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Role of prenatal magnetic resonance imaging in fetuses with isolated severe ventriculomegaly at neurosonography: A multicenter study

This is the peer reviewd version of the followng article:

Original
Role of prenatal magnetic resonance imaging in fetuses with isolated severe ventriculomegaly at neurosonography: A multicenter study / Di Mascio, D., Khalil, A., Pilu, G., Rizzo, G., Caulo, M., Liberati, M., Giancotti, A., Lees, C., Volpe, P., Buca, D., Oronzi, L., D'Amico, A., Tinari, S., Stampalija, T., Fantasia, I., Pasquini, L., Masini, G., Brunelli, R., D'Ambrosio, V., Muzii, L., et al.. - In: EUROPEAN JOURNAL OF OBSTETRICS, GYNECOLOGY, AND REPRODUCTIVE BIOLOGY. - ISSN 0301-2115. - 267:(2021), pp. 105-110. [10.1016/j.ejogrb.2021.10.014]

Availability:
This version is available at: 11381/2904052 since: 2022-01-08T23:53:06Z

Publisher:
Elsevier Ireland Ltd

Published
DOI:10.1016/j.ejogrb.2021.10.014

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note finali coverpage

(Article begins on next page)

12 October 2026

European Journal of Obstetrics & Gynecology and Reproductive Biology

Role of prenatal magnetic resonance imaging in fetuses with isolated severe ventriculomegaly at neurosonography: a multicenter study

--Manuscript Draft--

Manuscript Number:	EJOGRB-21-24476R1
Article Type:	Full Length Article
Section/Category:	Maternal-Fetal Medicine
Keywords:	ventriculomegaly; central nervous system; fetal magnetic resonance imaging; MRI; fetal ultrasound; neurosonography; Prenatal diagnosis
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	Francesco D'Antonio
Abstract:	Objective The aim of this study was to report the rate of additional anomalies detected exclusively at prenatal magnetic resonance imaging (MRI) in fetuses with isolated severe ventriculomegaly (VM) undergoing neurosonography. Method Multicenter, retrospective, cohort study involving 20 referral fetal medicine centers in Italy, United Kingdom, Spain and Denmark. Inclusion criteria were fetuses affected by isolated severe VM (> 15 mm), defined as VM with normal karyotype and no other additional central nervous system (CNS) and extra-CNS anomalies on ultrasound. In all cases, a multiplanar assessment of fetal brain as suggested by ISUOG guidelines on fetal neurosonography had been performed. The primary outcome was the rate of additional CNS anomalies detected exclusively at fetal MRI within two weeks from neurosonography. Subgroup analyses according to gestational age at MRI (< vs ≥ 24 weeks of gestation) and the laterality of VM (unilateral vs bilateral) were also performed. Univariate and multivariate logistic regression analysis was used to analyze the data. Results 187 fetuses with a prenatal diagnosis of isolated severe VM on neurosonography were included in the analysis. Additional structural anomalies were detected exclusively at prenatal MRI in 18.1% of cases. When considering the type of anomaly, malformations of cortical development were detected on MRI in 32.4% cases, while midline or acquired (hypoxemic/hemorrhagic) lesions were detected in 26.5% and 14.7% of cases, respectively. There was no difference in the rate of additional anomalies when stratifying the analysis according to either gestational age at MRI or laterality of the lesion. At logistic regression analysis, the laterality of ventricular dilatation (OR: 4.37, 95% CI 1.21-15.76; p= 0.038), but not maternal body mass index, age, severity of ventricular dilatation, interval between US and MRI or gestational age at MRI, was independently associated with the likelihood of detecting associated anomalies at MRI. Conclusion The rate of associated anomalies detected exclusively at prenatal MRI in fetuses with isolated severe VM is lower than previously reported, but higher compared to isolated mild and moderate VM. Fetal MRI should be considered as a part of the prenatal assessment of fetuses presenting with isolated severe VM at neurosonography.

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October 4, 2021

Dear Professor Gupta,
Thank you for the opportunity to provide a revised version of the present manuscript. You can find below the replies to yours' and reviewers' queries; we hope that you can find the manuscript improved and that all queries were satisfactorily addressed.
Thank you for giving us the opportunity to enhance our manuscript.

Editorial office comment:

1. The editors think it would read better with fewer non standard acronyms. MRI is OK. But US and VM would be better spelled out as ultrasound and ventriculomegaly respectively.
   Reply: *Thank you for the suggestion. We took out non-standard acronyms accordingly, such as US and VM.*
2. Could you also reduce percentages to two significant figures all through. Both in text and tables.
   Reply: *Thank you! We changed results accordingly.*
3. Please also check that no results are repeated in text and tables. If so please delete from text.
   Reply: *Thank you. It looks like there is no result repeated.*

Reviewer #1 comments:

1. Congratulations on a well-designed study, appropriately positioned to answer a relevant clinical question. I have strongly recommended that this paper should be published. I have two comments only: 1) microarray should be spelled as a single word and not as 'micro-array'.
   Reply: *Thank you for your kind feedback. We changed the word "microarray" accordingly.*

2. When referring to the significance of laterality: both in the text and in the table it is not immediately clear how the comparison has been made (ie, that there is a higher frequency of additional diagnoses following bilateral VM versus unilateral VM.).
   This should be explicit by both improving the description in the text and within the table.
   Reply: *Thank you for this suggestion. We clarified this issue both in the main text and in the abstract, while we believe the concept is quite clear in table 4, as we clearly specified "bilateral vs unilateral ventriculomegaly". However, we are ready to change further according to editor's preference.*

Reviewer #2 comments:

3. Excellent study giving important new information on severe ventriculomegaly and associated anomalies. It could be improved with better postnatal follow up data.
   Reply: *Thank you so much for your positive feedback.*

Thank you and we look forward to hearing from you!

