REVIEW ARTICLE

Mild Fetal Ventriculomegaly: Diagnostic Work-up and Management

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ABSTRACT

Mild ventriculomegaly (VM), also defined as "borderline", is a condition characterized by an atrial width between 10 and 15 mm independently from gestational age.

Fetuses with mild ventriculomegaly require an accurate morphological examination to rule out for associated neural and extraneural anomalies. The percentage of this association is 41%. However, in almost 13% of cases, the associated anomaly is not recognized at the time of the initial presentation. It is important to monitor the atrial width during the third trimester because in 15% of the cases it increases. Most of the cases missed at the first examination have a late onset diseases (migrational disorders, parenchimal damage, hemorrhage, etc). For these conditions MRI may play a useful role.

Maternal serum tests for congenital infections should be performed, since infections may be the cause of mild VM in 1.5% of the cases.

Fetal karyotype should also be evaluated, since chromosomal abnormalities may be associated in 2.8% of the cases of isolated VM.

The counseling in cases of apparently isolated mild VMs focuses on the possibility of neurodevelopmental delay in the surviving infants. The average percentage of neurodevelopmental delay reported in the literature is 10.9%. The possibility of late onset brain anomalies must be considered.

In conclusion, the most important prognostic factors are the association with other abnormalities not detected at the first examination and the progression of the ventricular dilatation.

Keywords: Mild ventriculomegaly, Fetus, Ultrasound, Prenatal.

INTRODUCTION

Ventriculomegaly (VM) is defined as an enlargement of lateral ventricles of the developing fetal brain. Measurement of the size of the fetal cerebral lateral ventricles is recommended as part of the fetal scan routinely performed during the second trimester to screen for fetal anomalies. The measurement is done at the level of the atria of the lateral ventricles filled by the echogenic choroid plexuses, visible in an axial plane of the fetal brain showing also the frontal horns of the lateral ventricles and the cavum septi pellucidi (CSP). The calipers are positioned on the internal margin of the medial and lateral wall of the atria, at the level of the glomus of the choroid plexus, on an axis perpendicular to the long axis of the lateral ventricle. 2,3

In order to standardize the correct technique of measurement, the following criteria should be fulfilled⁴ (Fig. 1):

- Midline structures should be equidistant from the proximal and distal calvarium margins
- The cavum septi pellucidi should be visualized as the anterior landmark and the ambient cistern as the posterior landmark
- The measurement should be performed opposite the internal parietoccipital sulcus
- The measurement should be perpendicular to the inner and outer borders of the ventricle
- The measurement should be done on the inner edges of the ventricular walls.

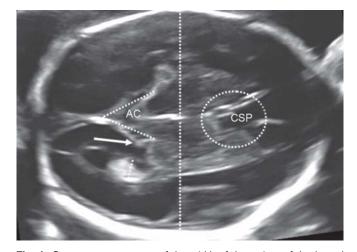


Fig. 1: Correct measurement of the width of the atrium of the lateral ventricle. The midline structures are equidistant from the proximal and distal calvarium margins; the anterior landmark (CSP – cavum septi pellucidi) and the posterior landmark (AC – ambient cistern) are visualized; the measurement is performed opposite the internal parietoccipital sulcus (arrow); the calipers are positioned on the internal margin of the medial and lateral wall of the atria, at the level of the glomus of the choroid plexus, on an axis perpendicular to the long axis of the lateral ventricle

An atrial width of less then 10 mm is considered normal. VM is diagnosed when the width of one or both lateral ventricles measured according to the criteria described so far, is ≥ 10 mm.

Measurements between 10 and 15 mm consitute mild VM; values above 15 mm constitute severe VM. Mild VM is also defined as borderline VM.⁵ Some authors⁶ use the term "milder VM" and "moderate VM" to indicate measurements of 10 to 12 mm and 12.1 to 15 mm respectively. Other authors⁷ restrict the term of mild VM to measurements between 10 and 12 mm. The most commonly used terminology, however, is "mild VM" referring to atrial measurements between 10 and 15 mm and this terminology will be used in the following discussion.

Mild VM may be the sign of a variety of anomalies (brain malformations, genetic syndromes, chromosomopathies infections) or can be isolated. The prevalence of isolated mild VM is extremely variable and has been reported ranging from 0.15% to 0.7%.

Mild VM can be bilateral or unilateral.¹⁰ Usually in the screening ultrasound examinations only the lateral ventricle distal to the transducer is measured since the proximal one is obscured by reverberation artefacts (Fig. 2). Efforts should be made in order to visualize both ventricles and recognize unilateral and bilateral mild VM (Figs 3A and B).

