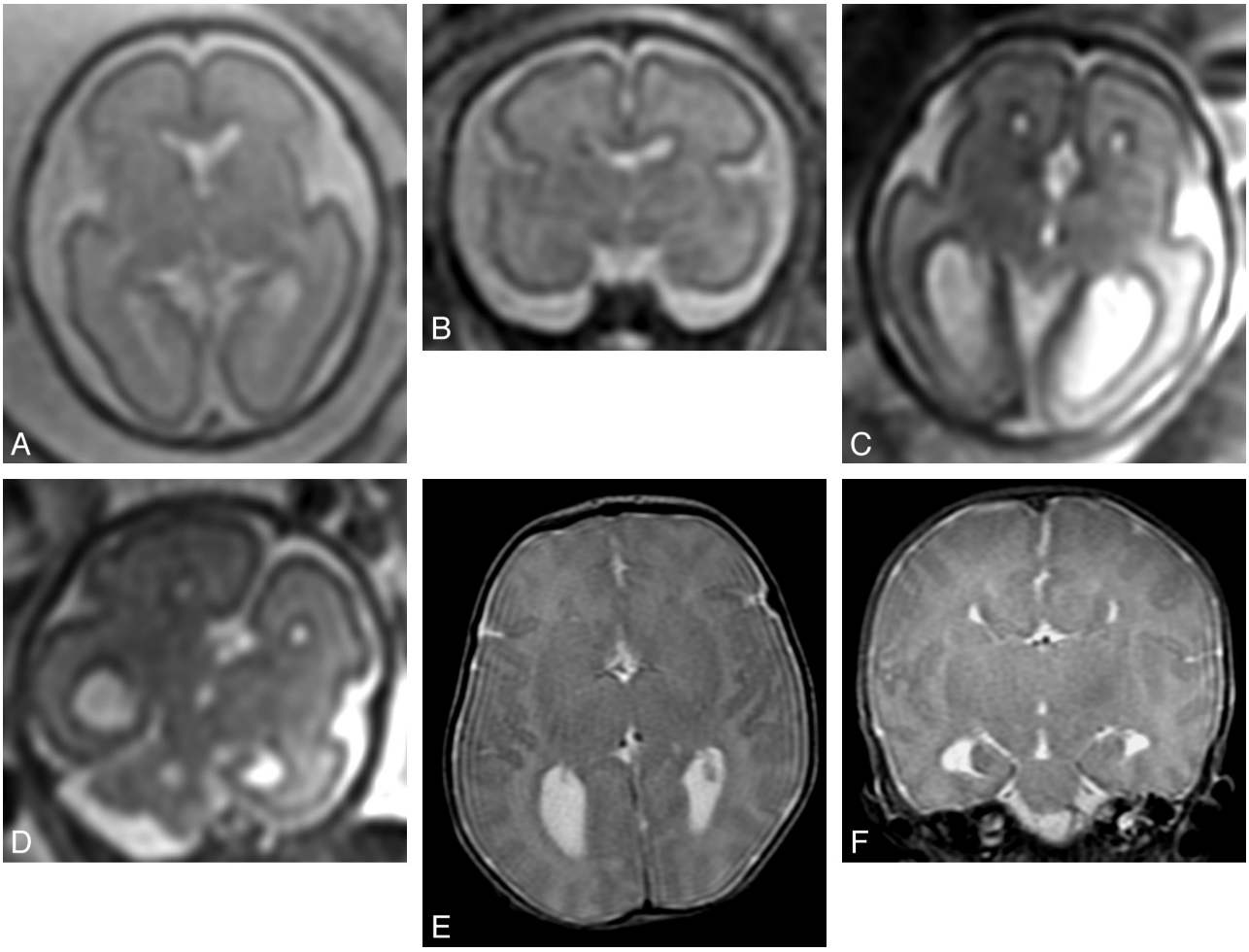

Fig 2. A case of disagreement between sonography and iuMR (study number 45). Sonography had shown VM in 1 twin and a normal intracranial appearance in the other. *A* and *B*, Axial and coronal iuMR images of the twin reported as healthy on sonography also show healthy findings on iuMR. *C–F*, Axial and coronal iuMR images of the twin with VM on sonography (*C* and *D*) show ACC, which was confirmed by using the same ultrafast sequences postnatally (*E* and *F*).

