

CLINICAL ARTICLE

Obstetrics

Prenatal findings and associated survival rates in fetal ventriculomegaly: A prospective observational study

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Abstract

Objectives: Fetal ventriculomegaly is associated with varying degrees of genetic and structural abnormalities. The objective was to present the experience of fetal ventriculomegaly in a large European center in relation to: 1. grade of ventriculomegaly; 2. additional chromosomal/structural abnormalities; and 3. perinatal survival rates.

Methods: This was a prospective observational study of patients referred with fetal ventriculomegaly from January 2011 to July 2020. Data were obtained from the hospital database and analyzed to determine the rate of isolated ventriculomegaly, associated structural abnormalities, chromosomal/genetic abnormalities, and survival rates. Data were stratified into three groups; mild ($V_p = 10\text{--}12\text{ mm}$), moderate ($V_p = 13\text{--}15\text{ mm}$) and severe ($V_p > 15\text{ mm}$) ventriculomegaly.

Results: There were 213 fetuses included for analysis. Of these 42.7% had mild ventriculomegaly, 44.6% severe and 12.7% had moderate ventriculomegaly. Initial ultrasound assessment reported isolated ventriculomegaly in 45.5% fetuses, with additional structural abnormalities in 54.5%. The rate of chromosomal/genetic abnormalities was high, 16.4%. After all investigations, the true rate of isolated VM was 36.1%. The overall survival was 85.6%. Survival was higher for those with isolated VM across all groups ($P < 0.05$).

Conclusion: Ventriculomegaly is a complex condition and patients should be counselled that even with apparently isolated VM, there remains the possibility of additional genetic and/or structural problems being diagnosed in up to 10% of fetuses.

KEYWORDS

fetal ventriculomegaly, isolated ventriculomegaly, mild ventriculomegaly, moderate ventriculomegaly, severe ventriculomegaly, survival rates in fetal ventriculomegaly

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1 | INTRODUCTION

Fetal ventriculomegaly (VM) is defined as an enlargement of the atrium of the lateral cerebral ventricles¹ and occurs in up to 2 per 1000 births.^{2,3} This measurement of the atrial diameter (Vp) remains stable between 15 and 40 weeks gestation.^{4,5} The classification of VM varies somewhat in the literature but it is generally classified into either mild (10–12 mm), moderate (13–15 mm), and severe VM (>15 mm)^{5–7} or mild (Vp 10–15 mm) and severe VM (Vp > 15 mm).^{2,6–10} The prognosis varies and is largely dependent on the presence of other co-existing factors. In the absence of other malformations, the prognosis is primarily related to the size of the ventricles, progression of the enlargement and the presence of bilateral VM.^{3,7}

Clinically, VM is defined as isolated if there is no ultrasound evidence of associated structural malformations nor markers of aneuploidy at the time of presentation.¹ When VM is identified, a thorough evaluation should be performed, including detailed ultrasound assessment of the fetal anatomy, consideration of fetal MRI, amniocentesis for karyotype and chromosomal microarray (CMA), and investigations for fetal infection.^{2,5,6} Chromosomal abnormalities have been reported in studies ranging from 2.7–7%.^{7,11,12} The incidence of additional CNS and non-CNS ultrasonographic abnormalities ranges from 10% to 76% but appears to be <50% in most studies.^{5,13–18} Antenatal MRI has an increasing role to investigate for underlying problems though its yield of additional information varies widely in reported series from 5%–50%.⁶

The objective of this study was to present the experience of fetal VM in a large European center in relation to; (1) grade of ventriculomegaly; (2) additional chromosomal/structural abnormalities; and (3) perinatal survival rates. We also sought to determine the rates of isolated VM and compare the results between those with mild, moderate, and severe VM.