The finding of mild VM represents a cause of anxiety for the parents and in order to counsel them properly an accurate diagnostic work-up is needed. The diagnostic work-up should include the following steps:

- Ruling out for associate neural and extraneural anomalies
- Ruling out for congenital infections
- · Ruling out for feto-neonatal alloimmune thrombocytopenia
- Ruling out for chromosomal abnormalities
- Monitoring the development of mild VM in the ongoing pregnancy.

The following discussion on the management of fetuses with mild ventriculomegaly is based on the review of the several papers published on the topic and reported in the reference list, including two recent review articles. 11,12

Ruling Out for Associated Neural and Extraneural Anomalies

Mild VM may be associated with neural and extraneural anomalies. The percentage of association ranges from 10



Fig. 2: Mild VM in the lateral ventricle distal to the transducer; the proximal one is obscured by reverberation artifacts





Figs 3A and B: Correct visualization of mild unilateral (A) and bilateral VM (B)

to 71% with an average value of 41.4%^{5,7,11-19} (Table 1). As regards the central nervous system anomalies, some of them may be easily recognized, such as neural tube defects (Figs 4A and B) or Dandy-Walker malformation (Fig. 5);²⁰ some others may be subtle anomalies requiring accurate evaluation, such as dysgenesis of the corpus callosum (Figs 6A to C) or velum interpositum cyst (Fig. 7).²¹

Mild VM may also be the first sign of brain anomalies recognizable only in the third-trimester or even after delivery,

Author	N cases	N malf	% malf
Goldstein ('90)	55	42	76
Bromley ('91)	44	17	38.6
Patel ('94)	37	6	16
Vergani ('98)	82	34	41.5
Pilu ('99)	31	3	10
Mercier ('01)	26	4	15.3
Breeze ('05)	30	9	30
Morris ('07)	18	8	44
Gaglioti ('09)	116	59	51
Total	439	182	41.4





Figs 4A and B: Mild VM and Chiari malformation in a fetus with open neural tube defect. The mild VM is associated with the typical sign of posterior fossa (small cerebellum and effaced cisterna magna) (B)



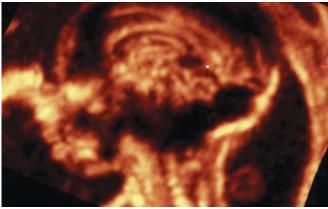
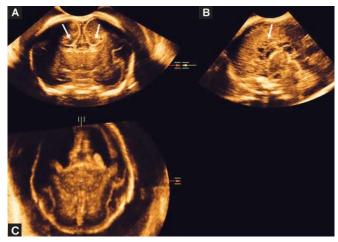


Fig. 5: Mild VM and Dandy-Walker malformation



Figs 6A to C: Mild VM and agenesis of the corpus callosum. The 3D multiplaner view shows mild VM in the axial plane (C); the typical "bull's head" appearance of the frontal horns in the coronal plane (A) and the absence of the corpus callosum in the sagittal plane (B)

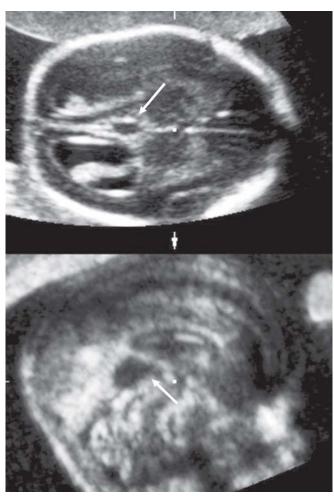


Fig. 7: Mild VM and velum interpositum cyst. The small cyst (arrow) is located below the splenium of the corpus callosum

such as cortical malformations. The mean percentage of anomalies not recognized at the time of the first diagnosis of mild VM is 12.8% (Table 2). 5-15,22-27 This limit of ultrasonography in recognizing associated anomalies should be taken in account when counseling the patient at the time of the first presentation of mild VM.

