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Counseling in isolated mild fetal ventriculomegaly

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KEYWORDS: management; outcome; ultrasound; ventriculomegaly

ABSTRACT

In this Review we aim to provide up-to-date and evidence-based answers to the common questions regarding the diagnosis of isolated mild fetal ventriculomegaly (VM). A literature search was performed to identify all reports of antenatal VM in the English language literature. In addition, reference lists of articles identified using the search were scrutinized to further identify relevant articles. Fetal mild VM is commonly defined as a ventricular atrial width of 10.0–15.0 mm, and it is considered isolated if there are no associated ultrasound abnormalities. There is no good evidence to suggest that the width of the ventricular atria contributes to the risk of neurodevelopmental outcome in fetuses with mild VM. The most important prognostic factors are the association with other abnormalities that escape early detection and the progression of ventricular dilatation, which are reported to occur in about 13% and 16% of cases, respectively. Most infants with a prenatal diagnosis of isolated mild VM have normal neurological development at least in infancy. The rate of abnormal or delayed neurodevelopment in infancy is about 11%, and it is unclear whether this is higher than in the general population. Furthermore, the number of infants that develop a real handicap is unknown. There are limitations of existing studies of mild VM. Although they address many of the relevant questions regarding the prognosis and management of fetal isolated mild VM, there is a lack of good-quality postnatal follow-up studies. The resulting uncertainties make antenatal counseling for this abnormality difficult. Copyright © 2009 ISUOG. Published by John Wiley & Sons, Ltd.

INTRODUCTION

Assessment of the width of the atria of the lateral cerebral ventricles is recommended as part of the routine anomaly scan[1–3]. The lateral ventricle should be measured in the axial plane, at the level of the frontal horns and cavum septi pellucidi, with the calipers positioned at the level of 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[3,4] (Figure 1). Some authors have described measurement of both atrial diameters on a coronal plane at the level of the atria with good visibility of the choroid plexuses and perpendicular to the long axis of the ventricles at the mid-height of the ventricles, positioning calipers inside the echoes of the ventricle walls. This approach is recommended when attempting to measure both atria and is in close agreement with magnetic resonance imaging (MRI) measurements[5–7].

A number of studies have assessed the normal size of the fetal atria. Most of these studies are in agreement with the original study by Cardoza *et al.*[4], who found that in the second trimester the mean ± SD measurement is 7.6 ± 0.6 mm and suggested a threshold of abnormality of 10 mm, corresponding to about 4 SD above the mean[4]. In a pooled analysis Almog *et al.* showed no significant change in width between 20 and 40 weeks of gestation (nine studies containing 8216 cases)[8]. In this study the mean ventricular width was 6.4 ± 1.2 mm, suggesting that a value of 10 mm is about 3 SDs above the mean.

Most studies have assessed ventricular measurements using parametric methods. Recently, Salomon *et al.* have constructed reference ranges using a statistical method that does not assume a normal distribution[9]. Based on a sample of 4769 fetuses between 17 and 36 weeks' gestation they were able to produce centile ranges for gestational age[9]. Although there were statistically significant changes of the 99th centile with gestation, the authors proposed using a single threshold (10.0 mm) because the absolute differences did not seem clinically relevant[9]. Using this cut-off predicts that about 1% of all fetuses will be classified as having ventriculomegaly (VM), a much higher proportion than expected based on previous studies[9].

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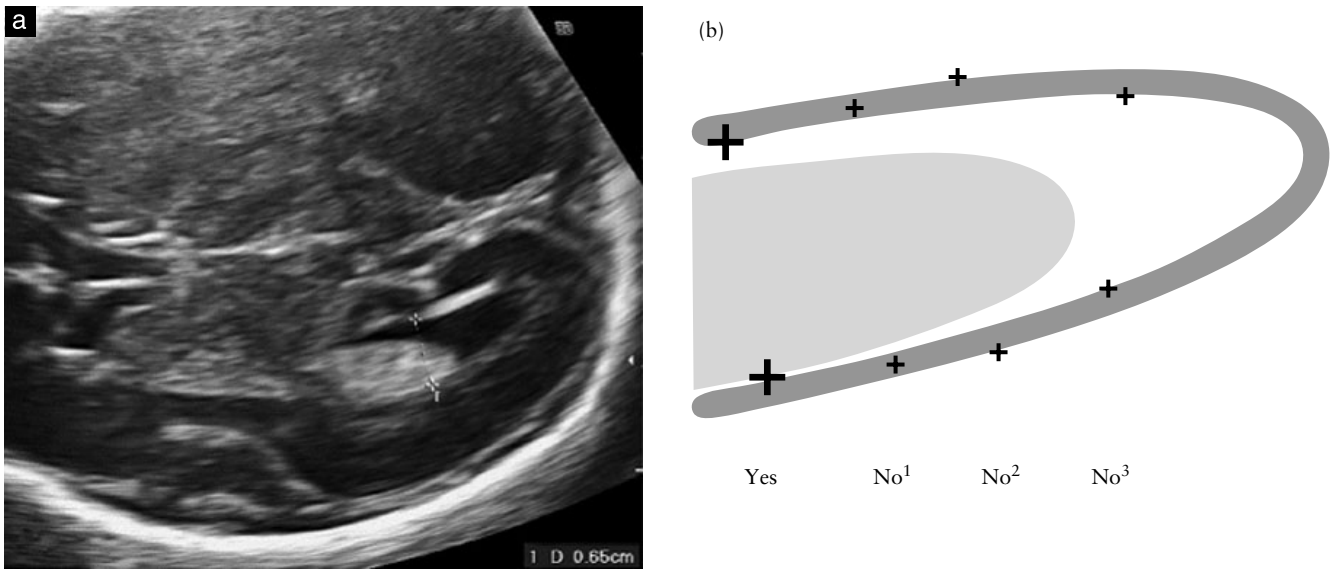