2 | METHODS

This was a prospective observational study, with Institutional Ethical Approval, of all patients with suspected fetal VM referred to the Department of Fetal Medicine, National Maternity Hospital, Dublin, Ireland, from January 1, 2011 to July 31, 2020. The department is a tertiary referral center for the Republic of Ireland with onsite fetal MRI facilities and a dedicated national fetal neurosurgical clinic where patients are seen jointly by fetal medicine and pediatric neurosurgery. All patients referred firstly have a detailed anatomical assessment performed by a fetal medicine consultant, where the VM is confirmed as per the following diagnostic criteria. For this study, we classified VM into mild, moderate, and severe groups as follows; mild Vp = 10–12 mm, moderate Vp = 13–15 mm or severe ventriculomegaly Vp > 15 mm.^{6,9} Patients were excluded where the Vp measurement did not meet the above diagnostic criteria and those with a diagnosis of a neural tube defect were also excluded. Data were entered into the hospital database prospectively by a specialist fetal medicine midwife. Measurement is performed at the level of the glomus of the

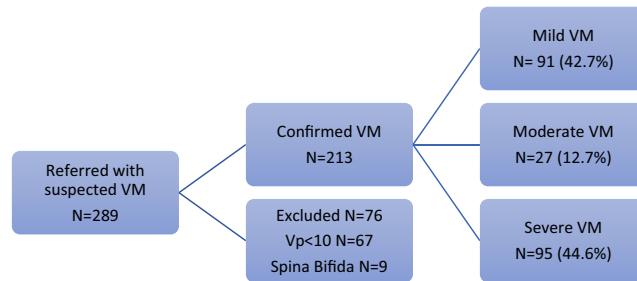


FIGURE 1 Patients referred with suspected ventriculomegaly. This figure highlights the number of patients referred to our unit with suspected fetal ventriculomegaly. VM was classified into mild, moderate, and severe groups as follows: mild Vp = 10–12 mm, moderate Vp = 13–15 mm or severe ventriculomegaly Vp > 15 mm.^{6,9} VM, Ventriculomegaly.

choroid plexus, perpendicular to the ventricular cavity, positioning the calipers inside the echoes generated by the lateral walls.⁴ It is important to measure the Vp correctly because small differences in technique can result in false-positive or false-negative results.⁵ The data were analyzed to determine the median gestational age at diagnosis and whether the VM was unilateral or bilateral. The data were then further categorized into isolated VM and those with associated structural and chromosomal/genetic abnormalities. Further information was obtained to determine the number of women who had fetal MRI scans and the yield of additional diagnostic information obtained from these scans. Data were also obtained on survival rates and were sub-divided by whether there was isolated VM on the initial ultrasound assessment or additional ultrasound features present. For the purposes of this study, data were extracted from hospital obstetric and relevant neonatal intensive care and neonatal developmental follow-up databases. Survival was defined as confirmed survival to discharge for all infants. For infants receiving follow up neurosurgical, pediatric care or palliative management further data on survival was obtained from the relevant databases and any deaths within the first year of life were recorded as non-survivors. Antenatal findings are presented for the overall group and further stratified into three distinct clinical groups; (1) Mild; (2) Moderate and (3) Severe VM. Statistical analysis was performed using the Chi-Square test.

3 | RESULTS

A total of 289 cases were referred to the fetal medicine unit with suspected VM over the study period, of which 76 were excluded as per the above exclusion criteria (nine had a subsequent diagnosis of spina bifida and the remainder had a normal Vp measurement) (Figure 1). A total of 213 cases of confirmed VM were included for analysis. This represents 6.4% (213/3331) of all fetal anomalies during this time period. Maternal demographics are presented in Table 1. The average maternal age at diagnosis was 31.7 years with a median maternal parity of 1 (range 0–7). The median gestation at diagnosis was 24 weeks and 4 days (range 16 weeks 5 days to 38 weeks and 5 days gestation). The latest diagnosis was at 38 weeks and 5 days. This was

a new diagnosis of severe VM of with a Vp of 25 mm noted on a routine scan and was subsequently confirmed to be secondary to hemorrhage. In this cohort most fetuses had bilateral VM 186/213 (87.3%) (Table 1). There were 91/213 (42.7%) with mild VM, 95/213 (44.6%) with severe and only 27/213 (12.7%) had moderate VM.

