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Role of prenatal magnetic resonance imaging in fetuses with isolated mild or moderate ventriculomegaly in the era of neurosonography: international multicenter study

The ENSO Working Group[#]

KEYWORDS: central nervous system; fetal magnetic resonance imaging; fetal ultrasound; MRI; neurosonography; prenatal diagnosis; ventriculomegaly

CONTRIBUTION

What are the novel findings of this work?
In fetuses with a sonographic diagnosis of isolated mild or moderate ventriculomegaly (VM), the incidence of an associated fetal anomaly missed on ultrasound and detected only on fetal magnetic resonance imaging (MRI) is lower than that reported previously in the literature. The large majority of anomalies detected exclusively on MRI involve mainly migration disorders and hemorrhage, which can be difficult to detect on ultrasound and tend to have a later presentation during pregnancy.

What are the clinical implications of this work?
This is the largest study exploring the role of fetal brain MRI in detecting an associated anomaly not diagnosed on ultrasound in fetuses with mild or moderate VM. The findings of this study support the practice of MRI assessment in every fetus with a prenatal diagnosis of VM, although parents can be reassured of the low risk of an associated anomaly when VM is isolated on neurosonography.

ABSTRACT

Objectives *To assess the role of fetal magnetic resonance imaging (MRI) in detecting associated anomalies in fetuses presenting with mild or moderate isolated ventriculomegaly (VM) undergoing multiplanar ultrasound evaluation of the fetal brain.*

Methods *This was a multicenter, retrospective, cohort study involving 15 referral fetal medicine centers in Italy, the UK and Spain. Inclusion criteria were fetuses affected by isolated mild (ventricular atrial diameter, 10.0–11.9 mm) or moderate (ventricular atrial diameter, 12.0–14.9 mm) VM on ultrasound, defined as VM with normal karyotype and no other additional central nervous system (CNS) or extra-CNS anomalies on ultrasound, undergoing detailed assessment of the fetal brain using a multiplanar approach as suggested by the International Society of Ultrasound in Obstetrics and Gynecology guidelines for the fetal neurosonogram, followed by fetal MRI. The primary outcome of the study was to report the incidence of additional CNS anomalies detected exclusively on prenatal MRI and missed on ultrasound, while the secondary aim was to estimate the incidence of additional anomalies detected exclusively after birth and missed on prenatal imaging (ultrasound and MRI). Subgroup analysis according to gestational age at MRI (< 24 vs ≥ 24 weeks), laterality of VM (unilateral* vs *bilateral) and severity of dilatation (mild* vs *moderate VM) were also performed.*

Results *Five hundred and fifty-six fetuses with a prenatal diagnosis of isolated mild or moderate VM on ultrasound were included in the analysis. Additional structural anomalies were detected on prenatal MRI and missed on ultrasound in 5.4% (95% CI, 3.8–7.6%) of cases. When considering the type of anomaly, supratentorial intracranial hemorrhage was detected on MRI in 26.7% of fetuses, while polymicrogyria and lissencephaly were detected in 20.0% and 13.3% of cases, respectively. Hypoplasia of the corpus callosum was detected on MRI in 6.7% of cases, while dysgenesis was detected in 3.3%. Fetuses with an associated anomaly detected only on MRI were more likely to have moderate than mild VM (60.0%* vs *17.7%; $P < 0.001$), while there was no significant difference in the proportion of cases with bilateral VM between the two groups ($P = 0.2$). Logistic regression analysis showed that lower maternal body mass index (adjusted odds ratio (aOR), 0.85 (95% CI, 0.7–0.99); $P = 0.030$), the presence of moderate*

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VM (aOR, 5.8 (95% CI, 2.6–13.4); P < 0.001) and gestational age at MRI ≥ 24 weeks (aOR, 4.1 (95% CI, 1.1–15.3); P = 0.038) were associated independently with the probability of detecting an associated anomaly on MRI. Associated anomalies were detected exclusively at birth and missed on prenatal imaging in 3.8% of cases.

