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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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Original

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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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Abstract:	<p>Objective</p> <p>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.</p> <p>Method</p> <p>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.</p> <p>Results</p> <p>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 (hypoxic/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.</p> <p>Conclusion</p> <p>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.</p>

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:

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

3
4 The European NeuroSONography (ENSO) working group*

5
6 *Full author list in the Appendix

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10 **Short running title:**
11 MRI in isolated severe ventriculomegaly

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32
33

34 **ABSTRACT**

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

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

48 **Results:** 187 fetuses with a prenatal diagnosis of isolated severe ventriculomegaly VM on
49 neurosonography were included in the analysis. Additional structural anomalies were detected
50 exclusively at prenatal MRI in 18.1% of cases. When considering the type of anomaly, malformations
51 of cortical development were detected on MRI in 32.4% cases, while midline or acquired
52 (hypoxic/hemorrhagic) lesions were detected in 26.5% and 14.7% of cases, respectively. There
53 was no difference in the rate of additional anomalies when stratifying the analysis according to either
54 gestational age at MRI or laterality of the lesion. At multivariate logistic regression analysis, the
55 presence of additional anomalies only found at MRI was significantly higher in bilateral compared
56 versus unilateral ventriculomegaly (OR: 4.37, 95% CI 1.21-15.76; p= 0.04), while neither maternal
57 body mass index, age, severity of ventricular dilatation, interval between ultrasound and MRI, nor
58 gestational age at MRI were associated with the likelihood of detecting associated anomalies at
59 MRI. At logistic regression analysis, the laterality of ventricular dilatation (OR: 4.37, 95% CI 1.21-
60 15.76; p= 0.038), but not maternal body mass index, age, severity of ventricular dilatation, interval
61 between US and MRI or gestational age at MRI, was independently associated with the likelihood of
62 detecting associated anomalies at MRI.

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

68

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

71

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

74

75 **INTRODUCTION**

76 The assessment of the size of cerebral ventricles is an integral part of the routine screening of the
77 central nervous system in the fetus. Ventriculomegaly (~~VM~~) is the most common brain anomaly
78 diagnosed during fetal life and encompasses a large spectrum of conditions characterized by a
79 dilatation of the lateral ventricles of the brain, typically defined as a diameter greater than 10 mm at
80 the level of the atria.¹⁻⁸

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

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

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

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

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

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

108

109 **METHODS**

110 *Study design and participants*

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

117

118 *Inclusion criteria*

- 119 • Fetuses affected by isolated severe (≥ 15 mm) ventriculomegaly VM at ultrasound US, defined
120 as ventriculomegaly VM with no other additional CNS and extra-CNS on ultrasound US
- 121 • Detailed, multiplanar assessment of fetal brain, as suggested by ISUOG guidelines on fetal
122 neurosonogram¹¹
- 123 • Normal karyotype (including chromosomal micro-array when available)
- 124 • Negative infection screening (including cytomegalovirus [CMV] and Toxoplasmosis)
- 125 • Maternal age ≥ 18 years
- 126 • Gestational age ≥ 18 weeks

127 *Exclusion criteria*

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

133

134 *Outcomes measures*

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

142

143

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

- 145 • Midline anomalies, including complete and partial agenesis (ACC), hypoplasia (HCC) and
146 dysgenesis of the corpus callosum or isolated absence of the cavum septum pellucidum
- 147 • Posterior fossa anomalies, including all defects involving the cerebellar vermis and/or
148 hemispheres
- 149 • Hemorrhagic or hypoxic lesions, including hemorrhage, porencephaly or periventricular
150 leukomalacia
- 151 • Malformations of cortical development, including lissencephaly, heterotopia or
152 polymicrogyria
- 153 • Complex brain anomalies, including all defects characterized by the presence of multiple
154 intra-cranial anomalies.

155

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

158

159 *Statistical analysis*

160 We investigated the relationship between the presence of ventriculomegaly VM-associated structural
161 anomalies, assessed through fetal MRI (primary outcome), and maternal and fetal characteristics,
162 including mother's age and body mass index (BMI), ventriculomegaly VM-laterality, degree of
163 ventricular size, gestational age at ultrasound US and MRI assessment.

