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# Evolution of fetal ventriculomegaly diagnosed in the second trimester of pregnancy: A retrospective study in Northern Greece

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## Abstract

**Introduction:** The present retrospective study aims to examine the course of ventriculomegaly (VM) during gestation, the association between the degree of VM and the presence of additional sonographic fetal malformations, as well as to inspect the prevalence of VM with reference to fetal gender.

**Materials and Methods:** The databases of two maternal-fetal ultrasound units were reviewed from 2010 to 2021. All cases were classified as either mild (10 to <12mm), moderate (12 to <15mm), or severe (≥15mm) according to the fetal posterior ventricle width measurement upon VM diagnosis, at 20-24 weeks of gestation. Furthermore, cases with additional fetal sonographic abnormalities were registered as cases of non-isolated VM, whereas those cases without further fetal malformations on ultrasound (US) scan were documented as cases of isolated VM. The final sonographic record of every participant, following VM diagnosis, was registered so that the evolution of VM during gestation could be monitored.

**Results:** The sonographic and medical records of 81 women diagnosed with fetal VM were studied. The prevalence of VM is about 0.24% and the male/female ratio was 2; 88.9% of the cases were mild, 9.9% moderate, while only 1 (1.2%) was severe at diagnosis. Among the initial 62 cases of mild VM, 24 (38.7%) regressed, 16 (25.8%) remained unchanged and 22 (35.5%) progressed. There was an association between a higher degree of VM and the presence of additional fetal abnormalities.

**Conclusions:** The majority of VM cases are mild at diagnosis and in isolated about one third resolves in the third trimester and about one third progresses but not to severe. Therefore, a follow up scan is useful to reassure most parents and identify those cases that may progress to moderate.

**Key Words:** Fetal ventriculomegaly, ultrasound scan, second trimester, isolated ventriculomegaly, non-isolated ventriculomegaly

## Introduction

Ventriculomegaly (VM) is well established as one the most frequent abnormalities detected on antenatal routine ultrasound scan at 20-24 weeks of gestation. Its prevalence ranges from 0.3 to 1.5 per 1,000 births and is subject to the gestational age during the examination, the sonographic method of measurement, as well as if one or both ventricles are being assessed.[1] Moreover, VM has been proven to be a more frequent finding in male fetuses than in the female ones. The ratio of male to female fetuses diagnosed with VM is estimated to be 1.7/1.[2] Additionally, VM may be attributed to various and heterogeneous causes or it may comprise an isolated finding. As far as the aspect of pathogenesis is concerned, there are three main mechanisms of fetal VM. These mechanisms include cerebral tissue destruction and atrophy, obstruction of cerebrospinal fluid (CSF) flow and overproduction of CSF.[3]

The most widely used and established definition of fetal VM is a measurement of posterior ventricular width ≥10mm, measured at 20-24 weeks of gestation.[4] The transabdominal scan is the preferred mode of examination but transvaginal scan is also an option, depending on the position of the fetus, the patient's choice and the physician performing the exam.[4] According to the International Society of Ultrasound in Obstetrics and Gynecology (ISUOG) guidelines on targeted neurosonography, the recommended frequency of the transabdominal transducer is 3-5 MHz and a 2-dimensional ultrasound scan using a gray scale imaging is suggested as the technique of choice.[4]

The precise prognosis and correct interpretation of VM's clinical significance has been a matter of dispute among authors for several years. However, the majority of published studies agree that the three principal factors defining the fetal and neonatal outcome of VM are: a) the existence of additional anomalies of genetic, infectious or anatomic nature, b) the extend of ventricular dilation and c) the evolution of VM throughout gestation.[5] Ultimately, the outcome of VM can turn out to be considerably poorer when VM is severe or associated with additional abnormalities or progresses in-utero. It is only plausible for a question regarding parental counseling of isolated VM cases to be raised. According to the Society of Maternal-Fetal Medicine (SMFM), counseling in cases of isolated mild VM should have a reassuring tone, since the outcome is normal for the neonates, in most of such cases. On the other hand, when isolated moderate VM is confirmed women should be informed that there is high chance that the outcome will be normal, but at the same time the increased likelihood of neurodevelopmental problems for the infant should be emphasized.[5]

The aim of this study was to investigate the distribution of VM severity at the time of first diagnosis, the association between the initial severity with other abnormalities as well as to assess the course of VM throughout gestation.