Initial antenatal ultrasound investigation reported isolated VM in 97/213 (45.5%), with high rates of additional structural abnormalities in 116/213 (54.5%). Of these 62/213 (29.1%) had additional intracranial abnormalities and 54/213 (25.4%) had additional extra-cranial abnormalities. Further chromosomal/genetic analysis was performed in 139/213 (65.3%) pregnancies. This included non-invasive pre-natal screening (NIPS) in 38/213 (17.8%), amniocentesis in 92/213 (43.2%) and postnatal testing in 25/213 (11.7%). In 16 cases patients had NIPS followed by invasive antenatal testing or postnatal genetic diagnostic tests. The rate of genetic abnormalities in those who had karyotype or CMA was 35/139 (25.2%), while the overall rate of chromosomal/genetic abnormalities in the group was 35/213 (16.4%), with 22/213

(10.3%) diagnosed antenatally and 13/213 (6.1%) postnatally. The chromosomal/genetic abnormalities included trisomy 21 $n = 11$, trisomy 18 $n = 2$, triploidy $n = 2$, tetrasomy 9p $n = 1$, Pallister Killian Syndrome $n = 1$, X-Linked hydrocephalus (L1 CAM) $n = 1$, chromosome 7p deletion $n = 1$, 47 XXX $n = 1$ and others $n = 15$. Congenital infections were found in 6/213 (2.8%) cases. There were five cases of confirmed cytomegalovirus (CMV) – of which two had a termination of pregnancy (TOP). One fetus was clinically well postnatally and on postnatal imaging the VM had resolved. Of the remaining two cases of CMV, one had both intra and extracranial abnormalities on US and the other had mild VM noted antenatally and was subsequently diagnosed with extensive periventricular deep white matter calcification on a postnatal MRI scan. The other congenital infection was a confirmed case of Zika virus and this fetus had ventriculomegaly and microcephaly only and survived in the neonatal period. There was one confirmed case of Fetal Neonatal Alloimmune Thrombocytopenia (FNAIT) in this cohort with underlying intra-ventricular hemorrhage present on antenatal MRI.

In 91/213 (42.7%) of cases a fetal MRI was performed and in 64/91 (70.3%) additional information was gathered. In 2/64 (3.1%) of cases additional extra-cranial information was found on the MRI scan and in 62/64 (96.9%) additional intracranial information was obtained to aide diagnosis and counseling. The additional intracranial findings from fetal MRI included absent corpus callosum (ACC) $n = 18$, intra-ventricular hemorrhage (IVH) $n = 13$, Aqueductal Stenosis $n = 9$, a dilated third ventricle $n = 4$, Schizencephaly $n = 2$, Lissencephaly $n = 1$, an Arachnoid cyst $n = 1$, Migrational disorder $n = 1$, Encephalocele $n = 1$, Dandy Walker Spectrum abnormality $n = 1$, Walker-Warburg Syndrome $n = 1$ and other abnormalities of the cerebellum and brain parenchyma $n = 10$.

Table 2 outlines the rates of isolated VM, the rates of chromosomal/genetic abnormalities and other structural abnormalities detected after the completion of additional testing and the figures are presented for the overall group and for the mild, moderate, and severe VM groups respectively. After completion of all investigations, the true rate of isolated VM in this cohort was 36.1%. Those in the mild group had a higher rate of isolated VM than the other two groups at 54.9%, versus 40.7% for moderate and 16.8% for the

TABLE 1 Maternal demographics

Average maternal age	31.7 years
BMI (SD)	25.7 (5.9) kg/m ²
Nationality	
Irish	174/213 (81.7%)
EU	26/213 (12.2%)
Non-EU	13/213 (6.1%)
Median Gestation at Diagnosis	24 weeks and 4 days
Range (weeks + days)	(16+4 – 38+4)
Median Gestation at Delivery	38 weeks 4 days
Range (weeks + days)	(29+1 – 42+4)
Median Maternal Parity	1
Range	(0–7)
Bilateral VM	186/213 (87.3%)
Unilateral VM	27/213 (12.7%)

Abbreviations: BMI, body mass index; EU, European Union; kg/m² = kilogram per meter squared; VM, ventriculomegaly.

