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

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CONTRIBUTION

What are the novel findings of this work?

The rate of fetal anomalies missed at US and detected only at fetal MRI is lower than what was previously reported in the published literature. The large majority of anomalies detected exclusively on MRI involve mainly migration disorders and hemorrhage which can be difficult to detect on US 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 associated anomalies not diagnosed on US in fetuses with mild and moderate VM. 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 associated anomalies, when VM is isolated.

ABSTRACT

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

Methods: Multicenter, retrospective, cohort study involving 15 referral fetal medicine centers in Italy, United Kingdom, and Spain. Inclusion criteria were fetuses affected by isolated VM on US, defined as VM with normal karyotype and no other additional central nervous system (CNS) and extra-CNS anomalies on US, undergoing detailed assessment of fetal brain via a multiplanar approach as suggested by ISUOG guidelines on fetal neurosonogram. The primary outcome of the study was to report the rate of additional CNS anomalies detected exclusively at prenatal MRI and missed at US, while the secondary aim was to estimate the incidence of additional anomalies detected exclusively after birth and missed at prenatal imaging (US and MRI). Sub-group analyses according to the gestational age at MRI (< vs ≥ 24 weeks of gestation), laterality of VM (unilateral vs bilateral), and severity of dilatation (mild vs moderate VM) were also performed.

Results: Five-hundreds and fifty-six fetuses with a prenatal diagnosis of isolated fetal VM on US were included in the analysis. Additional structural anomalies were detected at prenatal MRI and missed at US in 5.4% (95% CI 3.8-7.6) of cases. When considering the type of anomalies, supra-tentorial intra-cranial hemorrhage was detected on MRI in 26.7% of fetuses, while polymicrogyria and lissencephaly in 20.0% and 13.3% of cases, respectively. Hypoplasia of the corpus callosum was detected at MRI in 6.7% of cases, while dysgenesis in 3.3%. Fetuses with an associated anomaly detected only at MRI were more likely to have moderate compared to mild VM (60.0% vs 17.7%, p<0.001), while there was no significant difference between the proportion of cases with bilateral VM between the two groups (p=0.2). The results of the logistic regression analysis showed that maternal body mass index (OR: 0.85, 95% CI 0.7-0.99, p= 0.030), the presence of moderate VM (OR: 5.8, 95% CI 2.6-13.4, p<0.001) and gestational age at MRI ≥24 weeks of gestation (OR: 4.1, 95% CI 1.1-15.3, p= 0.038) were independently associated with the probability of detecting associated anomalies at MRI. Associated anomalies were detected exclusively at birth and missed at prenatal imaging in 3.8% of cases.

Conclusions: The rate of associated fetal anomalies missed at US and detected only at fetal MRI in fetuses with isolated mild and moderate VM undergoing neurosonography is lower than that previously reported. 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 associated anomalies, when VM is isolated on US.

INTRODUCTION

Ventriculomegaly (VM) is the most common brain anomaly diagnosed during fetal life and encompasses a large spectrum of conditions characterized by a dilatation of the lateral ventricles of the brain, typically defined as 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 (10-12 mm), moderate (13-15 mm), or severe (>15 mm), with higher degrees of dilation 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 approaching a fetus with VM is to rule 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 examination through axial, coronal and sagittal views of the fetal brain, possibly performed with a high-resolution vaginal probe. Moreover, a detailed assessment of the entire fetal anatomy, including fetal echocardiography, should also be undertaken.[9]

Ultrasound (US) is the primary imaging tool for the assessment of fetal brain, while fetal magnetic resonance imaging (MRI) has been shown to detected 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 rate of CNS anomalies detected exclusively on MRI was lower than that previously reported when a multiplanar assessment of the fetal brain is undertaken.[9,12] However, the heterogeneity among the included studies make 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 and moderate VM undergoing multiplanar neurosonography and to ascertain whether the incidence of such anomalies is dependent upon 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 at prenatal imaging (US and MRI).