## Materials and Methods

This is a retrospective, descriptive, observational study on fetal VM diagnosed in the second trimester of pregnancy that also longitudinally assessed the evolution of this condition. The electronic databases of two prenatal ultrasound units in Thessaloniki, Greece, were retrospectively reviewed, from January 2010 to December 2021. In further detail, the population of the study consisted of women with singleton pregnancies and sonographic evidence of fetal VM during the routine scan at 20-24 weeks of gestation. The selected subjects fulfilled the following inclusion criteria: (a) having a posterior ventricle (PV) width ≥10mm at the US scan at 20-24weeks and (b) having at least one follow-up ultrasound of the fetus not earlier than 3 weeks after the initial diagnosis of VM, so that the in-utero evolution of VM could be evaluated. Cases lacking sonographic follow-up were excluded.

The subjects under investigation were divided into 3 groups according to PV width measurement. Cases with PV width of 10 to <12mm were defined as mild, those with width of ≥12 to <15mm as moderate, while cases having a width ≥15mm were considered as severe. Another division of the population was into cases of isolated VM (IVM) and non-isolated VM (NIVM). Namely, those cases in which no further fetal abnormalities, except for VM, were detected on prenatal sonographic imaging were classified as isolated. On the other hand, if additional malformations were detected on US scans the subject was considered as a non-isolated VM case.

During the follow-up US scan visits, except for the evaluation of the lateral ventricles, a thorough anatomic inspection of the fetus was performed as well. Further elaborated, the PV width in both mid-trimester and follow-up scans was assessed in a transventricular (axial) plane, at the level of the glomus of the choroid plexus. The calipers were placed on the inner margins of the ventricular wall, perpendicular to the long axis of the ventricle, in accordance with the ISUOG guidelines.[4]

In order for all the aims of this study to be achieved, the sonographic record of each subject was retrieved. That record contained data regarding the date of each scan, the gestational age (GA) and the PV width measurements at each scan, as well as the gender of the fetus, the presence of additional abnormalities and information about the outcome, including terminations of pregnancy (TOPs). As the medical records of the entire population of the study were collected, we were able to acquire information not only on the ultrasound scan findings, but also on whether the subjects were submitted to amniocentesis and subsequent karyotype testing, following VM diagnosis.

Moreover, all subjects having increased PV width measurement at the last scan, when compared with the first width measurement, were considered as cases of progressive VM. On the contrary, women showing no changes of PV width between the two scans, were defined as cases of stable VM. Lastly, those with reduced PV width at the last US scan were documented as cases of VM regression. If the PV width regressed and dropped <10mm, the cases were considered as having resolved in-utero.

Informed consent of the participating subjects was not compulsory for this retrospective study, in compliance with the local legislation.

### *Statistical analysis*

At first, the collected data were properly tabulated into the appropriate variables, either scale or categorical, depending on the nature of the information. The normality of the scale variables, such as the PV width measurements or the gestational age at VM diagnosis, was evaluated by Shapiro-Wilk test and by calculating the skewness. Furthermore, percentages and frequencies of individual groups of the sample were utilized to express the results of the categorical variables, whereas means, medians, standard deviations (SD), maximum and minimum values were used for continuous (scale) variables. The Chi-square test ($\chi^2$ Test) was performed to compare categorical variables, while the independent-samples T-test was employed to estimate the prevalence of a scale variable among the groups of a categorical one, using a 95% Confidence Interval (CI). In addition, the Mann-Whitney U test, from the group of nonparametric tests, was performed to compare qualitative data. One-way ANOVA test and Turkey b post-hoc test were used appropriately. A p-value <0.05 was considered statistically significant for all the above-mentioned tests. The entire dataset was arranged and statistically analyzed using the statistical package SPSS by IBM (version: 28, NY, USA).