TABLE 2 The percentage of patients with isolated, chromosomal and additional structural abnormalities after completion of the additional investigations

	Isolated ($n = 77$)	Chromosomal/Genetic abnormalities ($n = 35$)	Extra cranial defect ($n = 33$)	Intra-cranial defect ($n = 68$)
Mild VM ($n = 91$)	50/91 (54.9%)	14/91 (15.4%)	14/91 (15.4%)	13/91 (14.3%)
Moderate VM ($n = 27$)	11/27 (40.7%)	6/27 (22.2%)	5/27 (18.5%)	5/27 (18.5%)
Severe VM ($n = 95$)	16/95 (16.8%)	15/95 (15.8%)	14/95 (14.7%)	50/95 (52.6%)
Total	77/213 (36.1%)	35/213 (16.4%)	33/213 (15.5%)	68/213 (31.9%)
P-value	$P < 0.05$	NS	NS	$P < 0.05$
TOP	3/77 (3.9%)	12/35 (34.3%)	4/33 (12.1%)	13/68 (19.1%)
Survival (Ex-TOP)	72/74 (97.3%)	15/23 (65.2%)	22/29 (75.9%)	46/55 (83.6%)

Note: This table outlines the number and percentages of patients with true isolated ventriculomegaly, chromosomal/genetic abnormalities and those with additional intra-cranial and extra-cranial findings after completion of both antenatal and postnatal investigations. Ex-TOP, excluding TOP; TOP, termination of pregnancy; VM, Ventriculomegaly; A P-value of <0.05 is considered statistically significant.

severe group ($P < 0.05$). Furthermore, those in the severe group had significantly higher rates of additional CNS findings 52.6%, compared to the mild and moderate groups at 14.3% and 18.5%, respectively ($P < 0.05$). The survival rates of those with truly isolated VM versus those with confirmed genetic abnormalities, extra-cranial findings, and intra-cranial findings are presented in Table 2. Fetuses with truly isolated VM had high survival rates (97.3%) and those with intra-cranial findings only had survival rates of 83.6%. Those with chromosomal abnormalities had the lowest survival at 65.2%.

Of this cohort 32/213 (15%) opted for termination of pregnancy (TOP) and 4/213 (1.8%) had an intrauterine fetal demise (IUD). For the remainder the median gestation at delivery was 38 weeks and 4 days (range 29 weeks and 1 day–42 weeks and 4 days). The overall survival rate was 72.8%, while survival excluding TOP was 85.6%. For those with isolated VM on US the survival rate was 96.7% after exclusion of TOP, compared to 73.9% for those with additional ultrasound features ($P < 0.05$).

The groups were further subdivided into mild, moderate, and severe VM and the results are presented in Table 3. Those in the severe group had a significantly higher rate of additional findings on MRI than those in the mild and moderate groups, $P < 0.05$. No difference was observed in the rate of chromosomal abnormalities between the groups, however those with mild VM and additional US features had significantly higher rates of chromosomal/genetic abnormalities than those with isolated VM alone. Fetuses with severe VM had higher rates of TOP, neonatal death (NND) and lower survival rates than those in the mild and the moderate groups (Table 3). The overall survival in the severe group after exclusion of TOP was 71.6%, with 96.5% and 90.5% in the mild and moderate groups, respectively ($P < 0.05$).

4 | DISCUSSION

Fetal VM is one of the most frequently diagnosed abnormal brain findings on ultrasound.¹⁴ It is well established that VM is associated with additional structural abnormalities, with a reported incidence up to 50%.^{9,15,16} Fetal MRI is regularly used as an adjunct to improve diagnostic accuracy for fetal brain abnormalities⁷ and can be used to identify subtle CNS anomalies undetectable by ultrasound.^{6,7,14} In our series fetal MRI was performed in 42.7% cases and provided additional information in 70.3%. The most common intracranial MRI findings included ACC, IVH and Aqueductal stenosis, consistent with previous reports.^{5,13,17} Malformations were most frequently reported in cases of severe VM, ranging from 58%–65%^{13,18} and similarly high rates were confirmed in this review. The reported association of structural abnormalities with mild VM varies considerably from 10% to 76%^{10,13,15,19} with an average value of 41.4% quoted in one review.¹⁰ In our population rates of additional structural abnormalities of 30.8% and 37% were observed, after excluding chromosomal/genetic abnormalities, in mild and moderate VM respectively. It is recommended that fetal brain MRI is performed after a detailed anatomical and neurosonographic examination²⁰ by a maternofetal medicine specialist, following discussion with the performing

Pediatric Radiologist. VM is the most common indication for fetal MRI in our institution.