164 The potential association between all recorded maternal and fetal parameters and the two outcomes
165 were first evaluated with standard univariate analyses (chi-squared test for categorical variables;
166 Kruskal-Wallis test for continuous variables).

167 As regards the primary outcome, we investigated the potential independent predictors of a fetal MRI
168 diagnosis of ventriculomegaly VM-associated anomalies with a twofold approach. First, we
169 performed a random-effect logistic regression, with hospital region as the cluster unit. A stepwise
170 forward process was used for model building, and the following criteria were adopted for covariates
171 selection, which were limited to four in every step of the analysis to reduce the risk of overfitting: (1)
172 $p < 0.05$ at univariate analyses; (2) clinical significance; (3) the interval, expressed in weeks, between
173 ultrasound US and MRI examinations included a priori as a continuous variable. To avoid
174 multicollinearity between the mean dilatation of cerebral ventricle (in mm) and the severity of
175 ventriculomegaly VM, only the first covariate was included in the model as a continuous variable.

176 Standard post-estimation tests were used to check the validity of the final model, performing

177 multicollinearity and influential observation analyses (using standardized residuals, change in
178 Pearson and deviance chi-square).¹⁸⁻¹⁹

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

181 This study was reported following the STROBE guidelines.²¹

182

183

184 **RESULTS**

185

186 *Characteristics of the cohort*

187 One hundred and eighty-seven fetuses with a prenatal diagnosis of isolated fetal ventriculomegaly
188 ~~VM~~ at neurosonography were included in the analysis. The general characteristics of the study
189 population are shown in Table 1. The mean maternal age was 32.6±5.9 years, while the mean body
190 mass index (BMI) was 24.6±3.5. The mean gestational age at ultrasound US and MRI were 26.4±5.4
191 and 27.0±5.4 weeks, respectively. MRI was performed within one week in the majority of cases
192 (97.9%). Of the included cases, 79.1% were affected by bilateral ventriculomegaly~~VM~~, while 20.9%
193 of fetuses had unilateral ventriculomegaly~~VM~~. Overall, the mean ventricular diameter was 19.4±4.7
194 mm, and the majority of fetuses (72.7%) were included in the 15-19 mm group, with only 8.6%
195 presenting with a ventricular dilatation of more than 25 mm.

196

197 *Synthesis of the results*

198 Table 2 shows the results of the primary and secondary outcomes of study. Additional structural
199 anomalies were detected exclusively at prenatal MRI in 18.1% (34/187) of cases. When considering
200 the type of the anomaly, malformations of cortical development were detected on MRI in 32.4%
201 (11/34) of fetuses, while midline anomalies were detected in 26.5% (9/34) of cases, respectively.
202 Acquired (hemorrhagic or hypoxic) anomalies were diagnosed in 14.7% (5/34) of cases, while
203 associated complex malformations and those of posterior fossa were detected on MRI in 14.7% (5/34)
204 and 2.9% (1/34) of fetuses, respectively.

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

207 At multivariate logistic regression analysis, ~~the laterality of ventricular dilatation~~ the presence of
208 additional anomalies only found at MRI was significantly higher in bilateral compared versus
209 unilateral ventriculomegaly (OR: 4.37, 95% CI 1.21-15.76; p= 0.0438), ~~while but not~~ neither maternal
210 body mass index (p=0.3109), age (p=0.552), severity of ventricular dilatation (p=0.0655), interval
211 between ultrasound US and MRI (p=0.744) nor gestational age at MRI (p=0.3246) was were
212 ~~independently~~ associated with the likelihood of detecting associated anomalies at MRI (Table 4).

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

215

216

217

218 **DISCUSSION**

219

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

227

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

232 The retrospective design represents the main limitation of the study and led to challenges in obtaining
233 all the details on the imaging for all the fetuses in the participating centers, with some incomplete
234 follow-up and some missing data, mostly related to the postnatal MRI or ultrasound US. Finally, since
235 most of these anomalies have been diagnosed in the second half of pregnancy, these data might not
236 entirely represent the heterogeneity of severe ventriculomegaly VM diagnosed throughout pregnancy.