METHODS

Study design and participants

This was a multicenter, retrospective, cohort study involving 15 referral centers in Italy, United Kingdom, and Spain. The study included pregnant women who had fetal brain MRI following the diagnosis of isolated VM performed by neurosonography from January 2010 to March 2019. Only cases with at post-natal imaging or post-mortem examination, in case 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

- Fetuses affected by isolated mild (10-12 mm), moderate (13-15 mm) VM at US, defined as VM with no other additional CNS and extra-CNS on the scan
- Detailed assessment of fetal brain via a multiplanar approach as suggested by 2007 ISUOG guidelines on fetal neurosonogram[9]
- Detailed fetal assessment including echocardiography
- Normal karyotype (including chromosomal microarray, when available)
- Negative infection screening (including CMV and Toxoplasmosis)
- Maternal Age ≥ 18 years
- Gestational age ≥ 18 weeks

Exclusion criteria

- Fetuses affected by severe (> 15 mm) VM at US cases of severe VM
- Cases affected by chromosomal anomalies
- Cases affected by additional CNS and extra-CNS anomalies at the time of initial diagnosis
- Cases affected by congenital infections
- US protocol unclear or unavailable

Outcomes

The primary outcome of the study was to establish the rate 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 at prenatal imaging (US and MRI). Sub-group analyses according to the gestational age at MRI (< vs ≥ 24 weeks of gestation), laterality of VM (unilateral vs bilateral VM), and the severity of dilatation (mild vs moderate VM) were also performed.

For the purpose of the analysis, additional CNS anomalies were classified into:

- Callosal anomalies, including complete and partial agenesis (ACC), hypoplasia (HCC) and dysgenesis of the corpus callosum
- Septal anomalies, including all the 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
- Intra-ventricular hemorrhage
- Cortical anomalies, including all abnormalities associated with a primary defect in neuronal migration towards the cortical surface of the brain
- Peri-ventricular heterotopia
- Other white matter anomalies
- Peri-ventricular cysts
- Complex brain anomalies, including all defects characterized by the presence of multiple intra-cranial anomalies
- 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, as associated anomalies.

Statistical analysis

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

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

As regards the primary outcome, we investigated the potential independent predictors of a fetal MRI diagnosis of ventriculomegaly-associated anomalies with a twofold approach. First, we performed a random-effect logistic regression, with hospital region as the cluster unit. A stepwise forward process was used for model building, and the following criteria were adopted for covariates selection, which were limited to four in every step of the analysis to reduce the risk of overfitting: (1) $p<0.05$ at univariate analyses; (2) clinical significance; (3) the interval, expressed in weeks, between US and MRI examinations included a priori as a continuous variable. To avoid multicollinearity between the mean dilatation of cerebral ventricle (in mm) and the severity of ventriculomegaly (classified into "mild" and "moderate" according to the mm of dilatation), only the latter covariate was included in the model as a categorical variable. Standard post-estimation 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 bootstrap option for missing values (m=5, *mi* Stata command),[13-14] as 37% of the mother's BMI values were not reported. The results of the complete model were very similar to those of the random-effect logistic regression, and only the results of the model without missing imputation have been shown to avoid redundancy. Statistical significance was defined as a two-sided p-value<0.05 for all analyses,[15] which were carried out using Stata, version 13.1 (Stata Corp., College Station, Texas, USA, 2013). This 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 fetal VM were included in the analysis. The general characteristics of the study population are shown in Table 1. The mean maternal age was 32.0±5.9 years, while the mean BMI was 24.6±4.1. The mean gestational age at MRI was 26.7±4.4, with 30.9% of the scans performed before, while 69.1% performed at or after 24 weeks of gestation. Of the included cases, 36.5% (95% CI 32.6-40.4; 203/556) were affected by bilateral, while 63.5% (95% CI 59.4-67.4; 353/556) by unilateral VM. Finally, VM was mild (10-12 mm) in 80.0% (95% CI 76.5-83.2; 445/556) and moderate (13-15 mm) in 20.0% (95% CI 16.9-23.5; 111/556) of the cases.

Synthesis of the results

Table 2 shows the results of the primary and secondary outcomes of study. Additional structural anomalies were detected exclusively by MRI in 5.4% (95% CI 3.8-7.6; 30/556) of cases. When considering the type of anomalies, supra-tentorial intra-cranial hemorrhage was detected exclusively at MRI in 26.7% (8/30) of cases, while polymicrogyria and lissencephaly in 20.0% (6/30) and 13.3% (4/30) of cases, respectively. HCC was detected only at MRI in 6.7% (2/30) of cases, while dysgenesis in 3.3% (1/30).