## Results

Within the 11-year (2010-2021) period examined in the current study, among 40,452 singleton

pregnancies that were examined at 20-24 weeks of gestation, 98 (0.24%) were diagnosed as having sonographic evidence of VM. Of these, 17 cases were excluded due to lack of follow up. Consequently, a total of 81 women with fetal VM were included in the study. The mean gestational age (GA) at diagnosis was 22.4 ±1.2 weeks. Following the diagnosis of VM, 13 women (16%) underwent amniocentesis and subsequent karyotype testing, which turned out to be normal for all the tested subjects.

At the time of diagnosis, 72 (88.9%) of the cases were mild, 8 (9.9%) were moderate, while only 1 (1.2%) was a severe VM case. Following this diagnosis, 18 (22.2%) of the women diagnosed with fetal VM opted for termination of pregnancy (TOP), including the only case of severe VM (5.6%), 7 (38.9%) moderate and 10 (55.6%) mild cases. Therefore, 13.9% of the initial mild VM subjects, 87.5% of the moderate ones and 100% of the severe cases resulted in TOP. The remaining 62 (86.1%) of the mild and one (12.5%) of the moderate VM cases continued the pregnancy until delivery. No prenatal or perinatal fetal death was registered.

As far as the presence of further sonographic malformations in fetuses is concerned, a total number of 14 cases (17.3%) were found to bear such abnormalities, hence they were documented as cases of NIVM. In all those cases, the additional fetal anomalies were detected by US concurrently with the VM diagnosis at 20-24 weeks of gestation. The remaining 82.7% were registered as isolated. Among the 14 NIVM cases, 9 (64.3%) were mild, 4 (28.6%) were moderate and 1 (7.1%) was severe. In all 14 NIVM cases the parents opted for TOP (78.8%) and 4 (22.2%) were IVM cases. Out of those 4, three were moderate and one was mild VM. Regarding fetal intracranial and extracranial structural malformations found on US scan (Figure 1), agenesis of corpus callosum (ACC) was the most prevalent, as 6 (42.9%) out of the 14 cases were identified having that abnormality. Furthermore, 4 (28.6%) fetuses were diagnosed with spina bifida (SB), 2 (14.3%)

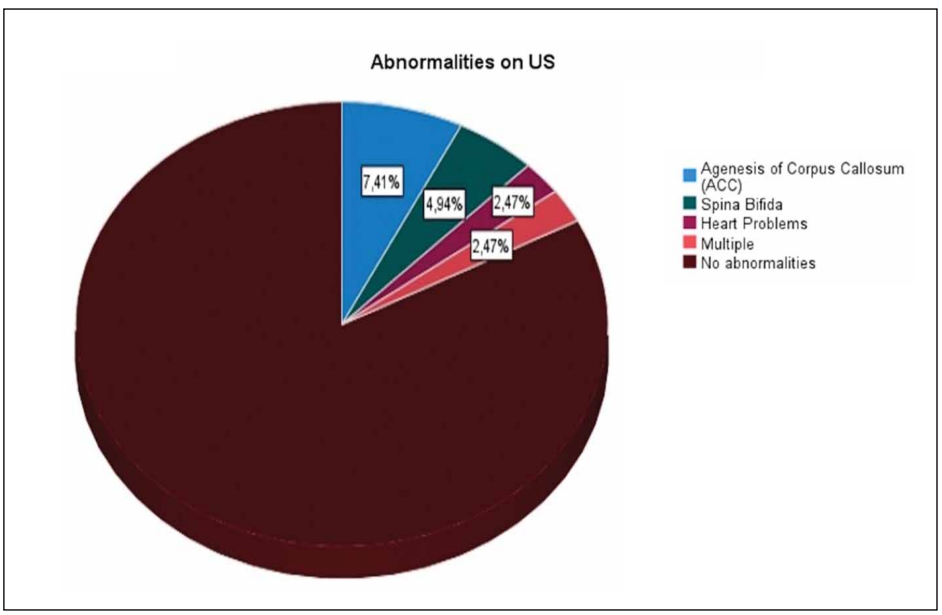


***Figure 1.*** Percentages of each malformation detected on the ultrasound scan.

had cardiac anomalies and 2 (14.3%) had multiple malformations on sonographic imaging.