The ENSO working group

Declaration of interests

☒ The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

☐The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

Role of prenatal magnetic resonance imaging in fetuses with isolated severe ventriculomegaly at neurosonography: a multicenter study

The European NeuroSOnography (ENSO) working group*

*Full author list in the Appendix

Short running title:

MRI in isolated severe ventriculomegaly

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Disclosure: the authors have no conflict of interest.

Funding: no funding was obtained for the present study.

ABSTRACT

Objective: The aim of this study was to report the rate of additional anomalies detected exclusively at prenatal magnetic resonance imaging (MRI) in fetuses with isolated severe ventriculomegaly ~~(VM)~~ undergoing neurosonography.

Method: Multicenter, retrospective, cohort study involving 20 referral fetal medicine centers in Italy, United Kingdom, Spain and Denmark. Inclusion criteria were fetuses affected by isolated severe ventriculomegaly ~~VM~~ (≥ 15 mm), defined as ventriculomegaly ~~VM~~ with normal karyotype and no other additional central nervous system (CNS) and extra-CNS anomalies on ultrasound. In all cases, a multiplanar assessment of fetal brain as suggested by ISUOG guidelines on fetal neurosonography had been performed. The primary outcome was the rate of additional CNS anomalies detected exclusively at fetal MRI within two weeks from neurosonography. Subgroup analyses according to gestational age at MRI (< vs ≥ 24 weeks of gestation) and the laterality of ventriculomegaly ~~VM~~ (unilateral vs bilateral) were also performed. Univariate and multivariate logistic regression analysis was used to analyze the data.

Results: 187 fetuses with a prenatal diagnosis of isolated severe ventriculomegaly ~~VM~~ on neurosonography were included in the analysis. Additional structural anomalies were detected exclusively at prenatal MRI in 18.1% of cases. When considering the type of anomaly, malformations of cortical development were detected on MRI in 32.4% cases, while midline or acquired (hypoxemic/hemorrhagic) lesions were detected in 26.5% and 14.7% of cases, respectively. There was no difference in the rate of additional anomalies when stratifying the analysis according to either gestational age at MRI or laterality of the lesion. At multivariate logistic regression analysis, the presence of additional anomalies only found at MRI was significantly higher in bilateral compared versus unilateral ventriculomegaly (OR: 4.37, 95% CI 1.21-15.76; p= 0.04), while neither maternal body mass index, age, severity of ventricular dilatation, interval between ultrasound and MRI, nor gestational age at MRI were associated with the likelihood of detecting associated anomalies at MRI~~At logistic regression analysis, the laterality of ventricular dilatation (OR: 4.37, 95% CI 1.21-15.76; p= 0.038), but not maternal body mass index, age, severity of ventricular dilatation, interval between US and MRI or gestational age at MRI, was independently associated with the likelihood of detecting associated anomalies at MRI~~.

Conclusion: The rate of associated anomalies detected exclusively at prenatal MRI in fetuses with isolated severe ventriculomegaly ~~VM~~ is lower than previously reported, but higher compared to isolated mild and moderate ventriculomegaly~~VM~~. Fetal MRI should be considered as a part of the prenatal assessment of fetuses presenting with isolated severe ventriculomegaly ~~VM~~ at neurosonography.

Keywords: ventriculomegaly, central nervous system, fetal magnetic resonance imaging, MRI, fetal ultrasound, neurosonography, prenatal diagnosis.

Abbreviations: ~~VM, ventriculomegaly;~~ MRI, magnetic resonance imaging; CNS, central nervous system~~; US, ultrasound~~.

INTRODUCTION

The assessment of the size of cerebral ventricles is an integral part of the routine screening of the central nervous system in the fetus. 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 a diameter greater than 10 mm at the level of the atria.[1-8]

The presence of associated anomalies and the degree of ventricular dilatation are among the main determinants of postnatal outcome in fetuses with ventriculomegaly~~VM~~.[9] Mild to moderate ventricular dilatation (10-14 mm) is associated with a lower risk of chromosomal disorders, associated anomalies undetected prenatally, and neurodevelopmental disabilities.[8-9] Conversely, severe ventriculomegaly~~VM~~, defined as ventricular dilation 15 mm or greater, carries a higher risk of adverse post-natal outcome, with a recent systematic review reporting 20% and 40% rates of moderate and severe neurodevelopmental disabilities respectively.[10]

A detailed evaluation of fetal brain in order to rule out associated anomalies potentially impacting the postnatal outcome is the mainstay of the prenatal management of fetuses with ventriculomegaly~~VM~~. The International Society of Ultrasound in Obstetrics and Gynecology (ISUOG) recommends that fetuses presenting with a central nervous system (CNS) anomaly (such as a ventricular dilatation of more than 10 mm) should undergo multiplanar assessment of the brain in axial, coronal and sagittal views of the fetal head to rule out associated anomalies.[11]

In clinical practice, fetuses affected by ventriculomegaly ~~VM~~ commonly undergo magnetic resonance imaging (MRI) assessment in order to identify anomalies that can possibly be overlooked at the ultrasound ~~(US)~~, although the actual contribution, as well as the proper timing of fetal MRI in the management of these fetuses remains debated.[8,12-13]

We have recently reported that about 5% of fetuses presenting with isolated mild or moderate ventriculomegaly ~~VM~~ on ultrasound ~~US~~ have associated anomalies detected exclusively at fetal MRI, mainly cortical malformations and hemorrhage.[12-13]

Conversely, there is no robust data on the role of MRI in fetuses affected by severe ventriculomegaly~~VM~~. The small sample size of previously published studies, the lack of clearly reported imaging protocols, and the inclusion of cases presenting with other anomalies, chromosomal disorders or infection, do not allow to extrapolate ~~a clear evidence~~clear evidence that could guide clinical practice.[14-17]

Thus, the aim of this study was to report the role of MRI in fetuses affected by isolated severe ventriculomegaly ~~VM~~ undergoing neurosonography.