Figure 1 (a) Measurement of the atrium of the lateral ventricles. The calipers are positioned at the level of the glomus of the choroid plexus, inside the echoes generated by the ventricular walls. (b) Diagram illustrating correct caliper placement for ventricular measurement. Calipers are correctly placed touching the inner edge of the ventricle wall at its widest part and aligned perpendicular to the long axis of the ventricle (Yes). Incorrect placements include middle–middle (No^1), outer–outer (No^2), and placement that is too posterior, in the narrower part of the ventricle or not perpendicular to the ventricle axis (No^3). Reproduced from the International Society of Ultrasound in Obstetrics and Gynecology guidelines[3].

An atrial width of less than 10.0 mm should be considered normal, a measurement between 10.0 and 15.0 mm constitutes mild VM, and a measurement in excess of 15.0 mm constitutes severe VM[10]; these cut-offs and terminology will be used in the following discussion. Previous studies have used varying definitions. For example, 'borderline ventriculomegaly' has been used in some studies as a synonym for mild VM[11]. 'Milder ventriculomegaly' and 'moderate ventriculomegaly' have been used to indicate measurements of 10–12 mm and 13–15 mm, respectively[12]. Some authors have restricted the diagnosis of mild VM to measurements of 10–12 mm[13].

VM is commonly defined as isolated if there is no sonographic evidence of associated malformations or markers of aneuploidy at the time of the initial presentation[10,11]. By definition this is a provisional diagnosis of exclusion. The incidence of isolated mild VM has been reported to be between one in 50 and one in 1600 in two prospective studies in low-risk populations[14,15]. This large discrepancy may be due to differences in technique or gestational age at examination; the study with a higher prevalence included a large number of third-trimester fetuses. In most studies mild VM was diagnosed only by measuring the lateral ventricle distal to the transducer, owing to technical difficulty in imaging the hemisphere closest to the transducer. It is now clear that mild VM may be unilateral. In a study by Kinzler et *al.*, 15 fetuses with unilateral mild VM were seen in a referral population of over 21 000 women (incidence 0.07%)[16]. In a more recent prospective study of 101 fetuses with prenatally diagnosed mild VM both hemispheres were always assessed[7]. In this study the incidence of unilateral VM among the fetuses with mild VM was 60%, much higher than previously reported[7].

Isolated mild VM represents a considerable diagnostic dilemma as it can be an apparently benign finding, but can also be associated with chromosomal abnormalities, congenital infection, cerebral vascular accidents or hemorrhage, and other fetal cerebral and extracerebral abnormalities; it may also have implications regarding long-term neurodevelopmental outcome. The aim of our Review is to support women, their partners and obstetricians in the task of understanding the implications by providing up-to-date evidence-based answers to the more common questions regarding the diagnosis of isolated mild fetal VM.

SEARCH STRATEGY AND SELECTION OF ARTICLES

A literature search was performed to identify all reports in the English language literature (Medline, National Library of Medicine). The search terms used were 'isolated' or 'mild' or 'borderline', 'fetus' or 'fetal' or 'ultrasound' or 'prenatal' and 'ventriculomegaly'. We also included abstracts of oral communications and posters of congresses where available on Medline. In addition, reference lists of articles identified using the search were scrutinized to further identify relevant articles.

The terms 'isolated' or 'mild' or 'borderline' and 'ventriculomegaly' yielded 249 articles, and the search 'fetus' or 'fetal' or 'ultrasound' or 'prenatal' and 'ventriculomegaly' yielded another 476. The combined set included 550 articles and these were supplemented by articles identified from reference lists of relevant articles, as well as relevant articles of which the authors were aware. The titles and abstracts of these were reviewed, and a total of 90 articles were considered relevant for this

Table 1 Studies included in this Review and data used in the analysis

Reference	*Chromosomal abnormality*	*Structural defects*	*Perinatal death*	*Neurodevelopmental delay*	*Subanalysis by progression of VM*	*Subanalysis by atrial width*	*Subanalysis by fetal sex*
Bromley *et al.* (1991)[13]	Yes	Yes	Yes	Yes		Yes	
Achiron *et al.* (1993)[15]	Yes	Yes	Yes	Yes	Yes		Yes
Patel *et al.* (1994)[85]	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Alagappan *et al.* (1994)[14]	Yes	Yes	Yes	Yes		Yes	
Bloom *et al.* (1997)[68]	Yes	Yes	Yes	Yes			
den Hollander *et al.* (1998)[86]	Yes	Yes	Yes	Yes			Yes
Vergani *et al.* (1998)[10]	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Lipitz *et al.* (1998)[77]	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Pilu *et al.* (1999)[11]	Yes	Yes	Yes	Yes		Yes	Yes
Senat *et al.* (1999)[17]	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Mercier *et al.* (2001)[75]	Yes	Yes	Yes	Yes	Yes		
Greco *et al.* (2001)[37]	Yes	Yes	Yes	Yes	Yes		
Kinzler *et al.* (2001)[16]	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Signorelli *et al.* (2004)[12]	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Breeze *et al.* (2005)[48]	Yes	Yes	Yes	Yes	Yes		
Ouahba *et al.* (2006)[6]	Yes	Yes	Yes	Yes		Yes	Yes

VM, ventriculomegaly.

paper. Data on relevant clinical questions were extracted from the papers (Table 1).