The rate of associated anomaly detected exclusively at MRI was significantly higher in fetuses affected by moderate VM (60%), compared with fetuses affected by mild VM (17.7%) ($p<0.001$), while there was no significant difference between the proportion of cases with bilateral VM between the two groups ($p=0.2$). The majority (90.0%) of fetuses with associated anomalies had MRI performed at ≥24 weeks of gestation (Supplementary Table 1).

The results of the logistic regression analysis showed that maternal BMI (OR: 0.85, 95% CI 0.7-0.99, $p= 0.030$), the presence of moderate VM (OR: 5.8, 95% CI 2.6-13.4, $p<0.001$) and gestational age at MRI ≥24 weeks of gestation (OR: 4.1, 95% CI 1.1-15.3, $p= 0.038$) were independently associated with the probability of detecting associated anomalies at MRI (Table 3).

After birth, 3.8% (11/278) of cases with an isolated VM confirmed at prenatal MRI had associated anomalies detected exclusively at post-natal imaging (cranial ultrasound and/or post-natal MRI). Mean ventricular dilatation was significantly higher in fetuses with a post-natal diagnosis of associated anomalies compared to those who had isolated VM confirmed at post-natal imaging (13.0±1.5 vs 11.5±1.3, p= 0002). Furthermore, fetuses with a post-natal diagnosis of associated

anomalies were more likely to be affected by bilateral 3 decimal points (81.8% vs 50.0%, p=0.04) and moderate (63.6% vs 18.7%, p<0.001) VM compared to those who were confirmed to be isolated after birth (Supplementary Table 2).

DISCUSSION

Summary of the main findings

The findings of this study show that in fetuses with prenatal diagnosis of isolated VM examined using multiplanar neurosonography, the rate of additional structural anomalies detected exclusively by fetal brain MRI was 5.4%. The most common type of anomalies included supra-tentorial intra-cranial hemorrhage, and neuronal migration disorders. Factors independently associated with a higher incidence of additional findings detected exclusively at fetal MRI were gestational age at MRI ≥ 24 weeks, moderate ventricular dilatation and maternal BMI. Finally, the rate of associated anomalies detected exclusively after birth and missed at prenatal imaging was 3.8%.

Strengths and limitations

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 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 the details on the imaging for all the fetuses in the participating centers, with some incomplete follow-up and some missing data, mostly related to the postnatal MRI or US and karyotyping. Furthermore, although 75.5% of fetuses underwent MRI two weeks or less after neurosonogram, 24.5% of fetuses underwent MRI after three to more than six weeks after US; therefore, it is likely that a prolonged interval between US and MRI may have somehow influenced our results. Finally, the present study included only cases having neurosonography performed in each participating center without exploring its feasibility according to different maternal and fetal characteristics.

Implications for clinical practice and research

Isolated VM represents a considerable diagnostic dilemma as it can be an apparently benign finding, but 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 of the general population.[17-19] Conversely, neurodevelopmental delay is higher in case of VM associated with additional CNS anomalies, and in case of severe ventricular dilatation.[20-22]

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

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

In 2017, a large prospective, multicenter study involving 16 centers across the United Kingdom (the MERIDIAN Study) was designed to evaluate the diagnostic and clinical role of fetal MRI in fetuses with a previous US with a suspicion or diagnosis of CNS anomaly.[11] This study showed a much greater diagnostic accuracy of MRI compared to US (93% versus 68%), with additional findings detected exclusively on MRI in 49% of brain abnormalities and in up to 19.4% when focusing on the subgroup analysis of fetuses with mild and moderate VM.[23] Of note, the rate of associated callosal anomalies detected exclusively on MRI was lower in our cohort compared to the MERIDIAN study (10% versus 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 (i.e. hemorrhage) which could be difficult to diagnose on ultrasound.[30-34] In this scenario, fetal MRI should always be performed in order to rule out associated anomalies which 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 was an independent factor which was associated with the risk of additional anomalies detected exclusively at MRI. This finding might

appear quite intuitive, as some abnormalities, such as malformations of cortical development, migration disorders and hemorrhage can become evident only later during pregnancy. Not surprisingly, the most frequent type of anomalies detected only at MRI in this study were hemorrhage and migration disorders, anomalies presenting mostly after the second trimester of pregnancy.[35] However, some authors have suggested that early MRI (before 24 weeks of gestations) may be reliable and has similar accuracy as MRI performed later in gestation,[11-12] with the advantage of an early diagnosis which can allow parents the option of earlier diagnosis, especially in countries where termination of pregnancy is not legal beyond the second trimester.