METHODS

Study design and participants

This was a multicenter, retrospective, cohort study involving 20 referral centers in Italy, United Kingdom, Spain and Denmark. The study included pregnant women who had fetal brain MRI within two weeks following the diagnosis of isolated severe ventriculomegaly ~~VM~~ obtained at dedicated neurosonography from January 2010 to July 2020. Both neurosonography and fetal MRI were performed by experienced operators in each center. The clinical records were examined, and data were collected in a dedicated merged database.

Inclusion criteria

- Fetuses affected by isolated severe (≥15 mm) ventriculomegaly ~~VM~~ at ultrasound~~US~~, defined as ventriculomegaly ~~VM~~ with no other additional CNS and extra-CNS on ultrasound~~US~~
- Detailed, multiplanar assessment of fetal brain, as suggested by ISUOG guidelines on fetal neurosonogram[11]
- Normal karyotype (including chromosomal micro~~-~~array when available)
- Negative infection screening (including cytomegalovirus [CMV] and Toxoplasmosis)
- Maternal age ≥ 18 years
- Gestational age ≥ 18 weeks

Exclusion criteria

- Fetuses affected by mild and moderate (< 15 mm) ventriculomegaly ~~VM~~ at ultrasound~~US~~
- Cases affected by chromosomal anomalies
- Cases affected by additional CNS and extra-CNS anomalies at the time of diagnosis
- Cases affected by congenital infections
- ~~US~~ Ultrasound and/or MRI protocol unclear or unavailable.

Outcomes measures

The primary outcome of the study was to assess the rate of additional CNS anomalies detected exclusively on fetal MRI within two weeks from neurosonography and confirmed at birth in fetuses with a prenatal diagnosis of isolated severe ventriculomegaly~~VM~~. The secondary aim was to evaluate the incidence of additional anomalies detected exclusively after birth and missed at prenatal imaging (ultrasound ~~US~~ and MRI). We aimed to perform sub-group analyses according to the gestational age at MRI (< vs ≥ 24 weeks of gestation) and laterality of ventriculomegaly ~~VM~~ (unilateral vs bilateral ~~VM~~) and in fetuses with chromosomal micro~~-~~array available.

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

- Midline anomalies, including complete and partial agenesis (ACC), hypoplasia (HCC) and dysgenesis of the corpus callosum or isolated absence of the cavum septum pellucidum
- Posterior fossa anomalies, including all defects involving the cerebellar vermis and/or hemispheres
- Hemorrhagic or hypoxic lesions, including hemorrhage, porencephaly or periventricular leukomalacia
- Malformations of cortical development, including lissencephaly, heterotopia or polymicrogyria
- Complex brain anomalies, including all defects characterized by the presence of multiple intra-cranial 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 ~~VM~~ associated structural anomalies, assessed through fetal MRI (primary outcome), and maternal and fetal characteristics, including mother's age and body mass index (BMI), ventriculomegaly ~~VM~~ laterality, degree of ventricular size, gestational age at ultrasound ~~US~~ and MRI assessment.

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).

As regards the primary outcome, we investigated the potential independent predictors of a fetal MRI diagnosis of ventriculomegaly ~~VM~~ 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 ultrasound ~~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~~VM~~, only the first covariate was included in the model as a continuous 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).[18-19]

Statistical significance was defined as a two-sided p-value<0.05 for all analyses,[20] which were carried out using Stata, version 13.1 (Stata Corp., College Station, Texas, USA, 2013).

This study was reported following the STROBE guidelines.[21]

RESULTS

Characteristics of the cohort

One hundred and eighty-seven fetuses with a prenatal diagnosis of isolated fetal ventriculomegaly ~~VM~~ at neurosonography were included in the analysis. The general characteristics of the study population are shown in Table 1. The mean maternal age was 32.6±5.9 years, while the mean body mass index (BMI) was 24.6±3.5. The mean gestational age at ultrasound ~~US~~ and MRI were 26.4±5.4 and 27.0±5.4 weeks, respectively. MRI was performed within one week in the majority of cases (97.9%). Of the included cases, 79.1% were affected by bilateral ventriculomegaly~~VM~~, while 20.9% of fetuses had unilateral ventriculomegaly~~VM~~. Overall, the mean ventricular diameter was 19.4±4.7 mm, and the majority of fetuses (72.7%) were included in the 15-19 mm group, with only 8.6% presenting with a ventricular dilatation of more than 25 mm.

Synthesis of the results

Table 2 shows the results of the primary and secondary outcomes of study. Additional structural anomalies were detected exclusively at prenatal MRI in 18.1% (34/187) of cases. When considering the type of the anomaly, malformations of cortical development were detected on MRI in 32.4% (11/34) of fetuses, while midline anomalies were detected in 26.5% (9/34) of cases, respectively. Acquired (hemorrhagic or hypoxic) anomalies were diagnosed in 14.7% (5/34) of cases, while associated complex malformations and those of posterior fossa were detected on MRI in 14.7% (5/34) and 2.9% (1/34) of fetuses, respectively.

There were no significant differences when comparing gestational and fetal characteristics of pregnancies with additional and those with no additional anomalies found at MRI. (Table 3).

At multivariate logistic regression analysis, ~~the laterality of ventricular dilatation~~the presence of additional anomalies only found at MRI was significantly higher in bilateral compared versus unilateral ventriculomegaly (OR: 4.37, 95% CI 1.21-15.76; p= 0.04~~38~~), while ~~but not~~neither maternal body mass index (p=0.31~~09~~), age (p=0.55~~2~~), severity of ventricular dilatation (p=0.06~~55~~), interval between ultrasound ~~US~~ and MRI (p=0.74~~1~~) nor gestational age at MRI (p=0.32~~16~~) ~~, was~~were ~~independently~~ associated with the likelihood of detecting associated anomalies at MRI (Table 4).

Postnatal imaging information was only available for 81 newborns. Associated anomalies were detected exclusively at birth and missed at prenatal imaging in 13.6% (11/81) of cases.