Due to the increased incidence of genetic abnormalities associated with VM, it is recommended that diagnostic testing should be offered.⁵ The genetic abnormality rate in our population was 16.4%, with 6.1% diagnosed postnatally. Those with isolated VM had chromosomal/genetic abnormalities in 7.7%, slightly higher than other studies reporting 2.7%–5%.^{1,7,9,13} The genetic abnormality rate in non-isolated VM was 24.1%, similar to published reports, 15%–36%.^{11,13,21} In severe VM the rate was not significantly greater in the isolated group (7%) versus the non-isolated group (19.4%). These findings support current available literature which have observed lower rates of aneuploidy in fetuses with severe isolated VM^{11,13} and high rates⁹ when an abnormality is present. The incidence of abnormal karyotype in fetuses with mild isolated VM is more controversial, with a reported range of 0%–26% with an average of 2.7%.⁹ The rate was 8.8% in this cohort.

The reasons for this variation is multifactorial and includes differences in the number of women having genetic testing, those opting for TOP when faced with a significant fetal abnormality, and it is also likely related to advances in genetic testing in recent times. Approximately 5%–12.1% of fetuses with isolated mild to moderate VM have an abnormal Karyotype,^{6,22,23} while another 10%–20.6% have abnormal findings on CMA.^{6,22–24} In our unit the standard protocol in the early years of the study was to perform karyotype and to offer CMA in the more recent years. In some cases, gene panel testing/exome sequencing were performed after genetics consultation. When performing genetic investigations for VM, amniocentesis with CMA is recommended,^{5,6} though it is also deemed reasonable to perform initial karyotype, with reflex to CMA if these tests are normal.⁵ Where there are additional anomalies, consanguinity, or a family history of a specific condition, gene panel testing, or exome sequencing is sometimes useful and appropriate genetic counseling is recommended.⁵ Specific testing for L1CAM mutations could also be considered where there is a family history consistent with X-linked hydrocephalus and a male fetus.⁵ NIPS is not recommended for genetic evaluation of ultrasound anomalies.²⁵ However, after appropriate counseling, NIPS may be considered for patients who decline diagnostic evaluation as Trisomy 21 is relatively common.^{5,14,15}

When VM is the only abnormal finding and the fetus euploid, counseling parents is partly based on the severity of the VM because increasing size of the ventricles is associated with a higher risk of a poor outcome.¹⁴ In this study, the overall survival was 85.6%. Survival was higher for isolated VM versus non-isolated VM, in line with other published series.^{1,6,8} Perinatal and neonatal death was higher in severe VM, than in mild and moderate VM, again in line with previous reports.^{1,6,8,21}

One of the strengths, and a central finding of this study, was the comparison of the rate of isolated VM after initial US assessment with the true rate of isolated VM after comprehensive antenatal and postnatal investigations. The initial rate of isolated VM in this cohort was 45.5%. However, after detailed investigations, the true rate of isolated VM was revealed to be much lower at 36.1%. This finding was consistent across the groups with the rate of true isolated VM

TABLE 3 Antenatal findings for each category of ventriculomegaly and survival rates