Table 2: Structural abnormalities not recognized at the time of the first presentation of mild VM (modified by ref. 11)

Author	N	%
Bromley ('91)	1/27	3.7
Achiron ('93)	2/5	40
Patel ('94)	6/36	16.7
Alagappan ('94)	2/11	18.2
Bloom ('97)	1/30	3.3
Den Hollander ('98)	2/5	40
Vergani ('98)	1/46	2.2
Lipitz ('98)	0/27	0
Pilu ('99)	3/25	12
Senat ('99)	2/12	16.7
Mercier ('01)	2/26	19.2
Greco ('01)	7/14	50
Kinzler ('01)	0/10	0
Signorelli ('04)	1/62	1.6
Breeze ('05)	3/21	14.3
Ouahba ('06)	31/167	18.6
Total	67/524	12.8

The use of magnetic resonance imaging (MRI) has been advocated as a useful tool in evaluating fetuses with mild VM;^{28,29} it adds important information in 6 to 10% of the cases, particularly in recognizing associated cortical anomalies. For this reason, the appropriate time to perform MRI is in the third trimester; it must be done by experienced operators in reference centers, following an accurate neurosonography in order to avoid useless request of such a sophisticated and expansive procedure.

Ruling Out for Congenital Infections

Toxoplasmosis and cytomegalovirus (CMV) infections have been reported in 0 to 5% of the cases of mild VM. The recent review by Devaseelan and coll¹² reports a percentage of 1.5%. In fetuses with proven CMV infection, VM is the most common ultrasound finding being present in 18% of the cases.³⁰ Further sonographic signs may be seen both in the brain, such as small periventricular calcifications (Fig. 8) or small subependymal cysts (Fg. 9) and in extraneural structures, such as liver calcifications, ascites, hepatosplenomegaly, echogenic bowel, placentomegaly, growth restriction.³¹⁻³³

MRI can provide important additional information with regard to subtle cerebral signs of infections, such as abnormal gyration, cerebellar hypoplasia, or abnormal signal in white matter.³⁴

Due to the simplicity of execution of the maternal serum toxoplasmosis and CMV screening test, these tests should be performed in all patients with fetuses presenting mild VM.

Ruling Out for Feto-Neonatal Alloimmune Thrombocytopenia

Feto-neonatal alloimmune thrombocytopenia is a rare condition, which can be complicated in 10 to 30% of the cases with



Fig. 8: Mild VM and a small periventricular calcification in a case of toxoplamosis infection

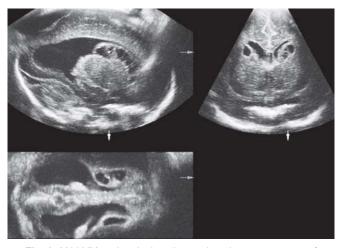


Fig. 9: Mild VM and multiple subependymal cysts in a case of CMV infection



Fig. 10: Mild VM with hyperechoic walls of the lateral ventricle and echogenic material in the ventricular cavity, as a sign of intraventricular hemorrhage

intracranial hemorrhage and ventriculomegaly.³⁵ In these cases, the VM is rarely isolated, but it is usually associated with hyperechogenicity of the ventricular walls or with the presence of intraventricular echogenic material, as a sign of the hemorrhage (Fig. 10). Therefore, the search for antiplatelet

antibodies is indicated when there are signs of intracranial hemorrhage at ultrasound, even though there are some authors who recommend this screening in all cases of apparently isolated mild VM.¹⁷

Ruling Out for Chromosomal Abnormalities

Mild VM has been considered as one of the several so-called "soft markers" of abnormal fetal karyotype. However, the correlation between mild VM and chromosomal abnormalities (mainly trisomy 21) is still a cause of debate. Several studies^{5-15, 22-27} have reported the percentage of abnormal karyotype in fetuses with apparently isolated mild VM and the results, as reviewed by Melchiorre and coll, ¹¹ are reported in Table 3.

The percentage of associated abnormal karyotype ranges from 0 to 28.6% with an average value of 2.8%. The more recent review from Devaseelan and coll¹² reports a percentage of 5%. The wide variation of results may depend by the prevalence of trisomies in the studied population, which in turn depends on previously applied screening programs.

Van der Hof and coll³⁶ report the presence of mild VM in 0.15% of euploid fetuses and 1.4% of fetuses with trisomy 21, providing a likelihood ratio of 9. Then the calculated risk will be high in the majority of the cases regardless of the previous low-risk results, thus justifying the invasive procedure.

Monitoring the Development of Mild VM in the Ongoing Pregnancy

When the diagnosis of apparently isolated mild VM is done, it is necessary to plan serial antenatal examinations, since there is a possibility of both worsening of the ventricular dilatation and late appearance of associated anomalies.

The percentage of appearance of late onset anomalies is 12.8% (range 0-50%) as previously reported in Table 2.^{5-15,22-27} They are mainly represented by cortical malformations.