237

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

248 Conversely, isolated severe ventriculomegaly VM is a rare anomaly, with a reported incidence of
249 2/10,000 pregnancies.⁹ The large majority of cases affected by severe ventriculomegaly VM present
250 with multiple associated anomalies which account for a high rate of termination of pregnancy - and
251 long term neurological sequelae reported in the published literature.^{9,15} A recent systematic review
252 reported that survival without neurodevelopmental delay was observed in just over one third of cases

253 affected by severe [ventriculomegaly](#) VM, while mild-moderate and severe handicap affected
254 respectively 18.6% and 39.6% of children.¹⁰

255 In the present study, the incidence of additional structural anomalies detected exclusively by fetal
256 MRI was 18.1%, lower than that reported in previous series in which associated abnormalities were
257 found exclusively at prenatal MRI in up to 57%,¹⁴⁻¹⁶ with a much greater diagnostic accuracy (92.3%
258 vs 61.5%) compared to [ultrasound](#) US¹⁶ and a 10-time higher risk of detecting other brain disorders
259 at MRI compared with mild [ventriculomegaly](#) VM.¹⁴

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

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

276

277 CONCLUSION

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

284

285 **REFERENCES**

- 286 1. Achiron R, Schimmel M, Achiron A, Mashiach S. Fetal mild idiopathic lateral
287 ventriculomegaly: is there a correlation with fetal trisomy? *Ultrasound Obstet Gynecol* 1993;
288 **3**:89-92.
- 289 2. Alagappan R, Browning PD, Laorr A, McGahan JP. Distal lateral ventricular atrium:
290 reevaluation of normal range. *Radiology* 1994; **193**:405-408.
- 291 3. Nomura ML, Barini R, De Andrade C, et al. Congenital hydrocephalus: gestational age and
292 neonatal outcomes. *Arch Gynecol Obstet* 2010; **282**:607-611.
- 293 4. Garel C, Luton D, Oury JF, Gressens P. Ventricular dilatations. *Childs Nerv Syst* 2003;
294 **19**:517-523.
- 295 5. Signorelli M, Tiberti A, Valsariati D, et al. Width of fetal lateral ventricular atrium between
296 10 and 12 mm: a simple variation of the norm? *Ultrasound Obstet Gynecol* 2004; **23**:14-18.
- 297 6. Melchiorre K, Bhide A, Gika AD, et al. Counseling in isolated mild fetal ventriculomegaly.
298 *Ultrasound Obstet Gynecol* 2009; **34**:212-224.
- 299 7. Shizuo OI. Controversies in definition and classification of hydrocephalus. *Neurol Med Chir*
300 2010; **50**:859-869.
- 301 8. Society for Maternal-Fetal Medicine (SMFM); Fox NS, Monteagudo A, Kuller JA, Craig S,
302 Norton ME. Mild fetal ventriculomegaly: diagnosis, evaluation, and management. *Am J*
303 *Obstet Gynecol* 2018; **219**:B2-B9.
- 304 9. Hannon T, Tennant PW, Rankin J, Robson SC. Epidemiology, natural history, progression,
305 and postnatal outcome of severe fetal ventriculomegaly. *Obstet Gynecol*. 2012; **120**:1345-53.
- 306 10. Carta S, Kaelin Agten A, Belcaro C, Bhide A. Outcome of fetuses with prenatal diagnosis of
307 isolated severe bilateral ventriculomegaly: systematic review and meta-analysis. *Ultrasound*
308 *Obstet Gynecol* 2018; **52**:165-173.
- 309 11. Malinger G, Paladini D, Haratz KK, et al. ISUOG Practice Guidelines (updated): sonographic
310 examination of the fetal central nervous system. Part 1: performance of screening examination
311 and indications for targeted neurosonography. *Ultrasound Obstet Gynecol*. 2020; **56**:476-484.
- 312 12. Di Mascio D, Sileo FG, Khalil A, et al. Systematic review and meta-analysis on the role of
313 prenatal magnetic resonance imaging in the era of fetal neurosonography: mild and moderate
314 ventriculomegaly. *Ultrasound Obstet Gynecol* 2019; **54**:164-171.
- 315 13. ENSO Working Group. Role of prenatal magnetic resonance imaging in fetuses with isolated
316 mild or moderate ventriculomegaly in the era of neurosonography: international multicenter
317 study. *Ultrasound Obstet Gynecol*. 2020;**56**:340-347