thology. There appears to be a significant improvement in the diagnostic accuracy for fetal brain pathology, both developmental and acquired, though there is a wide range to the quoted benefits. Many studies published so far have been biased by their recruitment patterns, such as "difficult cases" based on complicated pathology or unfavorable viewing conditions for sonography. The extra diagnostic yield for detecting CNS abnormalities in iuMR varies in most published series on the basis of their recruitment patterns. Our early studies quoted an improved diagnostic accuracy in 48% of unselected fetal brain referrals.[2] Our next contribution to the literature deliberately selected fetuses with isolated VM diagnosed on sonography under good viewing conditions.[3] As expected in that situation, we showed a lower overall extra pick-up rate of relevant brain pathology (17% of cases) compared with "difficult cases." In both of those studies, however, multifetal pregnancies were specifically excluded. There has been less published work on fetal spine pathology in singleton pregnancies, but our experience is that the added value of iuMR following sonography is less for the spine than it is for the brain.[10]

Most publications about the use of iuMR for multifetal pregnancies have either been case reports or small case series. The work is relevant, however, because of the increasing proportion of multifetal pregnancies (primarily as a result of assisted reproductive techniques)[11] and the increased risk of abnormalities within multifetal pregnancies. The 2 publications with the largest number of cases have primarily concentrated on acquired pathology secondary to the multifetal pregnancy per se.[8,9] Kline-Fath et al[8] described 37 multifetal pregnancies, 25 of which had twin-twin transfusion syndrome, and the authors concluded that iuMR had advantages over sonography in defining ischemic lesions complicating those pregnancies. Hu et al[9] studied 32 women with multifetal pregnancies with a wider range of pathology, most of which was acquired, including cases of twin-twin transfusion syndrome and co-twin demise with embolic disease to the survivor. Their conclusions were similar to those of Kline-Fath et al.

As far as we can ascertain, this is the first large study using iuMR and looking specifically at developmental CNS abnormalities in multifetal pregnancies. Our hypothesis stated that we would find a discrepancy rate between the iuMR and sonography reports comparable with that reported in singleton pregnancies. This has been shown to be correct and is generally attributed to improved contrast resolution and the ability to obtain images in all 3 orthogonal planes irrespective of fetal position or maternal size. The duration of the iuMR study can be much longer in multifetal pregnancies because of the extra number of targets and the difficulty in finding the