Among the 81 VM cases included in the present study, after excluding the TOP cases, the remaining 63 had a record of at least one US scan after the VM diagnosis. All these 63 cases were isolated and included of 1 case (1.6%) of moderate VM and 62 (98.4%) cases of mild VM. Based on the final PV width measurement documented, in the single case of moderate IVM that continued the pregnancy and had a follow up scan, the condition progressed. Among the initial 62 cases of mild VM, 24 (38.7%) regressed, 16 (25.8%) remained unchanged and 22 (35.5%) progressed.

The regression or progression of VM observed among the cases under-study was not always sufficient to change the degree of VM. In detail, out of the 24 cases of mild VM that regressed, 19 (79.2%) resolved in utero (i.e. the final width was <10mm). The mean gestational age of VM resolution was 25.7 ± 3.2 weeks. In the remaining 5 cases, the final PV width was lower but still >10mm, so they remained mild. Correspondingly, among the 22 mild cases that progressed, 17 (77.3%) remained within the range of mild VM (10 to <12mm), whereas 5 (22.7%) cases progressed enough to become moderate VM. Regarding the one fetus with moderate VM, its final width measurement did not reach the range of severe VM; thus, it remained moderate.

With regards to the fetal gender, among the fetuses examined and included in the current study, 32 (39.5%) were males, 16 (19.8%) were females and 33 (40.7%) were not reported. The male/female ratio was 2. Out of the 32 male fetuses, 25% (n=8) did not reach delivery as their mothers proceeded to elective termination of pregnancy. As for the female fetuses, the percentage of TOP was 31.3% (n= 5). No statistical association between the fetal gender and pregnancy outcome (TOP, live birth) was observed (p= 0.735). In addition, Mann-Whitney U test was utilized to evaluate whether there is any difference in the in-utero evolution of VM (VM regression, progression, stability) between the two fetal genders. According to the test's results, no statistically significant difference (U=153, p= 0.472) was found between the genders. No association was found between the degree of VM at diagnosis and the fetal gender (p= 0.286). A statistically significant difference was found in the pregnancy outcome in relation to the three VM groups (p <0.001).

A $\chi^2$ –Test was conducted as a means to assess whether there was any association between the presence of additional fetal malformations on US scan and the degree of VM upon diagnosis. The results revealed that an association between them actually exists (Likelihood Ratio: 0.006). However, the association was weak (Cramer's V value: 0.384). Furthermore, a significant association was found between the presence of additional fetal abnormalities and pregnancy outcome (p<0.001).

Finally, in search of a statistically significant difference among at least two of the three groups of in-utero VM evolution (regression, progression, stable) in relation to the gestational age at the final US scan, no statistically significant difference among the three groups was detected (p= 0.079). The Post-Hoc test confirmed that result.

## Discussion

This study has shown that 1. The prevalence of VM is about 0.24% and is more common but not more severe in male fetuses, 2. About 90% of cases are mild at the time of diagnosis, 3. Parents opted for termination in severe and in all but one moderate cases, 4. Parents opted for termination in all cases with additional abnormalities 5. Associated abnormalities are mainly agenesis of the corpus callosum, spina bifida and cardiac defects, 6. About one third of the isolated mild cases resolves and about one third progresses but none to severe.

VM is one of the most commonly detected abnormalities and was included among the very first mal-

formations recognized antenatally in the seventies.[6] In agreement with the results and numbers retrieved during the current retrospective study, we estimated that the prevalence of VM is about 0.24%, which is in line with a study conducted by Griffiths et al. in 2011.[7]

Sonography is undoubtedly the imaging method of choice as to VM diagnosis and monitoring its in-utero natural history. The utilization of 3D ultrasound modality during the past few years has revolutionized the field of prenatal sonography and especially the assessment of PV width, due to its advanced and enhanced imaging capabilities. The current retrospective study deployed the US findings of each subject included in it during the conclusion drawing processes, since those findings were the most abundant source of information regarding the diagnosis of VM and follow-up of each case.