- 318 14. Griffiths PD, Reeves MJ, Morris JE, et al. A prospective study of fetuses with isolated
319 ventriculomegaly investigated by antenatal sonography and in utero MR imaging. *AJNR Am*
320 *J Neuroradiol.* 2010; **31**:106-111.
- 321 15. Letouzey M, Chadie A, Brasseur-Daudruy M, et al. Severe apparently isolated fetal
322 ventriculomegaly and neurodevelopmental outcome. *Prenat Diagn.* 2017; **37**:820-826.
- 323 16. Griffiths PD, Brackley K, Bradburn M, et al. Anatomical subgroup analysis of the
324 MERIDIAN cohort: ventriculomegaly. *Ultrasound Obstet Gynecol.* 2017; **50**:736-744.
- 325 17. Dall'Asta A, van Oostrum NHM, Basheer SN, et al. Etiology and Prognosis of Severe
326 Ventriculomegaly Diagnosed at Late Gestation. *Ultraschall Med.* 2018; **39**:675-689.
- 327 18. Pizzi C, Costa GM, Santarella L, et al. Depression symptoms and the progression of carotid
328 intima-media thickness: A 5-year follow-up study. *Atherosclerosis* 2014; **233**:530-536.
- 329 19. White IR, Royston P, Wood AM. Multiple imputation using chained equations: Issues and
330 guidance for practice. *Stat Med* 2011; **30**:377-399.
- 331 20. McNamee R. Regression modelling and other methods to control confounding. *Occup*
332 *Environ Med* 2005; **62**:500-506.
- 333 21. Von Elm E, Altman DG, Egger M, et al. The strengthening the reporting of the observational
334 studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies.
335 *Lancet* 2007; **370**:1453-1457.
- 336 22. Pagani G, Thilaganathan B, Prefumo F. Neurodevelopmental outcome in isolated mild fetal
337 ventriculomegaly: Systematic review and meta-analysis. *Ultrasound Obstet Gynecol* 2014;
338 **44**:254-260.
- 339 23. Di Mascio D, Buca D, Khalil A, et al. Outcome of isolated fetal talipes: A systematic review
340 and meta-analysis. *Acta Obstet Gynecol Scand.* 2019; **98**:1367-1377.
- 341 24. Sileo FG, Di Mascio D, Rizzo G, et al. Role of prenatal magnetic resonance imaging in fetuses
342 with isolated agenesis of corpus callosum in the era of fetal neurosonography: A systematic
343 review and meta-analysis. *Acta Obstet Gynecol Scand.* 2021; **100**:7-16.
- 344 25. D'Antonio F, Sileo FG; Eurocanadian NeuroSONography (the ENSO) working group. Role
345 of prenatal magnetic resonance imaging in fetuses with isolated anomalies of the corpus
346 callosum: a multinational study. *Ultrasound Obstet Gynecol.* 2021 Feb 17. doi:
347 10.1002/uog.23612.
- 348 25-26. [Di Mascio D, Khalil A, Rizzo G, et al. Reference charts of fetal brain structures for](#)
349 [magnetic resonance imaging: a systematic review \[published online ahead of print, 2021 Aug](#)
350 [18\]. *Ultrasound Obstet Gynecol.* 2021;10.1002/uog.23762. doi:10.1002/uog.23762](#)

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

358

<i>Variables</i>	N = 187
<i>General characteristics:</i>	
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)
<i>Characteristics of fetal ventriculomegaly:</i>	
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)

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

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Table 2. Primary and secondary outcomes

<i>Outcomes</i>	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)

373 MRI, magnetic resonance imaging.

374

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

377

378 **Table 3. Selected gestational and fetal characteristics in pregnancies with additional versus no**
 379 **additional anomalies found at MRI**
 380