DISCUSSION

The findings of this study show that, in fetuses with prenatal diagnosis of isolated severe ventriculomegaly ~~VM~~ examined using multiplanar neurosonography, the rate of additional structural anomalies detected exclusively by fetal brain MRI was 18.1%. The most common type of anomalies included malformations of cortical development and midline disorders. The laterality of ventricular dilatation was independently associated with an increased likelihood of detecting anomalies at MRI. Finally, the rate of associated anomalies detected exclusively after birth and missed at prenatal imaging was 13.6%.

To our knowledge, this is the largest study exploring the role of MRI in fetuses with isolated severe ventriculomegaly ~~VM~~ undergoing neurosonography. Large, homogenous sample size, inclusion of cases examined using a multiplanar approach as proposed by ISUOG guidelines and the short time interval between ultrasound ~~US~~ and MRI represent the main strengths of this study.
The retrospective 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 ultrasound~~US~~. Finally, since most of these anomalies have been diagnosed in the second half of pregnancy, these data might not entirely represent the heterogeneity of severe ventriculomegaly ~~VM~~ diagnosed throughout pregnancy.

Ventriculomegaly ~~VM~~ is a relatively common finding on prenatal ultrasound~~US~~. Cause, severity and presence of associated anomalies are the major determinants in predicting the outcome of fetuses affected by ventriculomegaly~~VM~~; thus, the main issue when approaching a fetus with ventriculomegaly ~~VM~~ is to rule out CNS and extra-CNS anomalies.[8-9,12-13] Mild and moderate isolated ventriculomegaly ~~VM~~ often represent a diagnostic dilemma, as measurements closer to 10 mm might represent a normal variant, mostly when no other structural abnormalities are found, or diagnostic genetic testing are normal.[8] Furthermore, the rate of abnormal neurodevelopmental outcome in fetuses with mild ventriculomegaly ~~VM~~ is not significantly higher to that reported in some population studies, thus challenging the concept that ventriculomegaly ~~VM~~ is strong marker of neurodevelopmental delay in childhood.[22]
Conversely, isolated severe ventriculomegaly ~~VM~~ is a rare anomaly, with a reported incidence of 2/10,000 pregnancies.[9] The large majority of cases affected by severe ventriculomegaly ~~VM~~ present with multiple associated anomalies which account for a high rate of termination of pregnancy - and long term neurological sequelae reported in the published literature.[9,15] A recent systematic review reported that survival without neurodevelopmental delay was observed in just over one third of cases

affected by severe ventriculomegaly~~VM~~, while mild-moderate and severe handicap affected respectively 18.6% and 39.6% of children.[10]

In the present study, the incidence of additional structural anomalies detected exclusively by fetal MRI was 18.1%, lower than that reported in previous series in which associated abnormalities were found exclusively at prenatal MRI in up to 57%,[14-16] with a much greater diagnostic accuracy (92.3% vs 61.5%) compared to ultrasound~~US~~[16] and a 10-time higher risk of detecting other brain disorders at MRI compared with mild ventriculomegaly~~VM~~.[14]

The majority of anomalies detected exclusively on prenatal MRI in this study involved malformations of cortical development (such as lissencephaly, heterotopia or polymicrogyria) and midline anomalies (mainly hypoplasia or dysgenesis of the corpus callosum). While the first group of disorders might be more challenging to diagnose with ultrasound ~~US~~ and represents the most common group of abnormalities missed at neurosonography also in case of mild and moderate ventriculomegaly~~VM~~,[13] the reason of the lower diagnostic accuracy of neurosonography for midline anomalies found in this series may be explained by the increase of size of lateral ventricles that may intuitively hamper a clear assessment of the midline structures.

The findings from this multicenter cohort confirm that the contribution of prenatal MRI in fetuses undergoing detailed neurosonography is lower compared to that reported in studies not adopting a multiplanar assessment of the brain. Despite this, MRI remains fundamental in identifying associated abnormalities.[12-13,23-2~~5~~] However, in contrast to fetuses presenting with mild to moderate ventricular dilatation, where detecting additional anomalies is very relevant in defining prognosis given the relatively low risk of neurodevelopmental delay, in those with severe ventriculomegaly~~VM~~, who commonly present with several degrees of neurological anomalies after birth, the additional information of MRI may have a lesser prognostic advantage.

CONCLUSION

The rate of associated anomalies missed at ultrasound ~~US~~ and detected only at fetal MRI is lower than previously reported in literature when a thorough multiplanar examination of fetal brain performed through neurosonography. The anomalies detected exclusively on MRI mainly includes malformations of cortical development and midline anomalies. Based on these findings, fetal MRI should be considered as a part of the prenatal assessment of fetuses presenting with isolated severe ventriculomegaly ~~VM~~ at neurosonography.

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Table 1. **Selected gestational and fetal characteristics in singleton pregnancies with a sonographic diagnosis of isolated severe ventriculomegaly**

Variables	**N = 187**
General characteristics:	
Mean maternal age in years (SD)	32.35 (5.9)
Mean maternal BMI in kg/m^2 (SD)	24.560(3.5)
- Mean gestational age at last US before MRI in weeks (SD)	26.39 (5.4)
- Last ultrasound <24 weeks, %	67 (35.8)
- Last ultrasound ≥24 weeks, %	120 (64.2)
- Mean gestational age at MRI diagnosis in weeks (SD)	26,97 (5.4)
- Diagnosis <24 weeks, %	67 (35.8)
- Diagnosis ≥24 weeks, %	120 (64.2)
Interval between prenatal US and MRI examinations in weeks:	
- Mean interval (SD)	0.91 (1.9)
- ≤1 week, %	183 (97.9)
- 2 weeks, %	4 (2.1)
Characteristics of fetal ventriculomegaly:	
Bilateral ventriculomegaly, %	148 (79.1)
Unilateral ventriculomegaly, %	39 (20.9)
Mean ventricular dilatation in mm (SD):	19.40 (4.7)
Ventricular dilatation in mm, %	
- 15-20 mm	136 (72.7)
- 21-25 mm	35 (18.7)
- ≥ 26 mm	16 (8. 6)

SD: Standard deviation; US: ultrasound; MRI, magnetic resonance imaging.