CLINICAL QUESTIONS

Should women with isolated mild fetal ventriculomegaly be sent to a referral center for a detailed anomaly scan?

Several studies have reported an incidence of associated anomalies (neural and extraneural) as high as 50%[10,11,17]. Some of these malformations may be easily recognizable at the routine scan, for example open neural tube defects. However, other malformations, such as agenesis of the corpus callosum and cortical malformations, may be more difficult to detect. As mild VM is considered to be associated with an increased risk of fetal infections and aneuploidies, ultrasound features of these conditions, which may be very subtle, should be sought[10,11].

Isolated mild VM is a diagnosis of exclusion. Because the prognosis can be altered drastically depending on coexisting anomalies, expert ultrasound examination is needed. Women with pregnancies in which mild VM is suspected would therefore benefit from referral to a center with a high level of expertise in fetal ultrasound assessment.

Should a transvaginal scan be performed in order to assess the fetal brain?

Some cerebral anomalies potentially associated with mild VM, such as agenesis of the corpus callosum and cortical malformations, may be difficult or impossible to detect with standard axial views. The use of a multiplanar approach is therefore recommended[10,18,19]. A transvaginal approach with a high-resolution probe usually results in the greatest resolution of detail. However, when the fetus is not in a cephalic presentation this is not possible. Although some investigators have suggested performing an external version in these cases, many would consider a transabdominal neurosonogram an acceptable alternative. There are no reliable data available comparing accuracy of the two different approaches.

Detailed fetal neurosonographic evaluation should be performed in each fetus with mild VM; whether this is obtained with a transvaginal or transabdominal scan depends on the fetal position and the preference of the patient and the operator.

Should magnetic resonance imaging be considered as a part of assessment of isolated mild ventriculomegaly?

Many studies have indicated that MRI adds important information to that obtained by ultrasound imaging[6,20–25]. In the largest study involving third-trimester fetuses with a ventricular width of 10–12 mm, information relevant enough to modify obstetric management was obtained in 11/185 (6%) cases[21]. Similarly, in 167 fetuses with apparently isolated mild VM, Ouahba *et al.* showed that MRI diagnosed major cerebral anomalies in 15 cases (9.0%), including cortical malformations, absence of the septum pellucidum, partial agenesis of the corpus callosum and agenesis of the cerebellar vermis; of these, only four were seen on follow-up ultrasound examination[6].

Most studies have demonstrated a marginal superiority of MRI over ultrasound examination. Nevertheless, it is important to bear in mind that differences in detection rates between MRI and ultrasound imaging can be affected by the competence of the operators; for example, comparing a routine referral examination and an MRI performed at a tertiary-level unit may overemphasize the role of MRI. Another important factor is gestational age

at examination, with MRI usually being performed later in gestation[26].

A particular advantage of fetal brain MRI is that it allows analysis of gyration, and this is best assessed in the third trimester[27–29]. Even when late pregnancy termination is not available, fetal MRI may prove useful for perinatal management and to enhance parental understanding or relieve anxiety[30]. However, findings of unknown significance that increase patient anxiety may also be found[31].

Isolated mild VM can be associated with abnormal cerebral development which may be better demonstrated with fetal MRI. Some authors advocate MRI only when ultrasound imaging is inadequate or if there is a suspicion of an associated brain abnormality. Others recommend routine use in all fetuses with mild VM, and the largest studies suggest that it adds important information in 6–10% of cases. Its use should take into account resource allocation and MRI should be carried out only if there is sufficient technical expertise. The optimal time to perform the scan, whether at the time of the primary diagnosis or in late gestation as part of follow-up studies, remains unclear. As the main advantage is analysis of gyration, MRI examination between 30 and 32 weeks may be the most appropriate.

Should serial antenatal examinations be arranged?

In fetuses with mild VM, both worsening of ventricular dilatation and late appearance of associated anomalies have been documented[11]. In a large study by Ouahba *et al.* follow-up ultrasound scans in 167 fetuses with mild VM referred to a specialist center showed that there was progression in 11% of cases (defined as an increase in the ventricular measurement of more than 3 mm); infants with progression were at higher risk of subsequent neurodevelopmental delay than those with non-progression[6]. Furthermore, in 10/146 (7%) ongoing pregnancies major abnormalities not seen at the initial scan were detected on follow-up ultrasound examination[6]. Our study suggests that the risk of progression of ventricular dilatation is 15.7%, and anomalies not visible initially are seen in 12.8% (Tables 2 and 3).

There is no agreement regarding the timing and frequency of follow-up in fetuses with mild VM, and this will depend on the gestational age at diagnosis. Some authors have suggested that the minimal time interval before performing a follow-up study should be 2 weeks after detailed initial assessment[32].

Follow-up ultrasound examinations should be performed because the risk of progression of ventricular dilatation is about 16%, and because anomalies not visible initially may be seen in about 13%. Depending on the gestational age at diagnosis, at least one additional detailed ultrasound examination of the whole fetus should be performed at between 28 and 34 weeks in order to search for cerebral and extracerebral abnormalities that may not be evident during the second-trimester examination.

Should screening for congenital infection be performed?

Congenital infection can be a cause of mild VM, and possible pathogens include *Toxoplasma*, cytomegalovirus (CMV) and rubella. There is a wide variation in the incidence of infection as the underlying cause, depending on the population studied[17,33–35].