Conclusions

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

Disclosure:

Authors report no conflict of interest.

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Table 1. Selected gestational and fetal characteristics in a sample of singleton pregnancies with a prenatal sonographic diagnosis of ventriculomegaly

Variables	**N = 556**
General characteristics:	
Mean maternal age in years (SD)	32.0 (5.9)
Mean maternal BMI in kg/m^2 (SD)	24.6 (4.1)
Gestational age at prenatal MRI diagnosis of additional anomalies in weeks:	
- Mean gestational age at diagnosis (SD)	26.7 (4.4)
- Diagnosis <24 weeks, %	30.9
- Diagnosis ≥24 weeks, %	69.1
Interval between prenatal US and MRI examinations in weeks:	
- Mean interval (SD)	2.2 (2.5)
- ≤2 weeks, %	75.5
- 3-5 weeks, %	11.3
- ≥6 weeks, %	13.2
Characteristics of fetal ventriculomegaly:	
Bilateral ventriculomegaly, %	36.5
Severity, %	
- Mild	80.0
- Moderate	20.0
Mean ventricular dilatation in mm (SD):	
- Overall	11.6 (1.3)
- Mild ventriculomegaly	11.1 (0.7)
- Moderate ventriculomegaly	13.8 (0.8)
Mean dilatation of the controlateral ventricle in mm (SD)**	11.8 (1.4)

SD: Standard deviation; US: ultrasound; MRI, magnetic resonance imaging
*Data available only for 425 and 148 fetuses, respectively. **Based on 203 fetuses with bilateral ventriculomegaly

Table 2. Primary and secondary outcomes

Outcomes	
Fetuses with additional structural anomalies detected through prenatal MRI, %	5.4
Type of prenatal-diagnosed anomaly, % *	
- Hemorrhage	26.7
- Polymicrogyria	20.0
- Lissencephaly	13.3
- Corpus Callosum hypoplasia	6.7
- Periventricular heterotopia	6.7
- Others	26.6
Newborn with additional structural anomalies detected through postnatal MRI, % **	3.8

* N=30 fetuses with additional anomalies detected through prenatal MRI
** Analyses restricted to 289 newborn (both the fetuses with a prenatal diagnosis of structural anomaly and the newborn without a postnatal MRI exam were excluded).

Table 3. Logistic regression models evaluating the potential independent predictors of a prenatal MRI diagnosis of ventriculomegaly-associated anomalies

Covariates	**Adjusted OR (95% CI)**	**P value**
Model 1 *		
Maternal BMI, 1-unit increase	0.85 (0.74-0.99)	0.030
Severity of ventriculomegaly, moderate vs mild	5.84 (2.55-13.4)	**<0.001**
Interval between US and MRI assessment, 1-week increase	1.00 (0.84-1.21)	0.919
Gestational age at MRI diagnosis, ≥ versus < 24 weeks	4.07 (1.09-15.3)	**0.038**

* Random-effect logistic regression with Hospital region as the cluster level.

Supplementary Table 1. Comparison of selected gestational characteristics according to whether ventriculomegaly-associated anomalies were detected by prenatal MRI or not