Table 2. Primary and secondary outcomes

Outcomes	**N=187 (%)**
Fetuses with additional structural anomalies detected through prenatal MRI	34 (18.1)
Type of additional anomaly detected through prenatal MRI*	N=34
- Malformations of cortical development	11 (32.4)
- Midline anomalies	9 (26.5)
- Hemorrhagic or hypoxic anomalies	5 (14.7)
- Posterior fossa	1 (2.9)
- Complex anomalies	5 (14.7)
- Other anomalies	3 (8.8)
Newborns with additional structural anomalies detected through postnatal MRI**	11/81 (13.6)

MRI, magnetic resonance imaging.

** Analyses restricted to 81 newborns (both the fetuses with a prenatal diagnosis of structural anomaly and the newborn without a postnatal MRI exam were excluded).

Table 3. Selected gestational and fetal characteristics in pregnancies with additional versus no additional anomalies found at MRI

Variables			
	Additional anomalies at MRI (n= 34)	**No additional anomalies at MRI (n= 153)**	**p**
General characteristics:			
Mean maternal age in years (SD)	31.7 (5.8)	32.5 (5.9)	0.5105
Mean maternal BMI in kg/m^2 (SD)	25.0 (4.1)	24.5 (3.4)	0.4436
- Mean gestational age at ultrasound diagnosis in weeks (SD)	27.5 (5.7)	26.1 (5.3)	0.183
- Diagnosis <24 weeks, %	11 (32.3)	56 (36.6)	0.70697
- Diagnosis ≥24 weeks, %	23 (67.7)	97 (63.4)	0.70697
- Mean gestational age at MRI diagnosis in weeks (SD)	28.1 (5.9)	26.7 (5.3)	
- Diagnosis <24 weeks, %	11 (32.4)	56 (36.6)	0.700.697
- Diagnosis ≥24 weeks, %	23 (67.7)	97 (63.4)	0.700.697
Interval between prenatal US and MRI examinations in weeks:			
- Mean interval (SD)	1.1 (2.3)	0.9 (1.8)	0.584
- ≤1 week, %	33 (97.1)	150 (98.0)	0.5655
- 2 weeks, %	1 (2.9)	3 (2.0)	0.5655
Characteristics of fetal ventriculomegaly:			
Bilateral ventriculomegaly, %	31 (91.2)	117 (76.5)	0.063
Unilateral ventriculomegaly, %	3 (8.8)	36 (23.5)	0.063
Mean maximum ventricular dilatation in mm (SD):	18.5 (3.2)	19.6 (5.0)	0.193
Ventricular dilatation in mm, %			
- 15-20 mm	28 (82.4)	108 (70.6)	0.0101
- 21-25 mm	5 (14.7)	30 (19.6)	0.631
- ≥ 26 mm	1 (2.9)	15 (9.8)	0.312

SD: Standard deviation; US: ultrasound; MRI, magnetic resonance imaging

Table 4. Logistic regression models evaluating the potential independent predictors of a prenatal MRI diagnosis of ventriculomegaly-associated anomalies

Covariates	**Adjusted OR (95% CI)**	**P value**
Bilateral vs unilateral ventriculomegaly~~VM~~	4.37 (1.21-15.76)	***0.04~~38~~***
Maternal BMI, 1-unit increase	1.06 (0.95-1.17)	0.31~~09~~
Age	0.98 (0.92-1.05)	0.55~~2~~
Maximum ventricular dilatation (1 mm increase)	0.90 (0.81-1.00)	0.06~~55~~
Interval between US and MRI assessment, 1-week increase	1.03 (0.85-1.25)	0.74~~1~~
Gestational age at ultrasound, ≥ versus < 24 weeks	1.56 (0.66-3.72)	0.32~~16~~

OR, odds ratio; BMI, body mass index; ~~VM, ventriculomegaly,~~ US, ultrasound;
* Random-effect logistic regression with Hospital region as the cluster level.

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Role of prenatal magnetic resonance imaging in fetuses with isolated severe ventriculomegaly at neurosonography: a multicenter study

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Short running title:

MRI in isolated severe ventriculomegaly

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Disclosure: the authors have no conflict of interest.

Funding: no funding was obtained for the present study.

ABSTRACT

Objective: The aim of this study was to report the rate of additional anomalies detected exclusively at prenatal magnetic resonance imaging (MRI) in fetuses with isolated severe ventriculomegaly undergoing neurosonography.

Method: Multicenter, retrospective, cohort study involving 20 referral fetal medicine centers in Italy, United Kingdom, Spain and Denmark. Inclusion criteria were fetuses affected by isolated severe ventriculomegaly (≥ 15 mm), defined as ventriculomegaly with normal karyotype and no other additional central nervous system (CNS) and extra-CNS anomalies on ultrasound. In all cases, a multiplanar assessment of fetal brain as suggested by ISUOG guidelines on fetal neurosonography had been performed. The primary outcome was the rate of additional CNS anomalies detected exclusively at fetal MRI within two weeks from neurosonography. Subgroup analyses according to gestational age at MRI (< vs ≥ 24 weeks of gestation) and the laterality of ventriculomegaly (unilateral vs bilateral) were also performed. Univariate and multivariate logistic regression analysis was used to analyze the data.

Results: 187 fetuses with a prenatal diagnosis of isolated severe ventriculomegaly on neurosonography were included in the analysis. Additional structural anomalies were detected exclusively at prenatal MRI in 18.1% of cases. When considering the type of anomaly, malformations of cortical development were detected on MRI in 32.4% cases, while midline or acquired (hypoxemic/hemorrhagic) lesions were detected in 26.5% and 14.7% of cases, respectively. There was no difference in the rate of additional anomalies when stratifying the analysis according to either gestational age at MRI or laterality of the lesion. At multivariate logistic regression analysis, the presence of additional anomalies only found at MRI was significantly higher in bilateral compared versus unilateral ventriculomegaly (OR: 4.37, 95% CI 1.21-15.76; p= 0.04), while neither maternal body mass index, age, severity of ventricular dilatation, interval between ultrasound and MRI, nor gestational age at MRI were associated with the likelihood of detecting associated anomalies at MRI.