	Mild total (n = 91)		Moderate total (n = 27)		Severe total (n = 95)		P-values
	Isolated (n = 57)	Additional US Findings (n = 34)	Isolated (n = 13)	Additional US Findings (n = 14)	Isolated (n = 28)	Additional US Findings (n = 67)	
^a Additional intracranial MRI findings	2/57 (3.5%)	8/34 (23.5%)	10/91 (10.9%)	4/14 (28.5%)	6/27 (22.2%)	37/67 (55.2%)	46/95 (48.4%) P < 0.05
Chromosomal/Genetic abnormalities	14/91 (15.4%)				6/27 (22.2%)		15/95 (15.7%) P = 0.68
^b Antenatal diagnosis	1/57 (1.8%)	7/34 (20.5%)	8/91 (8.8%)	6/14 (42.9%)	6/27 (22.2%)	7/67 (10.4%)	8/95 (8.4%)
^c Postnatal diagnosis	4/57 (7.0%)	2/34 (5.8%)	6/91 (6.6%)	0/14 (0%)	0/27 (0%)	6/67 (8.9%)	7/95 (7.3%)
TOP/IUD	0/57 (0%)	7/34 (20.6%) (2 IUD)	7/91 (7.7%)	0/13 (0%)	6/27 (22.2%)	18/67 (26.9%) (2 IUD)	23/95 (24.2%) P < 0.05
NND	0/57 (0%)	1/34 (2.9%)	1/91 (1.1%)	0/13 (0%)	2/27 (7.4%)	16/67 (23.9%)	19/95 (20%) P < 0.05
Survival	57/57 (100%)	26/34 (76.5%)	83/91 (91.2%)	13/13 (100%)	19/27 (70.4%)	33/67 (49.2%)	53/95 (55.8%) P < 0.05
Survival Ex TOP	57/57 (100%)	26/29 (89.7%)	83/86 (96.5%)	13/13 (100%)	19/21 (90.5%)	33/51 (64.7%)	53/74 (71.6%) P < 0.05

Note: Fetuses are categorized as either isolated or having additional US findings as per the detailed fetal medicine anatomical assessment at the time of the initial presentation.

Abbreviations: Isolated, isolated ventriculomegaly; IUD, intrauterine death; Mild, mild ventriculomegaly; Moderate, moderate ventriculomegaly; MRI, magnetic resonance imaging; NND, neonatal death; Severe, severe ventriculomegaly; TOP, termination of pregnancy; US, ultrasound.

A P-value of 0.05 was considered statically significant.

^aAdditional intracranial MRI findings refers to those diagnosed on MRI performed in the antenatal period.

^bAntenatal diagnosis refers to the diagnosis of chromosomal/genetic abnormalities in the antenatal period.

^cPostnatal diagnosis refers to the diagnosis of additional chromosomal/genetic abnormalities after birth.

in the mild, moderate and severe groups 54.9%, 40.7% and 16.8%, respectively, contrasting to initial US findings of isolated VM in mild 62.6%, moderate 48.1% and severe 29.5% groups. Other strengths of this study include that this is a tertiary referral center with a national fetal neurosurgical clinic and as such the population attending our unit is representative of the obstetric population across the country. Furthermore, that this is a large prospective study it adds to the body of evidence in European obstetric populations and aides in the counseling of women in this cohort. The lack of long-term neurological follow up data in our population is a limitation of this study and the topic of ongoing review. A further limitation includes the lack of comprehensive postnatal imaging on all fetuses to assess the degree of VM.

Fetal VM is multifactorial in origin and carries a varied prognosis. Detailed anatomical surveillance, expert neurosonography and fetal MRI are the cornerstone of the initial assessment allowing clinicians to guide counseling and management. Patients should be advised that even in situations where isolated VM is suspected, there is still the possibility of additional findings during pregnancy or the neonatal period. The development of a national fetal neurosurgical clinic, with integrated multi-disciplinary management, has allowed for more robust counseling of patients, which has ultimately resulted in enhanced patient care.

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CONFLICTS OF INTEREST

The authors have no conflicts of interest.

AUTHOR CONTRIBUTIONS

GR and AS performed manual data collection and data analysis. GR was involved in planning the design of the study, wrote and edited the manuscript. FMA conceived the original idea of the study and oversaw overall direction and planning, discussed, commented, edited and finally approved the manuscript. DC, JC were involved in planning the design of the study, supervised the work, discussed, commented, edited, and finally approved the manuscript. BD, BC, HH, SC, JW, SC, SH, RM, GC, IR, PMcP participated in data collection, discussed, commented, edited, and finally approved the manuscript.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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