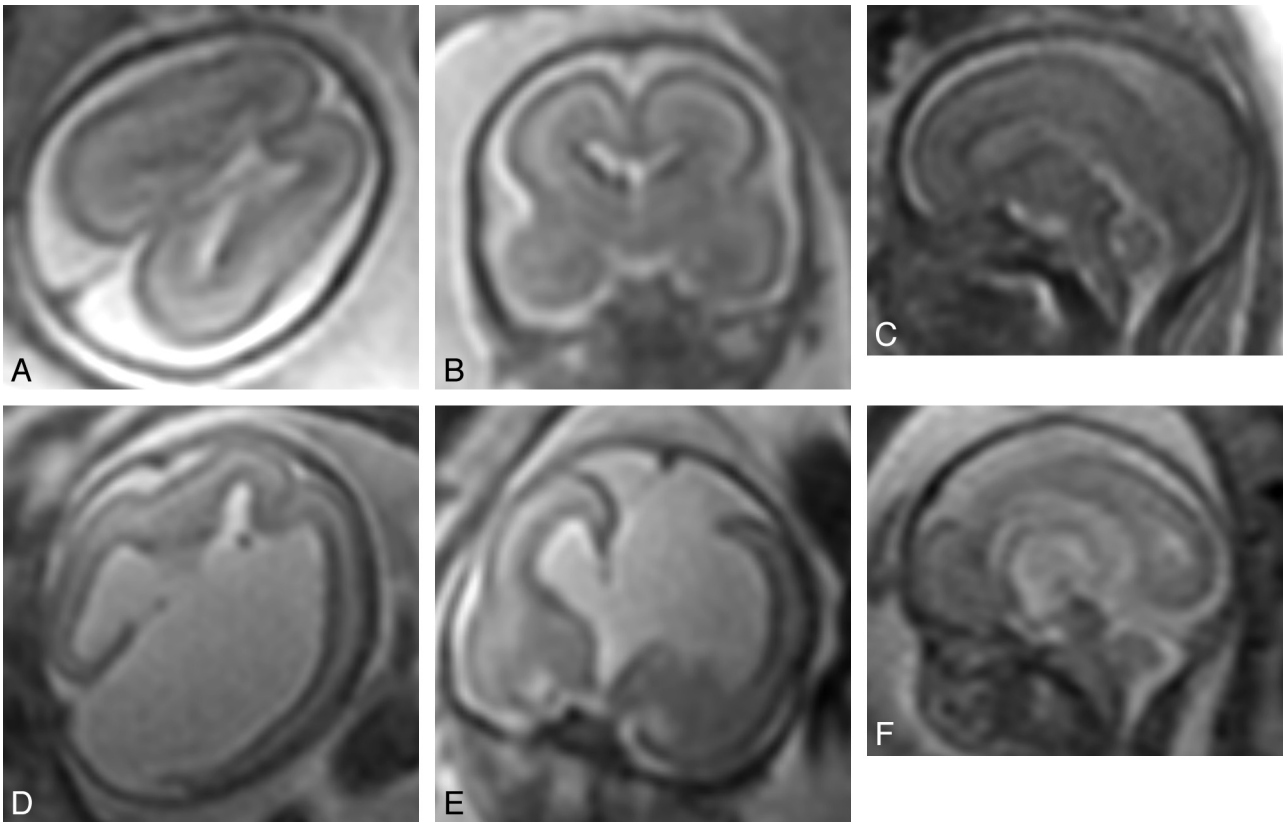

Fig 3. A case of disagreement between sonography and iuMR (study number 30). Sonography had shown VM in 1 twin and a normal intracranial appearance in the other. *A–C*, Axial, coronal, and sagittal iuMR images of the twin reported as normal on sonography also show normal findings on iuMR. *D–F*, Axial, coronal, and sagittal iuMR images of the twin with VM on sonography show severe hypogenesis of the corpus callosum and type 1 interhemispheric cyst.

targets. When we perform examinations on a singleton fetus, the median time to obtain a diagnostic study for the brain only is approximately 15–17 minutes, and for brain and spine, approximately 30 minutes. We always attempt to obtain imaging in all fetuses of a multifetal pregnancy to ensure that we have identified the correct fetus. This is probably more of an issue for iuMR because of the lack of real-time visualization that is inherent in sonography. We have found that most women are not happy to remain on the scanner for >45 minutes, so this is the upper limit of the examination time we will offer. This can present problems particularly in earlier gestation studies (because the fetuses tend to be more mobile), triplets more so than twins, and when we need to image the brain and spine on all fetuses. Despite the compromises that must be made, iuMR of diagnostic quality was obtained in all 50 multifetal pregnancies in our study.

The greatest discrepancy between sonography and iuMR found in the present study was in the diagnosis of abnormalities of the corpus callosum, and this is consistent with our experience in singleton pregnancies. In this study, nearly 60% (10/17 cases) of discrepancies between sonography and iuMR were either a missed diagnosis or an overdiagnosis of a corpus callosum abnormality. Six of these cases (study numbers 5, 7, 25, 30, 36, and 45) were fetuses with isolated VM recognized on sonography, but with ACC diagnosed on iuMR. As stated earlier, we have not been able to obtain postnatal imaging in all of the cases in the study, which would provide a reference standard. We would argue that the recognition of an absent corpus callosum on iuMR is a high-confidence diagnosis that is unlikely to be mistaken for other pathology or normality. In 3 further cases, ACC was suspected on sonography but not confirmed on iuMR. In 1 additional case in which ACC was "missed," the cavum septum pellucidum was thought to be absent on sonography. Many fetomaternal experts would say that this finding implies a problem of the corpus callosum[12,13] and should not be classified as a "miss." In a recent publication, we have rejected that argument because the septum pellucidum can be absent in isolation or in conditions other than ACC. Conversely, when the corpus callosum is absent, there is no embryologic reason for the septum pellucidum and fornix to be absent, and in some cases those structures retain their parasagittal position.[14]