Conclusion: The rate of associated anomalies detected exclusively at prenatal MRI in fetuses with isolated severe ventriculomegaly is lower than previously reported, but higher compared to isolated mild and moderate ventriculomegaly. Fetal MRI should be considered as a part of the prenatal assessment of fetuses presenting with isolated severe ventriculomegaly at neurosonography.

Keywords: ventriculomegaly, central nervous system, fetal magnetic resonance imaging, MRI, fetal ultrasound, neurosonography, prenatal diagnosis.

Abbreviations: MRI, magnetic resonance imaging; CNS, central nervous system.

INTRODUCTION

The assessment of the size of cerebral ventricles is an integral part of the routine screening of the central nervous system in the fetus. Ventriculomegaly 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 a diameter greater than 10 mm at the level of the atria.[1-8]

The presence of associated anomalies and the degree of ventricular dilatation are among the main determinants of postnatal outcome in fetuses with ventriculomegaly.[9] Mild to moderate ventricular dilatation (10-14 mm) is associated with a lower risk of chromosomal disorders, associated anomalies undetected prenatally, and neurodevelopmental disabilities.[8-9] Conversely, severe ventriculomegaly, defined as ventricular dilation 15 mm or greater, carries a higher risk of adverse post-natal outcome, with a recent systematic review reporting 20% and 40% rates of moderate and severe neurodevelopmental disabilities respectively.[10]

A detailed evaluation of fetal brain in order to rule out associated anomalies potentially impacting the postnatal outcome is the mainstay of the prenatal management of fetuses with ventriculomegaly. The International Society of Ultrasound in Obstetrics and Gynecology (ISUOG) recommends that fetuses presenting with a central nervous system (CNS) anomaly (such as a ventricular dilatation of more than 10 mm) should undergo multiplanar assessment of the brain in axial, coronal and sagittal views of the fetal head to rule out associated anomalies.[11]

In clinical practice, fetuses affected by ventriculomegaly commonly undergo magnetic resonance imaging (MRI) assessment in order to identify anomalies that can possibly be overlooked at the ultrasound, although the actual contribution, as well as the proper timing of fetal MRI in the management of these fetuses remains debated.[8,12-13]

We have recently reported that about 5% of fetuses presenting with isolated mild or moderate ventriculomegaly on ultrasound have associated anomalies detected exclusively at fetal MRI, mainly cortical malformations and hemorrhage.[12-13]

Conversely, there is no robust data on the role of MRI in fetuses affected by severe ventriculomegaly. The small sample size of previously published studies, the lack of clearly reported imaging protocols, and the inclusion of cases presenting with other anomalies, chromosomal disorders or infection, do not allow to extrapolate clear evidence that could guide clinical practice.[14-17]

Thus, the aim of this study was to report the role of MRI in fetuses affected by isolated severe ventriculomegaly undergoing neurosonography.

METHODS

Study design and participants

This was a multicenter, retrospective, cohort study involving 20 referral centers in Italy, United Kingdom, Spain and Denmark. The study included pregnant women who had fetal brain MRI within two weeks following the diagnosis of isolated severe ventriculomegaly obtained at dedicated neurosonography from January 2010 to July 2020. Both neurosonography and fetal MRI were performed by experienced operators in each center. The clinical records were examined, and data were collected in a dedicated merged database.

Inclusion criteria

- Fetuses affected by isolated severe (≥15 mm) ventriculomegaly at ultrasound, defined as ventriculomegaly with no other additional CNS and extra-CNS on ultrasound
- Detailed, multiplanar assessment of fetal brain, as suggested by ISUOG guidelines on fetal neurosonogram[11]
- Normal karyotype (including chromosomal microarray when available)
- Negative infection screening (including cytomegalovirus [CMV] and Toxoplasmosis)
- Maternal age ≥ 18 years
- Gestational age ≥ 18 weeks

Exclusion criteria

- Fetuses affected by mild and moderate (< 15 mm) ventriculomegaly at ultrasound
- Cases affected by chromosomal anomalies
- Cases affected by additional CNS and extra-CNS anomalies at the time of diagnosis
- Cases affected by congenital infections
- Ultrasound and/or MRI protocol unclear or unavailable.

Outcomes measures

The primary outcome of the study was to assess the rate of additional CNS anomalies detected exclusively on fetal MRI within two weeks from neurosonography and confirmed at birth in fetuses with a prenatal diagnosis of isolated severe ventriculomegaly. The secondary aim was to evaluate the incidence of additional anomalies detected exclusively after birth and missed at prenatal imaging (ultrasound and MRI). We aimed to perform sub-group analyses according to the gestational age at MRI (< vs ≥ 24 weeks of gestation) and laterality of ventriculomegaly (unilateral vs bilateral) and in fetuses with chromosomal microarray available.

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

- Midline anomalies, including complete and partial agenesis (ACC), hypoplasia (HCC) and dysgenesis of the corpus callosum or isolated absence of the cavum septum pellucidum
- Posterior fossa anomalies, including all defects involving the cerebellar vermis and/or hemispheres
- Hemorrhagic or hypoxic lesions, including hemorrhage, porencephaly or periventricular leukomalacia
- Malformations of cortical development, including lissencephaly, heterotopia or polymicrogyria
- Complex brain anomalies, including all defects characterized by the presence of multiple intra-cranial 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 maternal and fetal characteristics, including mother's age and body mass index (BMI), ventriculomegaly laterality, degree of ventricular size, gestational age at ultrasound and MRI assessment.

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).

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 ultrasound 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, only the first covariate was included in the model as a continuous 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).[18-19]

Statistical significance was defined as a two-sided p-value<0.05 for all analyses,[20] which were carried out using Stata, version 13.1 (Stata Corp., College Station, Texas, USA, 2013).