<i>Variables</i>	Additional anomalies at MRI (n= 34)	No additional anomalies at MRI (n= 153)	p
<i>General characteristics:</i>			
Mean maternal age in years (SD)	31.7 (5.8)	32.5 (5.9)	0.51 05
Mean maternal BMI in kg/m ² (SD)	25.0 (4.1)	24.5 (3.4)	0.44 36
- Mean gestational age at ultrasound diagnosis in weeks (SD)	27.5 (5.7)	26.1 (5.3)	0.18 3
- Diagnosis <24 weeks, %	11 (32.3)	56 (36.6)	0.70 697
- Diagnosis ≥24 weeks, %	23 (67.7)	97 (63.4)	0.70 697
- 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)	0.70 697
- Diagnosis ≥24 weeks, %	23 (67.7)	97 (63.4)	0.70 697
Interval between prenatal US and MRI examinations in weeks:			
- Mean interval (SD)	1.1 (2.3)	0.9 (1.8)	0.58 4
- ≤1 week, %	33 (97.1)	150 (98.0)	0.56 55
- 2 weeks, %	1 (2.9)	3 (2.0)	0.56 55
<i>Characteristics of fetal ventriculomegaly:</i>			
Bilateral ventriculomegaly, %	31 (91.2)	117 (76.5)	0.06 3
Unilateral ventriculomegaly, %	3 (8.8)	36 (23.5)	0.06 3
Mean maximum ventricular dilatation in mm (SD):	18.5 (3.2)	19.6 (5.0)	0.19 3
Ventricular dilatation in mm, %			
- 15-20 mm	28 (82.4)	108 (70.6)	0.01 04
- 21-25 mm	5 (14.7)	30 (19.6)	0.63 +
- ≥ 26 mm	1 (2.9)	15 (9.8)	0.31 2

381 SD: Standard deviation; US: ultrasound; MRI, magnetic resonance imaging
 382

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

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<i>Covariates</i>	Adjusted OR (95% CI)	P value
Bilateral vs unilateral ventriculomegaly VM	4.37 (1.21-15.76)	0.0438
Maternal BMI, 1-unit increase	1.06 (0.95-1.17)	0.3109
Age	0.98 (0.92-1.05)	0.552
Maximum ventricular dilatation (1 mm increase)	0.90 (0.81-1.00)	0.0655
Interval between US and MRI assessment, 1-week increase	1.03 (0.85-1.25)	0.741
Gestational age at ultrasound, \geq versus $<$ 24 weeks	1.56 (0.66-3.72)	0.3216

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

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

3
4 The European NeuroSONography (ENSO) working group*

5
6 *Full author list in the Appendix

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10 **Short running title:**
11 MRI in isolated severe ventriculomegaly

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33

34 **ABSTRACT**

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

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

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

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

63
64 **Keywords:** ventriculomegaly, central nervous system, fetal magnetic resonance imaging, MRI,
65 fetal ultrasound, neurosonography, prenatal diagnosis.

66
67 **Abbreviations:** MRI, magnetic resonance imaging; CNS, central nervous system.

68

69 **INTRODUCTION**

70 The assessment of the size of cerebral ventricles is an integral part of the routine screening of the
71 central nervous system in the fetus. Ventriculomegaly is the most common brain anomaly diagnosed
72 during fetal life and encompasses a large spectrum of conditions characterized by a dilatation of the
73 lateral ventricles of the brain, typically defined as a diameter greater than 10 mm at the level of the
74 atria.¹⁻⁸

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

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

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

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

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

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

101

102 **METHODS**

103 *Study design and participants*

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

110

111 *Inclusion criteria*

- 112 • Fetuses affected by isolated severe (≥ 15 mm) ventriculomegaly at ultrasound, defined as
113 ventriculomegaly with no other additional CNS and extra-CNS on ultrasound
- 114 • Detailed, multiplanar assessment of fetal brain, as suggested by ISUOG guidelines on fetal
115 neurosonogram¹¹
- 116 • Normal karyotype (including chromosomal microarray when available)
- 117 • Negative infection screening (including cytomegalovirus [CMV] and Toxoplasmosis)
- 118 • Maternal age ≥ 18 years
- 119 • Gestational age ≥ 18 weeks