CMV infection is of particular concern because of the poor prognosis of affected newborns when cerebral findings are present[36]. The incidence of CMV as a cause of mild VM varies from 0 to 5%[37,38], but in the majority of cases mild VM is not the only ultrasound feature of congenital infection[39]. On the other hand, cerebral VM is one of the more common prenatal ultrasound abnormalities in fetuses with proven intrauterine transmission of CMV, being present in around 18% of cases[40]. Picone *et al.* reported the ultrasound and MRI findings of 38 fetuses with proven CMV infection, 14 with intracranial findings[41]. Of these nine had VM, which was isolated at ultrasound examination in two cases[41].

Given the possible association with mild VM, the difficulty in early ultrasound detection of fetal infection, the guarded prognosis in cases of affected children, the potential for treatment, and the simplicity, safety and relatively low cost of the screening test, maternal serum CMV and Toxoplasma studies should be considered.

Should prenatal karyotyping be offered in isolated mild ventriculomegaly?

Isolated VM has been associated with chromosomal abnormalities – mainly trisomy 21 – in a large number of studies (Table 2). The strength of any association will depend on the prevalence of Down syndrome in the population, which in turn will depend on previous screening for the condition. In our Review the rate of chromosomal abnormalities was found to be 2.8% (15/529) (Table 2).

A recent paper addressing the issue of the risk of trisomy 21 in idiopathic mild VM highlighted that this finding is present in 0.15% of euploid fetuses and in 1.4% of trisomy 21 fetuses, providing a likelihood ratio of 9 for the risk of aneuploidy[42]. Investigation for aneuploidy in the presence of this finding may therefore be appropriate[42], depending on the prior risk.

Given that previous studies have different screening strategies, report on different populations and use different protocols, it is difficult to be certain regarding the incidence of chromosomal abnormalities in isolated mild VM. Nevertheless, given the strength of the association between mild VM and chromosomal abnormalities, it is likely that the risk will be high in the majority of cases regardless of a previous low-risk result.

Table 2 Studies reporting outcome of fetuses with a diagnosis of isolated mild ventriculomegaly (VM) at the time of the initial presentation

Reference	*Study type*	*Atrial width (mm)*	*Ventricles assessed*	*Cases included*	*Chromosomal abnormalities* (n *(%))*	*Structural abnormalities, normal karyotype* (n *(%))*	*Perinatal deaths, normal karyotype* (n *(%))*	*Neurodev delay, normal karyotype* (n *(%))*	*Duration of follow-up (months) and method of neurodev assessment*	*Total cases with abnormal outcome* (n *(%))**
Bromley *et al.* (1991)[13]	R	10–12	Distal	—	0/27 (0)	1/27 (3.7)	0/26 (0)	5/26 (19.2)	3–18 Subjective	5/26 (19.2)
Achiron *et al.* (1993)[15]	P	10–15	Distal	—	2/7 (28.6)	2/5 (40)	0/3 (0)	0/3 (0)	12 Unspecified	4/7 (57.1)
Patel *et al.* (1994)[85]	R	10–15	Distal	—	1/37 (2.7)	6/36 (16.7)	2/36 (5.6)	6/34 (17.6)	1.5–70.3 Subjective	12/37 (32.4)
Alagappan *et al.* (1994)[14]	P	10–13	Distal	—	0/11 (0)	2/11 (18.2)	0/11 (0)	0/11 (0)	1.5–18 Subjective	2/11 (18.2)
Bloom *et al.* (1997)[68]	R	10–15	Distal	—	0/30 (0)	1/30 (3.3)	1/30 (3.3)	9/29 (31)	21.6 ± 17.4† Objective	10/30 (33.3)
den Hollander *et al.* (1998)[86]	R	10–15	Distal	—	0/5 (0)	2/5 (40)	0/5 (0)	2/5 (40)	10–18 Objective	2/5 (40)
Vergani *et al.* (1998)[10]	P	10–15	Distal	—	2/48 (4.2)	1/46 (2.2)	1/46 (2.2)	0/45 (0)	3–72 Objective	4/48 (8.3)
Lipitz *et al.* (1998)[77]	R	10–15	Both	U	1/28 (3.6)	0/27 (0)	0/26 (0)	1/26 (3.8)	6–32 Not specified	2/27 (7.4)
Pilu *et al.* (1999)[11]	R	10–15	Distal	—	2/31 (6.4)	3/25 (12)	0/25 (0)	2/25 (8)	21–72 Subjective	6/27 (22.2)
Senat *et al.* (1999)[17]	P	10–15	Both	U	0/12 (0)	2/12 (16.7)	0/11 (0)	1/11 (9.1)	3–48 Not specified	2/12 (16.7)
Mercier *et al.* (2001)[75]	R	10–15	Both	U + B	1/26 (4.5)	5/26 (19.2)	0/26 (0)	3/21 (14)	3–72 Not specified	4/22 (18)
Greco *et al.* (2001)[37]	R	10–15	Distal	—	1/14 (7.1)	7/14 (50)	3/14 (21.4)	3/11 (27.3)	0–30 Not specified	7/14 (50)
Kinzler *et al.* (2001)[16]	R	10–15	Both	U	0/3 (0)	0/10 (0)	0/10 (0)	0/10 (0)	0–36 Subjective	0/7 (0)
Signorelli *et al.* (2004)[12]	P + R	10–12	Both	B	1/62 (1.6)	1/62 (1.6)	0/60 (0)	0/60 (0)	18–120 Objective	0/60 (0)
Breeze *et al.* (2005)[48]	P	10–15	Distal	—	0/21 (0)	3/21 (14.3)	0/21 (0)	4/21 (19)	4 Objective	5/21 (23.8)
Ouahba *et al.* (2006)[6]	R	10–15	Both	U + B	4/167 (2.4)	31/167 (18.6)	0/146 (0)	12/101 (12)	2–127 months Objective	33/122 (27)
Total					15/529 (2.8)	67/524 (12.8)	7/496 (1.4)	48/439 (10.9)	—	98/476 (20.6)