This study was reported following the STROBE guidelines.[21]

RESULTS

Characteristics of the cohort

One hundred and eighty-seven fetuses with a prenatal diagnosis of isolated fetal ventriculomegaly at neurosonography were included in the analysis. The general characteristics of the study population are shown in Table 1. The mean maternal age was 32.6±5.9 years, while the mean body mass index (BMI) was 24.6±3.5. The mean gestational age at ultrasound and MRI were 26.4±5.4 and 27.0±5.4 weeks, respectively. MRI was performed within one week in the majority of cases (97.9%). Of the included cases, 79.1% were affected by bilateral ventriculomegaly, while 20.9% of fetuses had unilateral ventriculomegaly. Overall, the mean ventricular diameter was 19.4±4.7 mm, and the majority of fetuses (72.7%) were included in the 15-19 mm group, with only 8.6% presenting with a ventricular dilatation of more than 25 mm.

Synthesis of the results

Table 2 shows the results of the primary and secondary outcomes of study. Additional structural anomalies were detected exclusively at prenatal MRI in 18.1% (34/187) of cases. When considering the type of the anomaly, malformations of cortical development were detected on MRI in 32.4% (11/34) of fetuses, while midline anomalies were detected in 26.5% (9/34) of cases, respectively. Acquired (hemorrhagic or hypoxic) anomalies were diagnosed in 14.7% (5/34) of cases, while associated complex malformations and those of posterior fossa were detected on MRI in 14.7% (5/34) and 2.9% (1/34) of fetuses, respectively.

There were no significant differences when comparing gestational and fetal characteristics of pregnancies with additional and those with no additional anomalies found at MRI. (Table 3).

At multivariate logistic regression analysis, the presence of additional anomalies only found at MRI was significantly higher in bilateral compared versus unilateral ventriculomegaly (OR: 4.37, 95% CI 1.21-15.76; p= 0.04), while neither maternal body mass index (p=0.31), age (p=0.55), severity of ventricular dilatation (p=0.06), interval between ultrasound and MRI (p=0.74) nor gestational age at MRI (p=0.32) were associated with the likelihood of detecting associated anomalies at MRI (Table 4).

Postnatal imaging information was only available for 81 newborns. Associated anomalies were detected exclusively at birth and missed at prenatal imaging in 13.6% (11/81) of cases.

DISCUSSION

The findings of this study show that, in fetuses with prenatal diagnosis of isolated severe ventriculomegaly examined using multiplanar neurosonography, the rate of additional structural anomalies detected exclusively by fetal brain MRI was 18.1%. The most common type of anomalies included malformations of cortical development and midline disorders. The laterality of ventricular dilatation was independently associated with an increased likelihood of detecting anomalies at MRI. Finally, the rate of associated anomalies detected exclusively after birth and missed at prenatal imaging was 13.6%.

To our knowledge, this is the largest study exploring the role of MRI in fetuses with isolated severe ventriculomegaly undergoing neurosonography. Large, homogenous sample size, inclusion of cases examined using a multiplanar approach as proposed by ISUOG guidelines and the short time interval between ultrasound and MRI represent the main strengths of this study.

The retrospective 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 ultrasound. Finally, since most of these anomalies have been diagnosed in the second half of pregnancy, these data might not entirely represent the heterogeneity of severe ventriculomegaly diagnosed throughout pregnancy.

Ventriculomegaly is a relatively common finding on prenatal ultrasound. Cause, severity and presence of associated anomalies are the major determinants in predicting the outcome of fetuses affected by ventriculomegaly; thus, the main issue when approaching a fetus with ventriculomegaly is to rule out CNS and extra-CNS anomalies.[8-9,12-13] Mild and moderate isolated ventriculomegaly often represent a diagnostic dilemma, as measurements closer to 10 mm might represent a normal variant, mostly when no other structural abnormalities are found, or diagnostic genetic testing are normal.[8] Furthermore, the rate of abnormal neurodevelopmental outcome in fetuses with mild ventriculomegaly is not significantly higher to that reported in some population studies, thus challenging the concept that ventriculomegaly is strong marker of neurodevelopmental delay in childhood.[22]

Conversely, isolated severe ventriculomegaly is a rare anomaly, with a reported incidence of 2/10,000 pregnancies.[9] The large majority of cases affected by severe ventriculomegaly present with multiple associated anomalies which account for a high rate of termination of pregnancy - and long term neurological sequelae reported in the published literature.[9,15] A recent systematic review reported that survival without neurodevelopmental delay was observed in just over one third of cases affected by

severe ventriculomegaly, while mild-moderate and severe handicap affected respectively 18.6% and 39.6% of children.[10]

In the present study, the incidence of additional structural anomalies detected exclusively by fetal MRI was 18.1%, lower than that reported in previous series in which associated abnormalities were found exclusively at prenatal MRI in up to 57%,[14-16] with a much greater diagnostic accuracy (92.3% vs 61.5%) compared to ultrasound[16] and a 10-time higher risk of detecting other brain disorders at MRI compared with mild ventriculomegaly.[14]

The majority of anomalies detected exclusively on prenatal MRI in this study involved malformations of cortical development (such as lissencephaly, heterotopia or polymicrogyria) and midline anomalies (mainly hypoplasia or dysgenesis of the corpus callosum). While the first group of disorders might be more challenging to diagnose with ultrasound and represents the most common group of abnormalities missed at neurosonography also in case of mild and moderate ventriculomegaly,[13] the reason of the lower diagnostic accuracy of neurosonography for midline anomalies found in this series may be explained by the increase of size of lateral ventricles that may intuitively hamper a clear assessment of the midline structures.