One of the main objectives of the current research was to closely monitor the course of VM throughout gestation. It should be highlighted that all the fetuses that had a follow-up course until delivery were isolated cases of VM (as all the NIVM cases resulted in TOP). The sole moderate VM case that reached delivery had progressive tendency during gestation, 5 out of the 62 cases of mild VM progressed enough to become moderate, while, importantly, no case in our dataset progressed to severe VM. All the aforementioned findings suggest that isolated mild VM cases have a good chance of in-utero resolution and thus better prognosis.

There are numerous recently published studies that suggest that isolated mild VM should be treated as a variation of the norm, after excluding the presence of chromosomal abnormalities.[7,8] It has been indicated by certain studies that the neurodevelopmental outcome is advantageous in these cases.[7,8] Although our results cannot support such claims due to the relatively small sample size and information regarding karyotype testing of every participating subject, it is our belief that further research is mandatory on this issue. In further detail, future prospective studies could point their attention towards an appropriate long-term follow-up of the neonates diagnosed with VM antenatally and follow a strict protocol for the neurodevelopmental evaluation of the children. This would lead to safer results which could be brought into clinical practice and aid in parental counseling.

As it can be deduced from the existing literature, isolated mild VM cases tend to have more favorable results in terms of neonatal survival and neurodevelopment. In spite of that, we would like to emphasize the significance of a follow up detailed sonographic assessment at 28-34 weeks of gestation for all women diagnosed with isolated mild VM, since there is a 16% chance of VM progression.[2] The MRI of the fetal brain could also be utilized as a means of follow-up examination, especially in cases when the sonographic imaging available is of poor quality. Moreover, according to our cohort, when VM resolved, in most cases this was seen by the 26$^{th}$ week of pregnancy.

We also noticed that cases of moderate (50%) and severe (100%) VM (only one case) where more frequently related with additional fetal malformations on ultrasound scan, compared to mild VM cases (12,5%). Given these results, it seems that there is an association between the severity of VM and the presence of additional fetal abnormalities on ultrasound scan. This point was seen in our study, but the association was weak. Our results are consistent with two recent studies which had similar results as far as the relation between the degree of VM and the existence of further fetal sonographic malformations is concerned.[6,9]

Furthermore, the results of our study are in agreement with published data reporting a predominance of male over female fetuses diagnosed with VM.[6] Nevertheless, no significant association between the gender of the fetus and the severity of VM was observed in the present study, which suggests that VM degree at diagnosis is independent of fetal gender. In addition, our results indicate that there was no significant difference in terms of VM evolution

during gestation between the two genders.

There are various limitations in this study, which need to be addressed. One of them is its retrospective design with its inherent risks of bias. The limited number of cases and hence a rather small sample size poses an issue as well, when it comes to generalizing and applying our results in clinical practice. Lastly, the insufficient access to the complete medical records of each case except for all its US scans was an important limitation too (i.e. we did not have access mainly to MRI, karyotype testing, screening for maternal infections results). On the other hand, the current study had certain strengths as well. The conduction of all US scans by highly experienced specialists with great expertise on antenatal ultrasonography was one of them. Also, a strict protocol in the selection processes of our sample was followed, which was vital for the appropriate classification of the cases and their subsequent analysis.

## Conclusion

In conclusion, the majority of VM cases are mild at diagnosis and in isolated about one third resolves in the third trimester and about one third progresses but not to severe. Therefore, a follow up scan is useful to reassure most parents and identify those cases that mey progress to moderate. Future multicenter studies with large sample sizes and prospective designs are necessary. In this way the significance of the results will be less doubtful and their generalizability would be safer for application in clinical practice.

## Disclosure of conflicts of interest

The authors report no conflicts of interest.

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