*Cases lost to follow-up and terminations of pregnancy of fetuses without associated abnormalities were excluded from the analysis. Fetuses may have had more than one abnormal outcome. We present studies that assessed isolated mild VM at the time of the initial presentation; those with associated abnormalities or progression of VM discovered only during the prenatal or postnatal follow-up were not excluded from the analysis. For this reason some studies[7,38,57,69,87,88] were excluded from the pooled analysis. As some of these are useful for counseling of truly isolated mild VM (i.e. mild VM that has been confirmed to be an isolated finding at birth)[7,38,57,69] they are discussed in the text. Studies that provided incomplete information were also excluded[89,90]. †Mean ± SD.
B, bilateral; neurodev, neurodevelopmental; P, prospective; R, retrospective; U, unilateral.

Table 3 Studies reporting the rates of progression, stability and resolution of ventriculomegaly (VM) and the related outcome, in fetuses presenting with isolated mild VM

Reference	*Natural history* (n *(%))*	*Chromosomal abnormalities* (n *(%))*	*Structural abnormalities, normal karyotype* (n *(%))*	*Perinatal deaths, normal karyotype* (n *(%))*	*Neurodevelopmental delay, normal karyotype* (n *(%))*	*Total cases with abnormal outcome** (n *(%))*
Achiron *et al.* (1993)[15]	R: 1/8 (13)	0/1 (0)	0/1 (0)	0/1 (0)	0/1 (0)	0/1 (0)
	S: 7/8 (88)	2/7 (29)	2/5 (40)	0/5 (0)	0/2 (0)	4/6 (67)
Patel *et al.* (1994)[85]	R: 10/26 (38)	0/9 (0)	0/9 (0)	0/9 (0)	1/9 (11)	1/9 (11)
	S: 16/26 (62)	0/15 (0)	2/15 (13)	2/15 (13)	3/13 (23)	5/15 (33)
Vergani *et al.* (1998)[10]	R: 16/48 (33)	0/16 (0)	0/16 (0)	0/16	0/16 (0)	0/16 (0)
	S: 28/48 (58)	0/28 (0)	0/28 (0)	1/28 (3.6)†	0/27 (0)	0/27 (0)
	P: 4/48 (8)	2/4 (50)	2/2 (50)	0/2 (0)	0/2 (0)	2/4 (50)
Lipitz *et al.* (1998)[77]	R: 4/26 (15)	0/4 (0)	0/4 (0)	0/4 (0)	0/4 (0)	0/4 (0)
	S: 21/26 (81)	0/21 (0)	0/21 (0)	0/21 (0)	0/21 (0)	0/21 (0)
	P: 1/26 (4)	0/1 (0)	0/1 (0)	0/1 (0)	0/1 (0)	0/1 (0)
Senat *et al.* (1999)[17]	S: 10/12 (83)	0/12 (0)	0/10 (0)	0/10 (0)	0/10 (0)	0/10 (0)
	P: 2/12 (17)	0/2 (0)	2/2 (100)	0/2 (0)	1/1 (100)	2/2 (100)
Mercier *et al.* (2001)[75]‡	R: 10/26 (38)	0/10 (0)	1/10 (10)	0/10 (0)	0/7 (0)	0/7 (0)
	NR: 16/26 (62)	1/16 (6)	3/15 (20)	0/15 (0)	4/15 (27)	6/16 (27)
Greco *et al.* (2001)[37]‡	P: 2/14 (14)	0/2 (0)	1/2 (50)	0/2 (0)	0/2 (0)	0/2 (0)
	NP: 12/14 (86)	1/12 (8)	6/11 (55)	3/11 (27)	4/8 (50)	8/12 (67)
Kinzler *et al.* (2001)[16]‡	R: 4/9 (44)	0/4 (0)	1/4 (25)	0/4 (0)	0/2 (0)	0/2 (0)
	NR: 5/9 (56)	0/5 (0)	0/5 (0)	0/5 (0)	0/5 (0)	0/5 (0)
Signorelli *et al.* (2004)[12]	R: 18/60 (30)	0/18 (0)	0/18 (0)	0/18 (0)	0/18 (0)	0/18 (0)
	S: 42/60 (70)	0/42 (0)	0/42 (0)	0/42 (0)	0/42 (0)	0/42 (0)
Breeze *et al.* (2005)[48]	R (at birth): 15/21 (71)	0/15 (0)	0/15 (0)	0/15 (0)	2/15 (13)	2/15 (13)
	S (at birth): 6/21 (29)	0/6 (0)	3/6 (50)	0/6 (0)	2/6 (33)	2/6 (33)
Ouahba *et al.* (2006)[6]	R: 50/146 (34)	—	—	—	—	—
	S: 80/146 (55)					
	P: 16/146 (11)					
Parilla *et al.* (2006)[90]	R: 26/63 (41)	—	—	—	—	—
	S: 27/63 (43)					
	P: 10/63 (16)					
Tomlinson *et al.* (1997)[89]	R: 5/35 (14)	—	—	—	—	—
	S: 11/35 (31)					
	P: 19/35 (54)					
	NC: 2/37 (5)					
Total§	R: 159/468 (34)	—	—	—	—	—
	S: 248/445 (55.7)					
	P: 54/344 (15.7)					
Total with detailed outcome		R: 0/77 (0)	R: 2/77 (2.6)	R: 0/77 (0)	R: 3/72 (4.2)	R: 3/72 (4.2)
		S: 2/131 (1.5)	S: 7/127 (5.5)	S: 3/127 (2.4)	S: 5/121 (4.1)	S: 11/127 (8.7)
		P: 2/9 (22.2)	P: 5/7 (71.4)	P: 0/7 (0)	P: 1/6 (16.7)	P: 4/9 (44.4)