The findings from this multicenter cohort confirm that the contribution of prenatal MRI in fetuses undergoing detailed neurosonography is lower compared to that reported in studies not adopting a multiplanar assessment of the brain. Despite this, MRI remains fundamental in identifying associated abnormalities.[12-13,23-26] However, in contrast to fetuses presenting with mild to moderate ventricular dilatation, where detecting additional anomalies is very relevant in defining prognosis given the relatively low risk of neurodevelopmental delay, in those with severe ventriculomegaly, who commonly present with several degrees of neurological anomalies after birth, the additional information of MRI may have a lesser prognostic advantage.

CONCLUSION

The rate of associated anomalies missed at ultrasound and detected only at fetal MRI is lower than previously reported in literature when a thorough multiplanar examination of fetal brain performed through neurosonography. The anomalies detected exclusively on MRI mainly includes malformations of cortical development and midline anomalies. Based on these findings, fetal MRI should be considered as a part of the prenatal assessment of fetuses presenting with isolated severe ventriculomegaly at neurosonography.

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Table 1. **Selected gestational and fetal characteristics in singleton pregnancies with a sonographic diagnosis of isolated severe ventriculomegaly**

Variables	**N = 187**
General characteristics:	
Mean maternal age in years (SD)	32.35 (5.9)
Mean maternal BMI in kg/m^2 (SD)	24.560(3.5)
- Mean gestational age at last US before MRI in weeks (SD)	26.39 (5.4)
- Last ultrasound <24 weeks, %	67 (35.8)
- Last ultrasound ≥24 weeks, %	120 (64.2)
- Mean gestational age at MRI diagnosis in weeks (SD)	26,97 (5.4)
- Diagnosis <24 weeks, %	67 (35.8)
- Diagnosis ≥24 weeks, %	120 (64.2)
Interval between prenatal US and MRI examinations in weeks:	
- Mean interval (SD)	0.91 (1.9)
- ≤1 week, %	183 (97.9)
- 2 weeks, %	4 (2.1)
Characteristics of fetal ventriculomegaly:	
Bilateral ventriculomegaly, %	148 (79.1)
Unilateral ventriculomegaly, %	39 (20.9)
Mean ventricular dilatation in mm (SD):	19.40 (4.7)
Ventricular dilatation in mm, %	
- 15-20 mm	136 (72.7)
- 21-25 mm	35 (18.7)
- ≥ 26 mm	16 (8. 6)

SD: Standard deviation; US: ultrasound; MRI, magnetic resonance imaging.

Table 2. Primary and secondary outcomes

Outcomes	**N=187 (%)**
Fetuses with additional structural anomalies detected through prenatal MRI	34 (18.1)
Type of additional anomaly detected through prenatal MRI*	N=34
- Malformations of cortical development	11 (32.4)
- Midline anomalies	9 (26.5)
- Hemorrhagic or hypoxic anomalies	5 (14.7)
- Posterior fossa	1 (2.9)
- Complex anomalies	5 (14.7)
- Other anomalies	3 (8.8)
Newborns with additional structural anomalies detected through postnatal MRI**	11/81 (13.6)

MRI, magnetic resonance imaging.

** Analyses restricted to 81 newborns (both the fetuses with a prenatal diagnosis of structural anomaly and the newborn without a postnatal MRI exam were excluded).

Table 3. Selected gestational and fetal characteristics in pregnancies with additional versus no additional anomalies found at MRI

Variables			
	Additional anomalies at MRI (n= 34)	**No additional anomalies at MRI (n= 153)**	**p**
General characteristics:			
Mean maternal age in years (SD)	31.7 (5.8)	32.5 (5.9)	0.51
Mean maternal BMI in kg/m^2 (SD)	25.0 (4.1)	24.5 (3.4)	0.44
- Mean gestational age at ultrasound diagnosis in weeks (SD)	27.5 (5.7)	26.1 (5.3)	0.18
- Diagnosis <24 weeks, %	11 (32.3)	56 (36.6)	0.70
- Diagnosis ≥24 weeks, %	23 (67.7)	97 (63.4)	0.70
- Mean gestational age at MRI diagnosis in weeks (SD)	28.1 (5.9)	26.7 (5.3)	
- Diagnosis <24 weeks, %	11 (32.4)	56 (36.6)	0.70
- Diagnosis ≥24 weeks, %	23 (67.7)	97 (63.4)	0.70
Interval between prenatal US and MRI examinations in weeks:			
- Mean interval (SD)	1.1 (2.3)	0.9 (1.8)	0.58
- ≤1 week, %	33 (97.1)	150 (98.0)	0.56
- 2 weeks, %	1 (2.9)	3 (2.0)	0.56
Characteristics of fetal ventriculomegaly:			
Bilateral ventriculomegaly, %	31 (91.2)	117 (76.5)	0.06
Unilateral ventriculomegaly, %	3 (8.8)	36 (23.5)	0.06
Mean maximum ventricular dilatation in mm (SD):	18.5 (3.2)	19.6 (5.0)	0.19
Ventricular dilatation in mm, %			
- 15-20 mm	28 (82.4)	108 (70.6)	0.01
- 21-25 mm	5 (14.7)	30 (19.6)	0.63
- ≥ 26 mm	1 (2.9)	15 (9.8)	0.31

SD: Standard deviation; US: ultrasound; MRI, magnetic resonance imaging

Table 4. Logistic regression models evaluating the potential independent predictors of a prenatal MRI diagnosis of ventriculomegaly-associated anomalies

Covariates	**Adjusted OR (95% CI)**	**P value**
Bilateral vs unilateral ventriculomegaly	4.37 (1.21-15.76)	***0.04***
Maternal BMI, 1-unit increase	1.06 (0.95-1.17)	0.31
Age	0.98 (0.92-1.05)	0.55
Maximum ventricular dilatation (1 mm increase)	0.90 (0.81-1.00)	0.06
Interval between US and MRI assessment, 1-week increase	1.03 (0.85-1.25)	0.74
Gestational age at ultrasound, ≥ versus < 24 weeks	1.56 (0.66-3.72)	0.32

OR, odds ratio; BMI, body mass index; US, ultrasound;
* Random-effect logistic regression with Hospital region as the cluster level.

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