120 *Exclusion criteria*

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

126

127 *Outcomes measures*

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

135

136

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

- 138 • Midline anomalies, including complete and partial agenesis (ACC), hypoplasia (HCC) and
139 dysgenesis of the corpus callosum or isolated absence of the cavum septum pellucidum
- 140 • Posterior fossa anomalies, including all defects involving the cerebellar vermis and/or
141 hemispheres
- 142 • Hemorrhagic or hypoxic lesions, including hemorrhage, porencephaly or periventricular
143 leukomalacia
- 144 • Malformations of cortical development, including lissencephaly, heterotopia or
145 polymicrogyria
- 146 • Complex brain anomalies, including all defects characterized by the presence of multiple
147 intra-cranial anomalies.

148

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

151

152 *Statistical analysis*

153 We investigated the relationship between the presence of ventriculomegaly associated structural
154 anomalies, assessed through fetal MRI (primary outcome), and maternal and fetal characteristics,
155 including mother's age and body mass index (BMI), ventriculomegaly laterality, degree of
156 ventricular size, gestational age at ultrasound and MRI assessment.

157 The potential association between all recorded maternal and fetal parameters and the two outcomes
158 were first evaluated with standard univariate analyses (chi-squared test for categorical variables;
159 Kruskal-Wallis test for continuous variables).

160 As regards the primary outcome, we investigated the potential independent predictors of a fetal MRI
161 diagnosis of ventriculomegaly associated anomalies with a twofold approach. First, we performed a
162 random-effect logistic regression, with hospital region as the cluster unit. A stepwise forward process
163 was used for model building, and the following criteria were adopted for covariates selection, which
164 were limited to four in every step of the analysis to reduce the risk of overfitting: (1) $p < 0.05$ at
165 univariate analyses; (2) clinical significance; (3) the interval, expressed in weeks, between ultrasound
166 and MRI examinations included a priori as a continuous variable. To avoid multicollinearity between
167 the mean dilatation of cerebral ventricle (in mm) and the severity of ventriculomegaly, only the first
168 covariate was included in the model as a continuous variable. Standard post-estimation tests were

169 used to check the validity of the final model, performing multicollinearity and influential observation
170 analyses (using standardized residuals, change in Pearson and deviance chi-square).¹⁸⁻¹⁹
171 Statistical significance was defined as a two-sided p-value<0.05 for all analyses,²⁰ which were carried
172 out using Stata, version 13.1 (Stata Corp., College Station, Texas, USA, 2013).
173 This study was reported following the STROBE guidelines.²¹
174
175

176 **RESULTS**

177

178 *Characteristics of the cohort*

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

188

189 *Synthesis of the results*

190 Table 2 shows the results of the primary and secondary outcomes of study. Additional structural
191 anomalies were detected exclusively at prenatal MRI in 18.1% (34/187) of cases. When considering
192 the type of the anomaly, malformations of cortical development were detected on MRI in 32.4%
193 (11/34) of fetuses, while midline anomalies were detected in 26.5% (9/34) of cases, respectively.
194 Acquired (hemorrhagic or hypoxic) anomalies were diagnosed in 14.7% (5/34) of cases, while
195 associated complex malformations and those of posterior fossa were detected on MRI in 14.7% (5/34)
196 and 2.9% (1/34) of fetuses, respectively.

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

199 At multivariate logistic regression analysis, the presence of additional anomalies only found at MRI
200 was significantly higher in bilateral compared versus unilateral ventriculomegaly (OR: 4.37, 95% CI
201 1.21-15.76; $p= 0.04$), while neither maternal body mass index ($p=0.31$), age ($p=0.55$), severity of
202 ventricular dilatation ($p=0.06$), interval between ultrasound and MRI ($p=0.74$) nor gestational age at
203 MRI ($p=0.32$) were associated with the likelihood of detecting associated anomalies at MRI (Table
204 4).