*Cases lost to follow-up and terminations of pregnancy of fetuses without associated abnormalities were excluded from the analysis. †One fetus of 48 died near term from unexplained causes; the authors did not specify whether the ventricular dilatation in this fetus was stable or had regressed. Therefore, this death was not taken into account in the final analysis. ‡In these three studies, cases of no progression or no resolution were excluded from the analysis. Note that denominators in 'Total with detailed outcome' are different because of the exclusion of these cases. §This total was used to assess the total risk of progression/stabilization or resolution. Studies that did not specify the natural history of all cases[11,13,14,68,86] were not included in this table. NC, not classified in the other natural history groups; NP, no progression; NR, no regression; P, progression; R, regression; S, stability.

Should screening for platelet alloantibodies be performed?

The incidence of fetoneonatal alloimmune thrombocytopenia (FNAIT) is low (between one in 800 and one in 1000 in the general population[43]) and the risk of intracranial hemorrhage (ICH), which may lead to severe neurological sequelae and intrauterine death[44–48], among these cases is 10–30%. ICH can lead to hemispheric porencephaly and lateral VM seen at antenatal or postnatal imaging[49]. Other sonographic findings, such as echogenicity of the ventricular wall and intraventricular echoes, may be subtle and difficult to detect. Antenatally, MRI may be particularly useful to assess whether ICH has occurred[50,51].

There is no formalized or cost-effective antenatal screening program to detect women at risk of human platelet antigen (HPA) alloimmunization[46], and it is often found after investigations due to the birth of a thrombocytopenic infant. As the disorder can affect even the first pregnancy, screening has been recommended when conditions potentially associated with fetal bleeding are found[48,52].

In one study of 30 cases with mild VM, 16 underwent screening for anti-HPA antibodies. Two cases were found to be positive: one was detected postnatally after thrombocytopenia, petechiae and bruising were noted at birth, and neonatal ultrasound imaging showed an ICH. The second fetus had a normal platelet count[48]. Although the authors changed their practice and now recommend screening for antiplatelet antibodies in all cases of apparently isolated mild VM[48], we have found no other studies that support this clinical practice. Given that MRI should rule out ICH with a high level of precision, the value of FNAIT screening in isolated VM may be limited.

Even if FNAIT may be treatable if detected promptly, this condition is rarely found in association with apparently isolated mild VM; therefore, a search for anti-HPA antibodies may be justified only if there is a suspicion of ICH on imaging.

What is the risk that the mild ventriculomegaly is not truly isolated?

Counseling for mild VM usually takes place at the time of the initial ultrasound diagnosis before the results of longitudinal follow-up are available. The discussion should include the possibility that the apparently isolated mild VM is not, in fact, isolated. The issue is specifically assessed in a number of studies (Table 2) and this suggests a rate of associated abnormalities not detected at the time of the first examination (false-negative rate) of 12.8% (67/524).

How often an associated abnormality is not found at the initial assessment is likely to depend on the antenatal protocol used. In the study by Vergani *et al.* there were no cases of false-negative diagnosis[10], perhaps owing to the expert use of multiplanar transvaginal neurosonography at the time of diagnosis. It is possible that the introduction of more complete antenatal assessment and MRI in cases with VM will reduce the misclassified case rate, providing a more accurate prediction of outcome[6,7]. The study by Falip *et al.* assessed whether, after a complete prenatal work-up including MRI, there remains a risk of the mild VM not being truly isolated at birth[7]. Postnatal MRI was performed in 76 infants and 21 abnormalities not detected prenatally were found, including three arachnoid cysts, four subependymal pseudocysts and 14 white matter signal abnormalities, most of which were not visible before the age of 1 year[7]. Importantly, the study had no control group.

It is possible to speculate that the rate of false-negative cases depends on the antenatal protocol used at the time of the initial assessment. Nevertheless, the physiological development of the fetal brain must also be considered, and the parents should be informed that there are limitations in the capability of ultrasound imaging in differentiating truly isolated mild VM from that associated with initially occult abnormalities; this is in the region of 13%.

What is the neurological outcome of children with a prenatal diagnosis of mild ventriculomegaly?

There is wide variation in the reported incidence of neurodevelopmental delay[11], but pooled data suggest this is around 11% (48/439) (Table 2). If four recent oral communications are included[23,53–55], the figure is higher (14.5%, 89/615), but the limited details of these reports do not allow complete assessment. One of the limitations of pooled analysis is that different studies use different tests of neurodevelopmental assessment, assess infants at different ages, and often do not make the distinction between mild, moderate and severe delay. Few studies have used objective measures or assessed long-term follow-up[56] (Table 2).

Relation to incomplete antenatal diagnosis

As outlined above, mild VM is subsequently found not to be truly isolated in 13% (67/524) of cases. The problem of incomplete antenatal diagnosis is likely to affect subsequent outcome, and the antenatal protocol used for the assessment of fetuses with isolated mild VM may affect the postnatal outcome. Nevertheless, the rate of neurodevelopmental delay in infants with a diagnosis of mild VM confirmed as isolated at birth is about 10%, similar to that of VM isolated at the initial presentation[7,38,57].