Conclusions *The incidence of an associated fetal anomaly missed on ultrasound and detected only on fetal MRI in fetuses with isolated mild or moderate VM undergoing neurosonography is lower than that reported previously. The large majority of these anomalies are difficult to detect on ultrasound. The findings from this study support the practice of MRI assessment in every fetus with a prenatal diagnosis of VM, although parents can be reassured of the low risk of an associated anomaly when VM is isolated on neurosonography.*

INTRODUCTION

Ventriculomegaly (VM) is the most common brain anomaly diagnosed during fetal life, and encompasses a large spectrum of conditions characterized by dilatation of the lateral ventricles of the brain, typically defined as a diameter greater than 10 mm at the level of the atria[1–7]. VM is frequently classified according to the degree of ventricular dilatation as mild (10.0–11.9 mm), moderate (12.0–14.9 mm) or severe (≥ 15.0 mm), higher degrees of dilatation being associated with an increased risk of neurodevelopmental delay[8].

The cause, severity and presence of associated anomalies are the major determinants in predicting the outcome of fetuses affected by VM. Thus, the main issue when evaluating a fetus with VM is ruling out central nervous system (CNS) and extra-CNS anomalies[6]. The International Society of Ultrasound in Obstetrics and Gynecology (ISUOG) recommends that every fetus presenting with isolated VM on ultrasound should undergo a thorough multiplanar ultrasound examination through axial, coronal and sagittal views of the fetal brain, possibly performed using a high-resolution transvaginal probe. Moreover, a detailed assessment of the entire fetal anatomy, including fetal echocardiography, should also be undertaken[9].

Ultrasound is the primary imaging tool for assessment of the fetal brain, while fetal magnetic resonance imaging (MRI) has been shown to detect additional anomalies in 20% to 50% of cases[10,11]. In a recent systematic review, we found that, in fetuses diagnosed with isolated VM, the incidence of CNS anomalies detected exclusively on MRI was lower than that reported previously when a multiplanar ultrasound assessment of the fetal brain is undertaken[12]. However, heterogeneity among the included studies makes the results of this systematic review difficult to generalize.

The primary aim of this study was to evaluate the role of fetal MRI in detecting associated anomalies in fetuses presenting with isolated mild or moderate VM undergoing multiplanar neurosonography, and to ascertain whether the incidence of such anomalies depends on the degree and laterality of ventricular dilatation and gestational age at MRI. The secondary aim was to estimate the incidence of additional anomalies detected exclusively after birth and missed on prenatal imaging (ultrasound and MRI).

METHODS

Study design and participants

This was a multicenter, retrospective, cohort study involving 15 referral centers in Italy, the UK and Spain. The study included pregnant women who had fetal brain MRI following the diagnosis of isolated mild or moderate VM by neurosonography from January 2010 to March 2019. Only cases with postnatal imaging, or postmortem examination in cases of termination of pregnancy or fetal demise, were included. The clinical records were examined, and data were collected in a dedicated merged database.

Inclusion criteria were fetuses affected by isolated mild (ventricular atrial diameter, 10.0–11.9 mm) or moderate (ventricular atrial diameter, 12.0–14.9 mm) VM on ultrasound, defined as VM with no other additional CNS or extra-CNS anomalies on the scan, detailed assessment of the fetal brain via a multiplanar approach as suggested by 2007 ISUOG guidelines on the fetal neurosonogram[9], detailed fetal assessment including echocardiography, normal karyotype (including chromosomal microarray, when available), negative infection screening (including cytomegalovirus and toxoplasmosis), maternal age ≥ 18 years and gestational age ≥ 18 weeks. Exclusion criteria were fetuses affected by severe VM (ventricular atrial diameter ≥ 15 mm) on ultrasound, cases affected by chromosomal anomalies, cases affected by an additional CNS or extra-CNS anomaly at the time of the initial diagnosis, cases affected by congenital infection and ultrasound protocol unclear or unavailable.