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

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210 **DISCUSSION**

211

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

219

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

224 The retrospective design represents the main limitation of the study and led to challenges in obtaining
225 all the details on the imaging for all the fetuses in the participating centers, with some incomplete
226 follow-up and some missing data, mostly related to the postnatal MRI or ultrasound. Finally, since
227 most of these anomalies have been diagnosed in the second half of pregnancy, these data might not
228 entirely represent the heterogeneity of severe ventriculomegaly diagnosed throughout pregnancy.

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

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

245 severe ventriculomegaly, while mild-moderate and severe handicap affected respectively 18.6% and
246 39.6% of children.¹⁰

247 In the present study, the incidence of additional structural anomalies detected exclusively by fetal
248 MRI was 18.1%, lower than that reported in previous series in which associated abnormalities were
249 found exclusively at prenatal MRI in up to 57%,¹⁴⁻¹⁶ with a much greater diagnostic accuracy (92.3%
250 vs 61.5%) compared to ultrasound¹⁶ and a 10-time higher risk of detecting other brain disorders at
251 MRI compared with mild ventriculomegaly.¹⁴

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

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

268

269 **CONCLUSION**

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

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277 **REFERENCES**

- 278 1. Achiron R, Schimmel M, Achiron A, Mashiach S. Fetal mild idiopathic lateral
279 ventriculomegaly: is there a correlation with fetal trisomy? *Ultrasound Obstet Gynecol* 1993;
280 **3**:89-92.
- 281 2. Alagappan R, Browing PD, Laorr A, McGahan JP. Distal lateral ventricular atrium:
282 reevaluation of normal range. *Radiology* 1994; **193**:405-408.
- 283 3. Nomura ML, Barini R, De Andrade C, et al. Congenital hydrocephalus: gestational age and
284 neonatal outcomes. *Arch Gynecol Obstet* 2010; **282**:607-611.
- 285 4. Garel C, Luton D, Oury JF, Gressens P. Ventricular dilatations. *Childs Nerv Syst* 2003;
286 **19**:517-523.
- 287 5. Signorelli M, Tiberti A, Valsariati D, et al. Width of fetal lateral ventricular atrium between
288 10 and 12 mm: a simple variation of the norm? *Ultrasound Obstet Gynecol* 2004; **23**:14-18.
- 289 6. Melchiorre K, Bhide A, Gika AD, et al. Counseling in isolated mild fetal ventriculomegaly.
290 *Ultrasound Obstet Gynecol* 2009; **34**:212-224.
- 291 7. Shizuo OI. Controversies in definition and classification of hydrocephalus. *Neurol Med Chir*
292 2010; **50**:859-869.
- 293 8. Society for Maternal-Fetal Medicine (SMFM); Fox NS, Monteagudo A, Kuller JA, Craigo S,
294 Norton ME. Mild fetal ventriculomegaly: diagnosis, evaluation, and management. *Am J*
295 *Obstet Gynecol* 2018; **219**:B2-B9.
- 296 9. Hannon T, Tennant PW, Rankin J, Robson SC. Epidemiology, natural history, progression,
297 and postnatal outcome of severe fetal ventriculomegaly. *Obstet Gynecol*. 2012; **120**:1345-53.
- 298 10. Carta S, Kaelin Agten A, Belcaro C, Bhide A. Outcome of fetuses with prenatal diagnosis of
299 isolated severe bilateral ventriculomegaly: systematic review and meta-analysis. *Ultrasound*
300 *Obstet Gynecol* 2018; **52**:165-173.
- 301 11. Malinger G, Paladini D, Haratz KK, et al. ISUOG Practice Guidelines (updated): sonographic
302 examination of the fetal central nervous system. Part 1: performance of screening examination
303 and indications for targeted neurosonography. *Ultrasound Obstet Gynecol*. 2020; **56**:476-484.
- 304 12. Di Mascio D, Sileo FG, Khalil A, et al. Systematic review and meta-analysis on the role of
305 prenatal magnetic resonance imaging in the era of fetal neurosonography: mild and moderate
306 ventriculomegaly. *Ultrasound Obstet Gynecol* 2019; **54**:164-171.
- 307 13. ENSO Working Group. Role of prenatal magnetic resonance imaging in fetuses with isolated
308 mild or moderate ventriculomegaly in the era of neurosonography: international multicenter
309 study. *Ultrasound Obstet Gynecol*. 2020;**56**:340-347