Is the rate of developmental delay higher than in the background population?

Neurodevelopmental delay in preschool children is not infrequent and reliable data on its prevalence are limited,

as studies usually focus on selected populations or biologically at-risk children. The 1994–1995 National Health Interview Survey on Disability calculated the prevalence of developmental delay among United States (US) children aged 4–59 months as being approximately 3.4%[58]. Although this figure is comparable with data from other US studies[59], they are based on survey questions answered by parents and may be of limited accuracy. More recently, the Early Childhood Longitudinal Study Birth Cohort directly assessed development in a sample of US children aged 9–24 months and estimated the prevalence of developmental delay at approximately 13%[60].

Neurodevelopmental delay in preschool children does not necessarily lead to long-term problems or handicap. There are few prospective studies characterizing the outcome of young children diagnosed with developmental delay. Shevell *et al.* showed that 60–100% of a cohort of children diagnosed during preschool years with global developmental delay performed at least 1.5 SD below the mean when reassessed during early school years[61]. Developmental language impairment (DLI) is one of the most common developmental disabilities in preschool children, with a prevalence ranging from 2 to 19% in different studies[62–64]. It is thought to be more predictive of future intelligence and school performance than isolated delays in other domains of development[65]. When children with a diagnosis of DLI at preschool age were reassessed during school years, approximately 80% were found to have persistent language impairment with cognitive impairment being an important comorbidity[66], whereas approximately 50% had delay in fine or gross motor domains[67]. A significant proportion of young children diagnosed with developmental delay – whether associated with VM or not – go on to have handicap, but the likelihood of developing such handicap remains unclear.

To assess the real significance of isolated mild VM it would be necessary to include control groups. We were able to identify only two such studies[68,69]. Both studies used the Bayley Scale of infant Development-II to assess neurodevelopment outcome. Sadan *et al.* studied only mild unilateral VM (ULVM), confirmed to be isolated at birth, and found developmental delay (i.e. a Bayley developmental score < 85) in 4/20 (20%) children with ULVM vs. 1/20 (5%) from the control group ($P < 0.05$)[69]. Bloom *et al.*, who assessed only the distal ventricle, found a developmental delay in 8/22 (36.4%) children with antenatal isolated mild VM vs. 1/22 (4.5%) in the control group ($P = 0.021$)[68]. Both studies concluded that mild VM is a significant risk factor for developmental delay[68,69]. However, results from these studies should be interpreted with some caution because of the small number of cases and lack of long-term follow-up.

Wide variations exist in the reported prevalence of neurodevelopmental delay in infants with a prenatal diagnosis of isolated mild VM. The pooled prevalence is 11% (95% CI, 6.1–18.1%) including cases in which associated anomalies were identified at later gestation or after birth. Most studies have used qualitative assessments of development that may be inadequate, such as telephone interviews. However, even if only those studies using objective measures are included, the rate remains similar (12%; 95% CI, 3–26%). At present, the available evidence indicates that about 90% of children with a prenatal diagnosis of isolated mild VM have a normal neurodevelopmental outcome at least in infancy. Whether or not isolated mild VM is associated with an increased frequency of neurological problems over the general population remains uncertain.

Is there an association between isolated mild ventriculomegaly and neuropsychiatric disorders?

Several case series have suggested that isolated mild VM is associated with neuropsychiatric disorders, including autism, attention deficit hyperactivity disorder, learning disabilities and schizophrenia[70–73]. However there are no high-quality series suggesting an increased incidence compared with the normal population.

There are no solid data to suggest an increased rate of neuropsychiatric disorders in infants with a prenatal diagnosis of isolated mild VM.

Which factors influence the prognosis of fetuses with isolated mild ventriculomegaly?

Several studies have attempted to identify factors correlated with the outcome of isolated mild VM that could be potentially useful when counseling prospective parents.

Fetal sex

It has been reported previously that, excluding cases with chromosomal aberrations, there is a male predominance among fetuses with diagnosis of mild VM and that female gender significantly correlates with a worse neurodevelopmental outcome[11]. Our pooled data confirm a male predominance showing a fetal male to female sex ratio of 1.7 (280/167), but do not confirm a statistically significant worse prognosis in female infants, who had a rate of developmental delay of 10.7% (13/121) vs. 5.6% in male infants (11/197) (relative risk (RR), 1.924; 95% CI, 0.891–4.157; $P = 0.141$) (Table 4). Further evidence for this lack of prognostic influence is presented in the study by Falip *et al.*, in which 101 infants with truly isolated mild VM at birth were assessed at the age of 8 months to 6.5 years using objective methods (Brunet–Lezine psychomotor scale, MacCarthy scales, Weschsler Preschool and Primary Scale of Intelligence III)[7]. No differences between male and female infants were found[7].