Variables	**Ventriculomegaly-associated prenatal anomalies (n=30)**	**No prenatal anomalies (n=526)**	**P value ***
General characteristics:			
Mean maternal age in years (SD)	30.7 (6.8)	32.1 (5.9)	0.2
Mean maternal BMI in kg/m^2 (SD)	23.2 (3.2)	24.7 (4.2)	0.055
Gestational age at prenatal MRI diagnosis of additional anomalies in weeks:			
- Mean gestational age at diagnosis (SD)	28.2 (4.5)	26.6 (4.4)	0.05
- Diagnosis ≥24 weeks, %	90.0	67.9	0.011
Interval between prenatal US and MRI exams in weeks:			
- Mean interval (SD)	2.2 (2.3)	2.2 (2.5)	0.8
- ≤2 weeks, %	66.7	76.1	0.3
- 3-5 weeks, %	23.3	10.6	0.3
- ≥6 weeks, %	10.0	13.3	0.9
Characteristics of fetal ventriculomegaly:			
Bilateral ventriculomegaly, %	46.7	35.9	0.2
Moderate severity, %	60.0	17.7	<0.001
Mean ventricular dilatation in mm (SD):			
- Overall	12.9 (1.4)	11.5 (1.3)	<0.001
- Mild ventriculomegaly	11.4 (0.6)	11.0 (0.7)	0.09
- Moderate ventriculomegaly	13.9 (0.7)	13.7 (0.8)	0.3
Mean dilatation of the controlateral ventricle in mm (SD) **	12.7 (1.2)	11.7 (1.4)	0.007
Outcomes:			
Newborn with additional structural anomalies detected through postnatal MRI, % ***	--	3.8	--

SD: Standard deviation; ** Based on 203 fetuses with bilateral ventriculomegaly; *** Analyses restricted to 289 newborn (both the fetuses with a prenatal diagnosis of structural anomaly and the newborn without a postnatal MRI exam were excluded).
* Chi-squared test and Kruskal-Wallis test for categorical and continuous outcomes, respectively.

Supplementary Table 2. Comparison of selected gestational characteristics according to whether ventriculomegaly-associated anomalies were detected or not by postnatal MRI ψ

Variables	**Ventriculomegaly-associated postnatal anomalies (n=11)**	**No postnatal anomalies (n=278)**	**p ***
General characteristics:			
Mean maternal age in years (SD)	33.1 (4.9)	32.1 (5.9)	0.6
Mean maternal BMI in kg/m^2 (SD)	24.0 (2.6)	23.9 (3.2)	0.9
Interval between prenatal US and MRI exams in weeks:			
- Mean interval (SD)	1.5 (2.9)	2.2 (2.5)	0.37
- ≤2 weeks, %	90.9	77.0	0.3
- 3-5 weeks, %	0.0	9.7	-
- ≥6 weeks, %	9.1	13.3	0.9
Characteristics of fetal ventriculomegaly:			
Bilateral ventriculomegaly, %	81.8	50.0	0.04
Moderate severity, %	63.6	18.7	<0.001
Mean ventricular dilatation in mm (SD):			
- Overall	13.0 (1.5)	11.5 (1.3)	0.002
- Mild ventriculomegaly	11.4 (1.0)	11.0 (0.7)	0.2
- Moderate ventriculomegaly	13.9 (0.9)	13.7 (0.9)	0.7
Mean dilatation of the contralateral ventricle in mm (SD) **	13.1 (2.0)	11.6 (1.4)	0.004

* Chi-squared test and Kruskal-Wallis test for categorical and continuous outcomes, respectively.
ψ Analyses restricted to 289 newborn (both the fetuses with a prenatal diagnosis of structural anomaly and the newborn without a postnatal MRI exam were excluded); SD: Standard deviation; ** Based on 148 fetuses with bilateral ventriculomegaly.

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

The ENSO working group#

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CONTRIBUTION

What are the novel findings of this work?

The rate of an associated fetal anomaly missed on US and detected only on fetal MRI in fetuses with a sonographic diagnosis of isolated mild or moderate ventriculomegaly (VM) is lower than that reported previously in the published literature. The large majority of anomalies detected exclusively on MRI involve mainly migration disorders and hemorrhage, which can be difficult to detect on US 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 US 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 US.

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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 (US) evaluation of the fetal brain.