Table 3: Chromosomal abnormalities in apparently isolated mild VM (modified by ref. 11)

Author	N	%
Bromley ('91)	0/27	0
Achiron ('93)	2/7	28.6
Patel ('94)	1/37	2.7
Alagappan ('94)	0/11	0
Bloom ('97)	0/30	0
Den Hollander ('98)	0/5	0
Vergani ('98)	2/48	4.2
Lipitz ('98)	1/28	3.6
Pilu ('99)	2/31	6.4
Senat ('99)	0/12	0
Mercier ('01)	1/26	4.5
Greco ('01)	1/14	7.1
Kinzler ('01)	0/3	0
Signorelli ('04)	1/62	1.6
Breeze ('05)	0/21	0
Ouahba ('06)	4/167	2.4
Total	15/529	2.8

Table 4: Natural history of mild VM in ongoing pregnancies (modified by ref. 11)

	<	=	>
Author	N (%)	N (%)	N (%)
Achiron ('93)	1/8 (13)	7/8 (88)	0/8 (0)
Tomlinson ('97)	5/35 (14)	11/35 (31)	19/35 (54)
Vergani ('98)	16/48 (33)	28/48 (33)	4/48 (8)
Lipitz ('98)	4/26 (15)	21/26 (81)	1/26 (4)
Senat ('99)	0/12 (0)	10/12 (83)	2/12 (17)
Mercier ('01)	10/26 (38)	16/26 (62)	0/26 (0)
Greco ('01)	0/12 (0)	12/14 (86)	2/14 (14)
Kinzler ('01)	4/9 (44)	5/9 (56)	0/9 (0)
Signorelli ('04)	18/60 (30)	42/60 (70)	0/60 (0)
Breeze ('05)	15/21 (71)	6/21 (29)	0/21 (0)
Ouahba ('06)	50/146 (34)	80/146 (55)	16/146 (11)
Parilla ('06)	26/63 (41)	27/63 (43)	10/63 (16)
Total	34%	55.7%	15.7%

As regards the natural history of mild VM in ongoing pregnancy it can progress, decrease or remain stable. It progresses in 15.7% of the cases (range 0-54%); it decreases in 34% of the cases (range 0-71%) and remains stable in 55.7% of the cases (range 29-88%) (Table 4). 6,9,10,13,16,17, 24-27,37,38

The time and frequency of the follow-up in fetuses with mild VM depends from the gestational age at the time of the first diagnosis and from the protocol used by the different centers. A reasonable minimal time interval before performing a follow-up after the first diagnosis is two weeks, since a shorter time could not allow a variation of size of the ventricles to become evident. Anyway, at least one additional detailed examination should be performed in the third-trimester, between 30 and 34 weeks of gestation, to monitor the size of the ventricles and search for cerebral and extracerebral anomalies not visible in the second trimester.

Neurological Outcome of Fetuses with Isolated Mild VM

The neurological outcome of fetuses with prenatal diagnosis of isolated mild VM widely varies in different studies. The percentage of neurodevelopmental delay ranges from 0 to 28.6%, with an average value of 10.9% (Table 5). 5-9,13,14,16,17,22-27

Some authors have considered the neurological outcome in relationship to the degree of mild VM (10.0-11.9 mm and 12.0-15.0 mm). The mean rate of neurodevelopmental delay is slightly higher in the subgroup of mild VM between 12.0 and 15.0 mm (17.1%) in comparison to the subgroup between 10.0 and 11.9 mm (11.8%) (Table 6). $^{5-8,11,12,24,25,27}$

The percentages reported in the tables also include the cases in which associated anomalies were identified in late pregnancy or even after delivery.

The main explanation of the wide variation of the results reported by different authors mainly depends on the different protocols used to assess postnatal neurological development.

Table 5: Neurodevelopmental delay in fetuses with isolated mild VM (modified by ref. 11)

Author	N	%
Bromley ('91)	0/27	0
Achiron ('93)	2/7	28.6
Patel ('94)	1/37	2.7
Alagappan ('94)	0/11	0
Bloom ('97)	0/30	0
Den Hollander ('98)	0/5	0
Vergani ('98)	2/48	4.2
Lipitz ('98)	1/28	3.6
Pilu ('99)	2/31	6.4
Senat ('99)	0/12	0
Mercier ('01)	1/26	4.5
Greco ('01)	1/14	7.1
Kinzler ('01)	0/3	0
Signorelli ('04)	1/62	1.6
Breeze ('05)	0/21	0
Ouahba ('06)	4/167	2.4
Total	48/439	10.9