Outcomes

The primary outcome of the study was to establish the incidence of additional CNS anomalies detected exclusively on MRI and confirmed at birth in fetuses with a prenatal diagnosis of isolated VM following dedicated neurosonography. The secondary aim was to estimate the incidence of additional anomalies detected exclusively after birth and missed on prenatal imaging (ultrasound and MRI). Subgroup analysis according to gestational age at MRI (< 24 *vs* ≥ 24 weeks), laterality of VM (unilateral *vs* bilateral) and severity of dilatation (mild *vs* moderate VM) was also performed.

For the purpose of the analysis, additional CNS anomalies were classified into: callosal anomalies, including complete and partial agenesis of the corpus callosum, hypoplasia of the corpus callosum (HCC) and dysgenesis of the corpus callosum; septal anomalies, including all anomalies characterized by a primary defect involving the septum pellucidum with a normally

present corpus callosum; posterior fossa anomalies, including all defects involving the cerebellar vermis and/or hemispheres; intraventricular hemorrhage; cortical anomalies, including all abnormalities associated with a primary defect in neuronal migration towards the cortical surface of the brain; periventricular heterotopia; other white matter anomalies; periventricular cysts; complex brain anomalies, including all defects characterized by the presence of multiple intracranial anomalies; and other cerebral anomalies.

We did not consider biometric variation in brain structures, such as mega cisterna magna, increased or reduced degree of ventricular dilatation or of cranial size, to be associated anomalies.

Statistical analysis

We investigated the relationship between the presence of a VM-associated structural anomaly, assessed using fetal MRI (primary outcome), and a number of maternal and fetal characteristics, including maternal age and body mass index (BMI), VM severity and laterality and gestational age at ultrasound and MRI assessment. As a secondary outcome, we investigated the relationship between the same maternal/fetal parameters and a postnatal diagnosis of a VM-associated anomaly in fetuses with isolated VM (following negative prenatal imaging).

The potential association between all recorded maternal and fetal parameters and the two outcomes was first evaluated using standard univariate analysis (using the chi-square test for categorical variables and the Kruskal–Wallis test for continuous variables). For the secondary outcome, no multivariate analysis could be performed because the number of neonates with a postnatal diagnosis of a structural anomaly was limited to 11, and the likelihood of overfitting was too high.

With regard to the primary outcome, we investigated potential independent predictors of a fetal MRI diagnosis of a VM-associated anomaly using a two-fold approach. First, we performed random-effects logistic regression analysis, with 'hospital region' as the cluster unit. A stepwise forward process was used for model building, and the following criteria were adopted for covariate selection, with covariates being limited to four in every step of the analysis to reduce the risk of overfitting: (1) $P < 0.05$ on univariate analysis; (2) clinical significance; and (3) the interval, expressed in weeks, between ultrasound and MRI examinations included *a-priori* as a continuous variable. To avoid multicollinearity between mean dilatation of the cerebral ventricular atrium (in mm) and the severity of ventriculomegaly (classified into 'mild' or 'moderate' according to dilatation in mm), only the latter covariate was included in the model as a categorical variable. Standard postestimation tests were used to check the validity of the final model, performing multicollinearity and influential observation analyses (using standardized residuals, change in Pearson and deviance chi-square)[13,14].

Second, all analyses were repeated after multiple imputation with the bootstrap option for missing values (m = 5, *mi* Stata command)[13,14], as maternal BMI was not reported in 37% of cases. The results of the complete model were very similar to those of the random-effects logistic regression model, and only the results of the model without missing imputation have been shown to avoid redundancy. Statistical significance was defined as two-sided $P < 0.05$ for all analyses[15], which were carried out using Stata, version 13.1 (Stata Corp., College Station, TX, USA, 2013).