Methods: This was a multicenter, retrospective, cohort study involving 15 referral fetal medicine centers in Italy, United Kingdom and Spain. Inclusion criteria were fetuses affected by isolated mild (ventricular atrial diameter, 10-12mm) or moderate (ventricular atrial diameter, 13-15mm) VM on US, defined as VM with normal karyotype and no other additional central nervous system (CNS) or extra-CNS anomalies on US, undergoing detailed assessment of the fetal brain using a multiplanar approach as suggested by ISUOG guidelines for the fetal neurosonogram, followed by fetal brain MRI. The primary outcome of the study was to report the rate of additional CNS anomalies detected exclusively on prenatal MRI and missed on US, while the secondary aim was to estimate the incidence of additional anomalies detected exclusively after birth and missed on prenatal imaging (US and MRI). Sub-group analyses according to gestational age at MRI (<24 vs ≥ 24 weeks of gestation), 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 fetal VM on US were included in the analysis. Additional structural anomalies were detected on prenatal MRI and missed on US in 5.4% (95% CI 3.8-7.6%) of cases. When considering the type of anomaly, supra-tentorial intra-cranial 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 compared to 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 maternal body mass index (OR: 0.85, 95% CI 0.7-0.99, p= 0.030), the presence of moderate VM (OR: 5.8, 95% CI 2.6-13.4, p<0.001) and gestational age at MRI ≥24 weeks of gestation (OR: 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 rate of an associated fetal anomaly missed on US 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

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diagnosis of VM, although parents can be reassured of the low risk of an associated anomaly when VM is isolated on US.

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 (10-12 mm), moderate (13-15 mm), or severe (>15 mm), with 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 (US) examination through axial, coronal and sagittal views of the fetal brain, possibly performed using a high-resolution vaginal probe. Moreover, a detailed assessment of the entire fetal anatomy, including fetal echocardiography, should also be undertaken.[9]

US 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 rate of CNS anomalies detected exclusively on MRI was lower than that reported previously when a multiplanar US assessment of the fetal brain is undertaken.[9,12] However, the 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 is dependent upon 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 (US and MRI).

METHODS

Study design and participants

This was a multicenter, retrospective, cohort study involving 15 referral centers in Italy, United Kingdom and Spain. The study included pregnant women who had fetal brain MRI following the diagnosis of isolated mild or moderate VM performed by neurosonography from January 2010 to March 2019. Only cases with postnatal imaging, or post-mortem 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, 10-12 mm) or moderate (ventricular atrial diameter, 13-15 mm) VM on US, 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 CMV and Toxoplasmosis), maternal Age ≥ 18 years and gestational age ≥ 18 weeks. Exclusion criteria were fetuses affected by severe (ventricular atrial diameter, > 15 mm) VM on US, cases affected by chromosomal anomalies, cases affected by an additional CNS or extra-CNS anomaly at the time of initial diagnosis, cases affected by congenital infection and US protocol unclear or unavailable.

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Outcomes

The primary outcome of the study was to establish the rate 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 (US and MRI). Sub-group analyses according to gestational age at MRI (<24 vs ≥ 24 weeks of gestation), laterality of VM (unilateral vs bilateral) and the severity of dilatation (mild vs moderate VM) were also performed.

For the purpose of the analysis, additional CNS anomalies were classified into: callosal anomalies, including complete and partial agenesis (ACC), hypoplasia (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; intra-ventricular hemorrhage;

cortical anomalies, including all abnormalities associated with a primary defect in neuronal migration towards the cortical surface of the brain; peri-ventricular heterotopia; other white matter anomalies; peri-ventricular cysts; complex brain anomalies, including all defects characterized by the presence of multiple intra-cranial 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, as 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 US 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 analyses (chi-square test for categorical variables; 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 regards to the primary outcome, we investigated potential independent predictors of a fetal MRI diagnosis of a VM-associated anomaly using a twofold approach. First, we performed random-effect 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, which were 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 US 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 post-estimation 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-effect logistic regression model, and only the results of the model without missing imputation have been shown to avoid redundancy. Statistical significance was defined as a two-sided p-value <0.05 for all analyses,[15] which were carried out using Stata, version 13.1 (Stata Corp., College Station, Texas, USA, 2013). This 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 fetal VM on US 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. Mean gestational age at MRI was 26.7±4.4, with 30.9% of the scans performed before 24 weeks of gestation, while 69.1% were performed at or after 24 weeks of gestation. 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 (10-12 mm) in 80.0% (95% CI 76.5-83.2; 445/556) of cases and moderate (13-15 mm) in 20.0% (95% CI 16.9-23.5; 111/556).

Synthesis of the 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, supra-tentorial intra-cranial 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 rate of an associated anomaly detected exclusively on prenatal MRI was significantly higher in fetuses affected by moderate VM (60%), compared with 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 ≥24 weeks of gestation (Table S1).