One explanation of the problems associated with making the diagnosis of corpus callosum abnormalities may be a reflection of the difficulty in making this diagnosis on 20-week sonography. On the other hand, in this study, only 1 of the 10 discrepant cases involving a corpus callosum abnormality was referred for MR imaging before 22 weeks. This shows the limitation of sonography in detecting ACC even in more mature fetuses when the corpus callosum is larger. It is also possible that the published advantages of iuMR in this situation have caused sonographers to be more likely to refer cases for iuMR earlier because of the perception that it is a difficult diagnosis to make. In singleton pregnancies, many sonographers take the view that they would not be prepared to wait another 2 weeks. Rather, they would refer the patient for iuMR early because of the time constraints relating to fetocide and termination of pregnancy. Such matters could potentially be

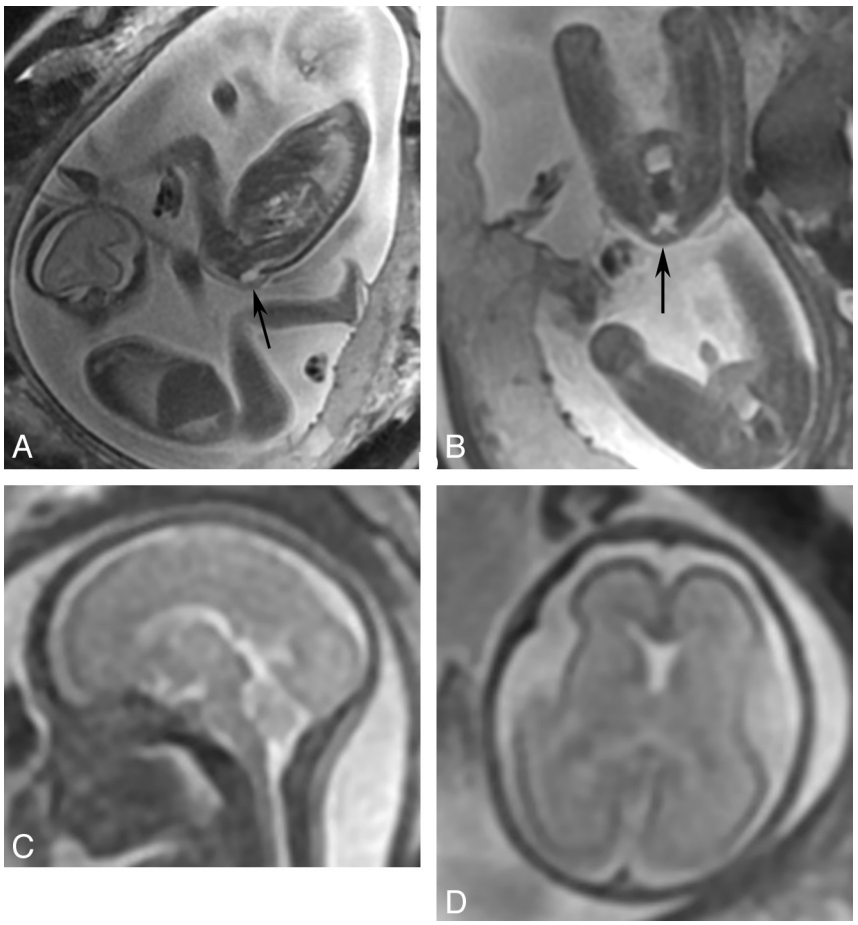

Fig 4. A case of discrepancy between sonography and iuMR (study number 46). Sonography depicted 1 twin with lumbar myelomeningocele and Chiari 2 malformation. *A* and *B*, In contrast, iuMR of the fetal spine showed a skin-covered abnormality (*arrows*) consistent with lipomyelomeningocele. *C* and *D*, Sagittal (*C*) and axial (*D*) images of the fetal brain show normal appearances.