The study was reported following the STROBE guidelines[16].

RESULTS

Characteristics of the women

Five hundred and fifty-six fetuses with a prenatal diagnosis of isolated mild or moderate VM on ultrasound were included in the analysis. The general characteristics of the study population are shown in Table 1. Mean maternal age was 32.0 ± 5.9 years, while mean BMI was 24.6 ± 4.1 kg/m^2. Mean gestational age at MRI was 26.7 ± 4.4 weeks, with 30.9% of the scans performed before 24 weeks' gestation, while 69.1% were performed at or after 24 weeks. Of the included cases, 36.5% (95% CI, 32.6–40.4%) (203/556) were affected by bilateral VM, while 63.5% (95% CI, 59.4–67.4%) (353/556) had unilateral VM. VM was mild (10.0–11.9 mm) in 80.0% (95% CI, 76.5–83.2%) (445/556) of cases and moderate (12.0–14.9 mm) in 20.0% (95% CI, 16.9–23.5%) (111/556).

Synthesis of results

Table 1 shows the results of the primary and secondary outcomes of the study. An additional structural anomaly was detected exclusively on MRI in 5.4% (95% CI, 3.8–7.6%) (30/556) of cases. When considering the type of anomaly, supratentorial intracranial hemorrhage was detected exclusively on MRI in 26.7% (8/30) of cases, while polymicrogyria and lissencephaly were detected in 20.0% (6/30) and 13.3% (4/30) of cases, respectively. HCC was detected only on MRI in 6.7% (2/30) of cases, while dysgenesis was detected in 3.3% (1/30).

The incidence of an associated anomaly detected exclusively on prenatal MRI was significantly higher in fetuses affected by moderate VM (60.0%) than in fetuses affected by mild VM (17.7%) ($P < 0.001$), while there was no significant difference in the proportion of cases with bilateral VM between the two groups ($P = 0.2$). The majority (90.0%) of fetuses with an associated anomaly had MRI performed at or after 24 weeks' gestation (Table S1).

Logistic regression analysis showed that lower maternal BMI (adjusted odds ratio (aOR), 0.85 (95% CI,

Table 1 Characteristics and rate of additional anomaly on magnetic resonance imaging (MRI) in 556 singleton pregnancies with prenatal sonographic diagnosis of isolated mild or moderate ventriculomegaly (VM)

Characteristic	*Value*
Maternal age (years)	32.0 ± 5.9
Maternal body mass index (kg/m^2)*	24.6 ± 4.1
GA at prenatal ultrasound (weeks)	24.8 ± 3.8
GA at prenatal MRI (weeks)	26.7 ± 4.4
< 24 weeks	172 (30.9)
≥ 24 weeks	384 (69.1)
Interval between prenatal ultrasound and MRI (weeks)	2.2 ± 2.5
≤ 2 weeks	420 (75.5)
3–5 weeks	63 (11.3)
≥ 6 weeks	73 (13.1)
Bilateral VM	203 (36.5)
Severity of VM	
Mild	445 (80.0)
Moderate	111 (20.0)
Ventricular atrial dilatation (mm) in:	
All fetuses	11.6 ± 1.3
Mild-VM group	11.1 ± 0.7
Moderate-VM group	13.8 ± 0.8
Dilatation of contralateral ventricular atrium (mm)†	11.8 ± 1.4
Additional anomaly on prenatal MRI	30 (5.4)
Hemorrhage	8/30 (26.7)
Polymicrogyria	6/30 (20.0)
Lissencephaly	4/30 (13.3)
Corpus callosum hypoplasia	2/30 (6.7)
Periventricular heterotopia	2/30 (6.7)
Other	8/30 (26.7)
Additional anomaly on postnatal MRI‡	11/289 (3.8)

Data are given as mean ± SD, *n* (%) or *n*/*N* (%). *Data available for 349 cases. †Based on 203 fetuses with bilateral VM. ‡Analysis restricted to 289 neonates without prenatal diagnosis of structural anomaly and that had postnatal MRI examination available.