Table 6: Neurodevelopmental delay in fetuses with isolated mild VM in relationship with the degree of the atrial width (10.0-11.9 mm and 12.0-15.00 mm) (modified by ref. 11)

	10.0-11.9 mm	12.0-15.0 mm
Author	N (%)	N (%)
Bromley ('91)	5/26 (19.2)	_
Patel ('94)	2/22 (9)	4/12 (33.3)
Alagappan ('94)	0/9 (0)	0/2 (0)
Vergani ('98)	0/42 (0)	0/3 (0)
Lipitz ('98)	0/14 (0)	1/12 (8.3)
Pilu ('99)	2/18 (11.1)	0/7 (0)
Senat ('99)	0/2 (0)	1/9 (11.1)
Kinzler ('01)	0/6 (0)	0/4 (0)
Signorelli ('04)	0/60 (0)	_
Ouahba ('06)	25/89 (72)	8/33 (24.2)
Total	34/288 (11.8)	13/82 (17.1)

In most cases, inadequate qualitative assessment, such as telephone interview, have been used. In other cases, a short period of follow-up has been planned; the infants have been assessed at different ages and often the distinction between mild, moderate and severe delay has not been made. An accurate evaluation of the neurodevelopmental delay in preschool children should include evaluation of locomotor activity, eye and hand coordination, hearing and speech capacity and learning performance. On the other hand, it should be stressed that a neurodevelopmental delay in preschool children does not necessarily lead to long-term handicap. For this reason, in order to evaluate exactly the contribution of isolated mild VM to the neurodevelopmental delay in infancy, a large collaborative prospective study using a unified protocol and long-term objective postnatal follow-up is needed.

A factor which can significantly influence the prognosis is the progression of the VM in the ongoing pregnancy. In 15.7% of the cases, the VM progresses and these are the cases where the prognosis is worse. The neurodevelopmental delay in cases of isolated progressive VM is 16.7%; in this group of fetuses there is also the highest incidence of chromosomal abnormalities (22.2%) and associated anomalies (71.4%); the overall abnormal outcome is 44.4% (Table 7).^{6,9-11,14,16,17,24-26}

Another factor which seems to influence the prognosis is the asymmetry of the mild VM, but the number of cases reported is still too low to draw conclusions.²⁷

CONCLUSION

Fetal mild VM is an uncommon but clinically relevant sonographic finding. According to the experience coming from the papers published on the topic and reviewed in this article, a possible diagnostic and prognostic work-up is that reported in Figure 11.

The association of mild VM with neural and extraneural anomalies, chromosomopathies and infections is the main factor to be considered in dealing with fetuses with this sonographic sign. Then the initial steps are accurate ultrasonic evaluation of the fetal anatomy, an invasive procedure for fetal karyotyping and maternal serum tests for infections.

Table 7: Outcome of mild VM in relation to progression, stability or regression of the ventricular dilatation (polled data from ref. 6, 9, 10, 13, 14, 16, 17, 24, 25, 26)

VM	Chromosomal abnormalities	Structural abnormalities, normal karyotype	Perinatal death, normal karyotype	Neurodevelopmental delay, normal karyotype	Total cases with abnormal outcome
	N (%)	N (%)	N (%)	N (%)	N (%)
Regression	0/77 (0)	2/77 (2.6)	0/77 (0)	3/72 (4.2)	3/72 (4.2)
Stable	2/131 (1.5)	7/127 (5.5)	3/127 (2.4)	5/121 (4.1)	11/127 (8.7)
Progression	2/9 (22.2)	5/7 (71.4)	0/7 (0)	1/6 (16.7)	4/9 (44.4)

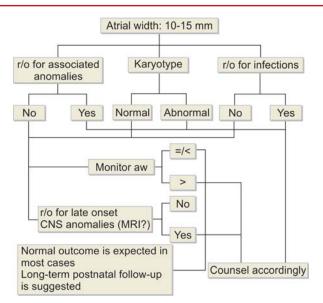


Fig. 11: Diagnostic and prognostic follow-up in fetuses with mild VM

Even in the presence of normal karyotype, absence of infection and apparently normal fetal anatomy, when counseling the patient one should be aware of the limited accuracy of ultrasound in distinguishing isolated from nonisolated ventriculomegaly. Furthermore, the possibility of progression of the VM and of late onset brain anomalies should be taken in account.

For this reason, serial ultrasound examinations have to be planned and the possibility of fetal MRI in the third-trimester should be considered. Special postnatal evaluation and care may be coordinated by appropriate pediatric specialists.

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