- 310 14. Griffiths PD, Reeves MJ, Morris JE, et al. A prospective study of fetuses with isolated
311 ventriculomegaly investigated by antenatal sonography and in utero MR imaging. *AJNR Am*
312 *J Neuroradiol.* 2010; **31**:106-111.
- 313 15. Letouzey M, Chadie A, Brasseur-Daudruy M, et al. Severe apparently isolated fetal
314 ventriculomegaly and neurodevelopmental outcome. *Prenat Diagn.* 2017; **37**:820-826.
- 315 16. Griffiths PD, Brackley K, Bradburn M, et al. Anatomical subgroup analysis of the
316 MERIDIAN cohort: ventriculomegaly. *Ultrasound Obstet Gynecol.* 2017; **50**:736-744.
- 317 17. Dall'Asta A, van Oostrum NHM, Basheer SN, et al. Etiology and Prognosis of Severe
318 Ventriculomegaly Diagnosed at Late Gestation. *Ultraschall Med.* 2018; **39**:675-689.
- 319 18. Pizzi C, Costa GM, Santarella L, et al. Depression symptoms and the progression of carotid
320 intima-media thickness: A 5-year follow-up study. *Atherosclerosis* 2014; **233**:530-536.
- 321 19. White IR, Royston P, Wood AM. Multiple imputation using chained equations: Issues and
322 guidance for practice. *Stat Med* 2011; **30**:377-399.
- 323 20. McNamee R. Regression modelling and other methods to control confounding. *Occup*
324 *Environ Med* 2005; **62**:500-506.
- 325 21. Von Elm E, Altman DG, Egger M, et al. The strengthening the reporting of the observational
326 studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies.
327 *Lancet* 2007; **370**:1453-1457.
- 328 22. Pagani G, Thilaganathan B, Prefumo F. Neurodevelopmental outcome in isolated mild fetal
329 ventriculomegaly: Systematic review and meta-analysis. *Ultrasound Obstet Gynecol* 2014;
330 **44**:254-260.
- 331 23. Di Mascio D, Buca D, Khalil A, et al. Outcome of isolated fetal talipes: A systematic review
332 and meta-analysis. *Acta Obstet Gynecol Scand.* 2019; **98**:1367-1377.
- 333 24. Sileo FG, Di Mascio D, Rizzo G, et al. Role of prenatal magnetic resonance imaging in fetuses
334 with isolated agenesis of corpus callosum in the era of fetal neurosonography: A systematic
335 review and meta-analysis. *Acta Obstet Gynecol Scand.* 2021; **100**:7-16.
- 336 25. D'Antonio F, Sileo FG; Eurocanadian NeuroSONography (the ENSO) working group. Role
337 of prenatal magnetic resonance imaging in fetuses with isolated anomalies of the corpus
338 callosum: a multinational study. *Ultrasound Obstet Gynecol.* 2021 Feb 17. doi:
339 10.1002/uog.23612.
- 340 26. Di Mascio D, Khalil A, Rizzo G, et al. Reference charts of fetal brain structures for magnetic
341 resonance imaging: a systematic review [published online ahead of print, 2021 Aug 18].
342 *Ultrasound Obstet Gynecol.* 2021;10.1002/uog.23762. doi:10.1002/uog.23762

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

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<i>Variables</i>	N = 187
<i>General characteristics:</i>	
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)
<i>Characteristics of fetal ventriculomegaly:</i>	
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)

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

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Table 2. Primary and secondary outcomes

<i>Outcomes</i>	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)

362 MRI, magnetic resonance imaging.

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

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

<i>Variables</i>	Additional anomalies at MRI (n= 34)	No additional anomalies at MRI (n= 153)	p
<i>General characteristics:</i>			
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
<i>Characteristics of fetal ventriculomegaly:</i>			
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

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

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

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<i>Covariates</i>	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, \geq versus $<$ 24 weeks	1.56 (0.66-3.72)	0.32

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