0.7–0.99); $P = 0.030$), the presence of moderate VM (aOR, 5.8 (95% CI, 2.6–13.4); $P < 0.001$) and gestational age at MRI at least 24 weeks (aOR, 4.1 (95% CI, 1.1–15.3); $P = 0.038$) were associated independently with the probability of detecting an associated anomaly on prenatal MRI. The interval in weeks between ultrasound and MRI assessment was not associated significantly with an anomaly on prenatal MRI (aOR, 1.00 (95% CI, 0.84–1.21); $P = 0.919$).

After birth, 3.8% (11/289) of cases with isolated VM confirmed on prenatal MRI had an associated anomaly detected exclusively on postnatal imaging (cranial ultrasound and/or postnatal MRI). Mean ventricular atrial dilatation was significantly higher in fetuses with a postnatal diagnosis of an associated anomaly than in those that had isolated VM confirmed on postnatal imaging (13.0 ± 1.5 mm *vs* 11.5 ± 1.3 mm; $P = 0002$). Furthermore, fetuses with a postnatal diagnosis of an associated anomaly were more likely to be affected by bilateral (81.8% *vs* 50.0%; $P = 0.04$) and moderate (63.6% *vs* 18.7%; $P < 0.001$) VM than were those with isolated VM confirmed after birth (Table S2).

DISCUSSION

Summary of main findings

The findings of this study show that, in fetuses with a prenatal diagnosis of isolated mild or moderate VM examined using multiplanar neurosonography, the rate of an additional structural anomaly detected exclusively on fetal brain MRI was 5.4%. The most common types of anomaly were supratentorial intracranial hemorrhage and neuronal migration disorders. Factors associated independently with a higher incidence of an additional finding detected exclusively on fetal MRI were gestational age at MRI ≥ 24 weeks, moderate ventricular atrial dilatation and lower maternal BMI. The rate of an associated anomaly detected exclusively after birth and missed on prenatal imaging was 3.8%.

Strengths and limitations

The large sample size, inclusion of cases examined using a multiplanar approach as proposed by ISUOG guidelines on fetal neurosonography and stratification of the analyses according to the degree and laterality of ventricular atrial dilatation represent the main strengths of this study. The retrospective non-randomized design represents the main limitation of the study, and led to challenges in obtaining all imaging details for all fetuses in the participating centers, with some cases of incomplete follow-up and some missing data, mostly related to postnatal MRI or ultrasound and karyotyping. Furthermore, although 75.5% of fetuses underwent MRI 2 weeks or less after the neurosonogram, 24.5% underwent MRI after 3 to more than 6 weeks after ultrasound; therefore, it is likely that a prolonged interval between ultrasound and MRI may have influenced our results. Finally, the present study included cases undergoing neurosonography performed in each participating center, without taking into account its feasibility according to different maternal and fetal characteristics.

Implications for research and clinical practice

Isolated VM represents a considerable diagnostic dilemma, as it can be an apparently benign finding, but it can also be associated with chromosomal abnormalities, congenital infections, cerebral vascular accidents or hemorrhage and other fetal cerebral and extracerebral abnormalities[5–7]. Even when isolated, VM has been reported to increase the risk of neurodevelopmental delay in childhood and adolescence. The prevalence of neurodevelopmental disorders in fetuses with both unilateral and bilateral mild VM has been reported to be only slightly higher than that in the general population[17–19]. Conversely, the rate of neurodevelopmental delay is higher in cases of VM associated with additional CNS anomalies and in cases of severe ventricular atrial dilatation[20–22].