Logistic regression analysis showed that maternal BMI (adjusted OR: 0.85, 95% CI 0.7-0.99, p= 0.030), the presence of moderate VM (adjusted OR: 5.8, 95% CI 2.6-13.4, $p<0.001$) and gestational age at MRI ≥24 weeks of gestation (adjusted OR: 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 US and MRI assessment was not associated significantly with an anomaly on prenatal MRI (aOR, 1.00; 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).

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Commented [MOU9]: AU: 11/278 changed to 11/289 based on Table 1. This also makes the percentage of 3.8% correct. Please check that this is correct now. (KP)

Mean ventricular atrial dilatation was significantly higher in fetuses with a postnatal diagnosis of an associated anomaly compared with those that had isolated VM confirmed on postnatal imaging (13.0±1.5 vs 11.5±1.3, 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 compared to 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 type of anomaly included supra-tentorial intra-cranial 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 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 US and karyotyping. Furthermore, although 75.5% of fetuses underwent MRI two weeks or less after the neurosonogram, 24.5% underwent MRI after three to more than six weeks after US; therefore, it is likely that a prolonged interval between US and MRI may have somehow influenced our results. Finally, the present study included only cases undergoing neurosonography performed in each participating center, without exploring its feasibility according to different maternal and fetal characteristics.

Implications for clinical practice and research

Isolated VM represents a considerable diagnostic dilemma as it can be an apparently benign finding, but 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]

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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 US examination.[9] Furthermore, in a recent consult series on mild VM, the Society for Maternal-Fetal Medicine (SMFM) stated that MRI may be considered in cases of mild or moderate fetal VM, although it may be of less value if the women has undergone detailed US assessment by an individual with specific experience and expertise in sonographic imaging of the fetal brain.[8]

MRI is the imaging technique of choice in analyzing brain anomalies postnatally. Compared to US, MRI has better regional resolution, thus being theoretically superior to US in 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 and timing of MRI examination. However, the large majority of studies on MRI do not specify which type of ultrasound imaging protocol was adopted to assess the fetal brain, and 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, a large prospective, multicenter study (the MERIDIAN study) involving 16 centers across the United Kingdom was designed to evaluate the diagnostic and clinical role of fetal MRI in fetuses with suspicion or diagnosis of a CNS anomaly on a previous US examination.[11] This study showed much greater diagnostic accuracy of MRI compared to US (93% versus 68%), with additional findings detected exclusively on MRI in 49% of brain abnormalities 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 compared with that in the MERIDIAN study (10% versus 55% of cases of failed commissuration).[23]

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In the present study, the large majority of anomalies detected exclusively on prenatal MRI included neuronal migration (lissencephaly, heterotopia) or acquired anomalies (i.e. hemorrhage) which 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 which 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 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 anomalies 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 of gestation) may be reliable and has similar accuracy to MRI performed later in gestation,[11-12] with the advantage of an early diagnosis which can allow parents the option of earlier diagnosis, 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 US and detected only on fetal MRI in fetuses with mild or moderate VM is lower than that reported previously in the published literature when a multiplanar US 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 prenatal diagnosis of isolated VM should aim for a multicenter prospective approach, mostly to establish the optimal timing and frequency of MRI examinations.

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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 in years	32.0 ± 5.9
Maternal BMI (kg/m²)*	24.6 ± 4.1
GA at prenatal MRI	26.7 ± 4.4
<24 weeks	172 (30.9)
≥24 weeks	384 (69.1)
Interval between prenatal US and MRI (weeks)	2.2 ± 2.5
≤2 weeks	420 (75.5)
3-5 weeks	63 (11.3)
≥6 weeks	73 (13.2)
Bilateral VM	203 (36.5)
VM severity	
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 in 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 (26.6)
Additional anomaly on postnatal MRI§	11/289 (3.8)

Data are given as mean ± SD, n (%) or n (%). US: ultrasound; MRI, magnetic resonance imaging
*Data available for xxx cases. †Data available for 425 and 148 fetuses, respectively. ‡Based on 203 fetuses with bilateral ventriculomegaly. §Analysis restricted to 289 neonates without prenatal diagnosis of structural anomaly and that had postnatal MRI examination available.