avoided if the diagnosis can be confirmed confidently on iuMR before 22 weeks. This is a more complex management decision in multifetal pregnancies, and the gestational ages at which women were referred argue against this being a major factor in our study.

As stated previously, the combination in a pregnancy of a fetus with a significant developmental CNS abnormality and a normal co-fetus presents a major dilemma for fetomaternal management. What are the differences between the management of brain abnormalities in singleton versus multifetal pregnancies? This scenario has recently been reviewed by Rochon and Stone.[1] They state that a woman has 3 options: She can continue with the pregnancy, terminate the entire pregnancy, or opt for a selective termination of the abnormal fetus. Much is based on the parents' perception of the risk of causing harm to the other healthy fetus during invasive procedures; however, it is often difficult to quantify these risks. A significant number of multifetal pregnancies arise from some form of infertility treatment, and this may also influence an individual's perspective.

The risk from selective termination of the pregnancy, when 1 fetus is abnormal is well-documented. The first large international study in the 1990s reported an 8.3% loss of the co-twin in pregnancies before 24 weeks' gestational age when potassium chloride was used as the agent.[15] This was supported by a second study in 1999 that showed an overall loss rate of 7.5%. The rate rose to 12% with ≥3 fetuses.[16] There was a nonstatistically significant trend toward worse outcomes with increasing gestational age at which the procedure was performed (eg, 6.8% at 19–24 weeks and 9.1% at ≥25 weeks). This is the basis on which many experts will quote a 10% risk of loss of the normal fetus for the procedure. However, intrathoracic injection of potassium chloride is applicable for dichorionic fetuses only. Selective termination in monochorionic fetuses is more hazardous because techniques such as cord ligation or cord coagulation are required. More recent data have suggested that the complication rates are lower.[17] In that study, the "unintended pregnancy loss rate" before 24 weeks' gestational age was 4% (2.4% for twins), and no significant deleterious effects were shown with increasing gestational age at termination.

The management of discordant cases from this study was discussed in a multidisciplinary meeting retrospectively and classified into 1 of 5 groups as previously described. iuMR would have changed the management plan significantly in 12/17 cases with discrepant sonography and iuMR findings, therefore in 24% of cases overall. Cases in which 1 twin was healthy but the other was identified as having ACC promoted the greatest discussion within the multidisciplinary team meeting. Although the outcome of prenatally diagnosed ACC is variable, it was thought that this finding would warrant the

offer of termination, whereas the finding of isolated, nonprogressive borderline VM would not.

The main limitation of this study was the lack of reference standard follow-up of the discrepant cases because no postnatal imaging was available at the time of writing the article. Based on the experience of our earlier studies, however, there has been very close agreement between the iuMR results and reference standard data for both brain[2] and spine[10] cases. Other limitations need to be acknowledged, such as bias in the cases recruited and the manner by which the iuMR cases were reported, inasmuch as the MR imaging reporter always had the sonography report at the time of the iuMR study, which may have influenced the report. In response to that criticism, however, because iuMR will not be performed without prior sonography (certainly in our institution), this reflects the scenario in clinical practice.

Conclusions

We conclude that iuMR has a similar rate of discrepancy to sonography in multifetal pregnancies compared with the published data concerning singleton pregnancies. Our analysis of the effect on management shows that changes in the decision to consider termination of pregnancy would have occurred in 12/17 of the discrepant cases (ie, in 24% of our cases overall). This work also highlights the problems presented by discordant anomalies in twins, with respect to counseling and management decisions made by the attending fetomaternal clinician.

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