The ISUOG guidelines on sonographic examination of the fetal CNS suggest that a multiplanar assessment of the

fetal head should be always performed when suspicion of a brain anomaly is raised at the basic ultrasound examination[9]. Furthermore, in a recent consult series on mild VM, the Society for Maternal-Fetal Medicine stated that MRI may be considered in cases of mild or moderate fetal VM, although it may be of less value if the woman has undergone detailed ultrasound assessment by an individual with specific experience and expertise in sonographic imaging of the fetal brain[8].

MRI is the imaging technique of choice for analyzing brain anomalies postnatally. MRI has better regional resolution than does ultrasound, thus it should, theoretically, be better than ultrasound at detecting abnormalities of cortical development. Based on these findings, current practice suggests a prenatal MRI examination in the late second or early third trimester of pregnancy, although there is no complete agreement among different researchers regarding the need for and timing of the MRI examination. However, the large majority of published studies on MRI do not specify which type of ultrasound imaging protocol was adopted to assess the fetal brain, but this is fundamental, as most CNS anomalies cannot be detected easily on the standard axial plane of the fetal brain[12,23–29].

In 2017, the results of a large, prospective, multicenter study (the MERIDIAN study) involving 16 centers across the UK and designed to evaluate the diagnostic and clinical role of fetal MRI in fetuses with suspicion or diagnosis of a CNS anomaly on a previous ultrasound examination were published[11]. This study showed much greater diagnostic accuracy of MRI compared with ultrasound (93% *vs* 68%), with additional findings detected exclusively on MRI in 49% of cases overall and in up to 19.4% when focusing on the subgroup of fetuses with mild or moderate VM[23]. Of note, the rate of associated callosal anomalies detected exclusively on MRI was lower in our cohort than that in the MERIDIAN study (10% *vs* 55% of cases of failed commissuration)[23].

In the present study, the large majority of anomalies detected exclusively on prenatal MRI included neuronal migration (lissencephaly, heterotopia) or acquired anomalies (e.g. hemorrhage) that can be difficult to diagnose on ultrasound[30–34]. In this scenario, fetal MRI should always be performed in order to rule out associated anomalies that can be potentially missed on ultrasound. Nevertheless, parents should be reassured regarding the low risk of such additional anomalies.

In the present study, MRI performed at or after 24 weeks' gestation was an independent risk factor for an additional anomaly detected exclusively on MRI. This finding might appear quite intuitive, as some abnormalities, such as malformations of cortical development, migration disorders and hemorrhage become evident only later during pregnancy. Not surprisingly, the most frequent types of anomaly detected only on MRI in this study were hemorrhage and migration disorders, which are anomalies presenting mostly after the second trimester of pregnancy[35]. However, some authors have suggested that early MRI (before 24 weeks) may be reliable and has similar accuracy to MRI performed later in gestation[11,12], with the advantage of an early diagnosis that can allow parents the option of earlier management, especially in countries in which termination of pregnancy is not legal beyond the second trimester.

Conclusions

The rate of an associated fetal anomaly missed on ultrasound and detected only on MRI in fetuses with mild or moderate VM is lower than that reported previously in the published literature when a multiplanar ultrasound examination of the fetal brain is performed. The large majority of anomalies detected exclusively on MRI involve mainly migration disorders and hemorrhage, which cannot be detected easily on ultrasound, thus highlighting the need for an MRI examination in fetuses with a prenatal diagnosis of VM undergoing neurosonography. Future research investigating the prenatal diagnosis of isolated VM should aim for a multicenter prospective approach, mainly to establish the optimal timing and frequency of MRI examinations.

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SUPPORTING INFORMATION ON THE INTERNET

The following supporting information may be found in the online version of this article:

Table S1 Characteristics of 556 singleton pregnancies with prenatal sonographic diagnosis of isolated mild or moderate ventriculomegaly (VM), according to whether associated anomaly was detected by prenatal MRI

Table S2 Characteristics of 556 singleton pregnancies with prenatal sonographic diagnosis of isolated mild or moderate ventriculomegaly (VM), according to whether associated anomaly was detected by postnatal MRI