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Commented [MOU14]: AU: I have changed 'GA at prenatal MRI diagnosis of additional anomalies' to 'GA at prenatal MRI'. OK? (KP)

Commented [MOU15]: AU: I have added the n-values to Table 1 based either on the main text or the reported % values. If you agree with the additions, could you please check that the n-values for GA at MRI and US/MRI interval are correct as these were estimated based on the % values. (KP)

Commented [MOU16]: AU: You state in the main text that BMI data were missing for 37% of women – to how many women did this equate? (KP)

Commented [MOU17]: AU: This footnote is not cited in Table 1 – please advise whether it should be removed or where it should be cited in the table. (KP)

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

Variables	**Ventriculomegaly-associated prenatal anomalies (n=30)**	**No prenatal anomalies (n=526)**	**P***
General characteristics:			
Mean maternal age in years (SD)	30.7 (6.8)	32.1 (5.9)	0.2
Mean maternal BMI in kg/m^2 (SD)	23.2 (3.2)	24.7 (4.2)	0.055
Gestational age at prenatal MRI diagnosis of additional anomalies in weeks:			
- Mean gestational age at diagnosis (SD)	28.2 (4.5)	26.6 (4.4)	0.05
- Diagnosis ≥24 weeks, %	90.0	67.9	0.011
Interval between prenatal US and MRI exams in weeks:			
- Mean interval (SD)	2.2 (2.3)	2.2 (2.5)	0.8
- ≤2 weeks, %	66.7	76.1	0.3
- 3-5 weeks, %	23.3	10.6	0.3
- ≥6 weeks, %	10.0	13.3	0.9
Characteristics of fetal ventriculomegaly:			
Bilateral ventriculomegaly, %	46.7	35.9	0.2
Moderate severity, %	60.0	17.7	<0.001
Mean ventricular dilatation in mm (SD):			
- Overall	12.9 (1.4)	11.5 (1.3)	<0.001
- Mild ventriculomegaly	11.4 (0.6)	11.0 (0.7)	0.09
- Moderate ventriculomegaly	13.9 (0.7)	13.7 (0.8)	0.3
Mean dilatation of the controlateral ventricle in mm (SD) **	12.7 (1.2)	11.7 (1.4)	0.007
Outcomes:			
Newborn with additional structural anomalies detected through postnatal MRI, % ***	--	3.8	--

** Based on 203 fetuses with bilateral ventriculomegaly. *** Analyses restricted to 289 newborn (both the fetuses with a prenatal diagnosis of structural anomaly and the newborn without a postnatal MRI exam were excluded). * Chi-squared test and Kruskal-Wallis test for categorical and continuous outcomes, respectively.

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

Variables	**Ventriculomegaly-associated postnatal anomalies (n=11)**	**No postnatal anomalies (n=278)**	**p ***
General characteristics:			
Mean maternal age in years (SD)	33.1 (4.9)	32.1 (5.9)	0.6
Mean maternal BMI in kg/m^2 (SD)	24.0 (2.6)	23.9 (3.2)	0.9
Interval between prenatal US and MRI exams in weeks:			
- Mean interval (SD)	1.5 (2.9)	2.2 (2.5)	0.37
- ≤2 weeks, %	90.9	77.0	0.3
- 3-5 weeks, %	0.0	9.7	-
- ≥6 weeks, %	9.1	13.3	0.9
Characteristics of fetal ventriculomegaly:			
Bilateral ventriculomegaly, %	81.8	50.0	0.04
Moderate severity, %	63.6	18.7	<0.001
Mean ventricular dilatation in mm (SD):			
- Overall	13.0 (1.5)	11.5 (1.3)	0.002
- Mild ventriculomegaly	11.4 (1.0)	11.0 (0.7)	0.2
- Moderate ventriculomegaly	13.9 (0.9)	13.7 (0.9)	0.7
Mean dilatation of the contralateral ventricle in mm (SD) **	13.1 (2.0)	11.6 (1.4)	0.004

* Chi-squared test and Kruskal-Wallis test for categorical and continuous outcomes, respectively.
Analyses restricted to 289 newborns (both the fetuses with a prenatal diagnosis of structural anomaly and the newborn without a postnatal MRI exam were excluded). ** Based on 148 fetuses with bilateral ventriculomegaly.