Gestational age at diagnosis

Reviews of existing studies present opposing views, suggesting that early detection of mild VM is associated

Table 4 Reported neurodevelopmental delay in infants with isolated mild ventriculomegaly (VM) at the time of the initial presentation and normal karyotype, according to fetal sex

	Neurodevelopmental delay (n *(%)*)	
Reference	*Females*	*Males*
Achiron *et al.* (1993)[15]*	0/1 (0)	0/0 (0)
Patel *et al.* (1994)[85]	3/9 (33)	3/25 (12)
Vergani *et al.* (1998)[10]	0/15 (0)	0/30 (0)
Lipitz *et al.* (1998)[77]	1/11 (9)	0/15 (0)
Senat *et al.* (1999)[17]	0/2 (0)	1/9 (11)
den Hollander *et al.* (1997)[86]	2/2 (100)	0/3 (0)
Pilu *et al.* (1999)[11]	2/7 (29)	0/18 (0)
Kinzler *et al.* (2001)[16]	0/3 (0)	0/7 (0)
Signorelli *et al.* (2004)[12]	0/27 (0)	0/33 (0)
Ouahba *et al.* (2006)[6]	5/44 (11)	7/57 (12)
Total	13/121 (10.7)	11/197 (5.6)

Bloom *et al.* (1997) studied 22 infants with mild VM and 22 controls[68]. The study was excluded from this analysis as the sex ratio among children with neurodevelopmental delay was not reported. However, the study reported that the sex of the child did not influence the rate of impairment. *In the study by Achiron *et al.* (1993) the sex was unknown in two cases and these have been excluded[15].

with worse outcome[74] or that it is of better outcome as it resolves during intrauterine life[75]. The study by Falip *et al.* specifically examined this issue in 101 cases, and no correlation between gestational age at diagnosis and outcome was found[7].

Size of the ventricles

Several investigators have suggested that the atrial width determines the final outcome[6,10–12,38,57] and suggest that a measurement of 10.0–11.9 mm is generally associated with a better outcome than 12.0–15.0 mm[16,48,76]. Our pooled data (Table 5) do not demonstrate a significant difference in abnormal neurological outcome in these two groups: 10/61 (16.4%) fetuses with atrial width 12–15 mm vs. 34/288 (11.8%) with atrial width 10–12 mm (RR, 1.39; 95% CI, 0.726–2.657; $P = 0.442$).

Bilateral vs. unilateral mild ventriculomegaly

The incidence of neurodevelopmental delay in cases of unilateral mild VM has been reported to be between 0%[16] and 7.5%[6]; our pooled data[6,12,16,17,77] show an incidence of 6% (6/100) in infants with unilateral mild VM, not significantly different from the incidence of 7.4% (8/108) among infants with bilateral mild VM (RR, 0.810; 95% CI, 0.291–2.253; $P = 0.898$).

Symmetrical vs. asymmetrical bilateral mild ventriculomegaly

Recent studies assessing both fetal hemispheres have provided information about the symmetry of the ventricular system[6,7,12]. Authors who addressed the presence of asymmetrical VM most often defined this as a difference in width of ≥ 2 mm[7]. Although studies assessing bilateral and symmetrical mild VM have suggested a low incidence of neurodevelopmental delay (4%, 4/100)[6,12], infants with asymmetrical bilateral mild VM may have higher rates (50%, 4/8)[6]. This is statistically significant (RR, 12.5; 95% CI, 3.825–40.848; $P < 0.0001$)[6], but the small number of cases of asymmetrical mild VM must be highlighted.

Table 5 Neurodevelopment delay in chromosomally normal infants presenting antenatally with isolated mild ventriculomegaly (VM) depending on atrial width

	Atrial width between 10.0 and 11.9 mm		*Atrial width between 12.0 and 15.0 mm*	
Reference	*Normal neurological outcome* (n *(%)*)	*Abnormal neurological outcome* (n *(%)*)	*Normal neurological outcome* (n *(%)*)	*Abnormal neurological outcome* (n *(%)*)
Bromley *et al.* (1991)[13]*	21/26 (81)	5/26 (19)	—	—
Patel *et al.* (1994)[85]	20/22 (91)	2/22 (9)	8/12 (67)	4/12 (33.3)
Alagappan *et al.* (1994)[14]	9/9 (100)	0/9 (0)	2/2 (100)	0/2 (0)
Vergani *et al.* (1998)[10]	42/42 (100)	0/42 (0)	3/3 (100)	0/3 (0)
Lipitz *et al.* (1998)[77]	14/14 (100)	0/14 (0)	11/12 (92)	1/12 (8)
Pilu *et al.* (1999)[11]	16/18 (89)	2/18 (11)	7/7 (100)	0/7 (0)
Senat *et al.* (1999)[17]	2/2 (100)	0/2 (0)	8/9 (89)	1/9 (11)
Kinzler *et al.* (2001)[16]	6/6 (100)	0/6 (0)	4/4 (100)	0/4 (0)
Signorelli *et al.* (2004)[12]*	60/60 (100)	0/60 (0)	—	—
Ouahba *et al.* (2006)[6]	64/89 (72)	25/89 (28)	8/12 (67)	4/12 (33)
Total	254/288 (88)	34/288 (12)	51/61 (84)	10/61 (16)

Cases lost to follow-up and pregnancies that underwent termination were excluded from the analysis. *Assessed the outcome of children with a prenatal diagnosis of mild VM defined as atrial width between 10 and 12 mm; we included their series in the group with atrial width < 12 mm arbitrarily as it was not possible to deduce how many fetuses (if any) had an atrial width of 12 mm and how many had one of < 12 mm. The studies by Achiron *et al.* (1993)[15], Bloom *et al.* (1997)[68], den Hollander *et al.* (1998)[86], Mercier *et al.* (2001)[75], Greco *et al.* (2001)[37] and Breeze *et al.* (2005)[48] were excluded from the analysis in this table as it was not possible to deduce how many children had an atrial width > or ≤ 12 mm in the normal and abnormal groups.

Progression

Pooled data analysis suggests that the proportion with progression is 16%, and that the outcome in the progression group seems to be worse than in cases with no progression (i.e. stable and regression), with chromosomal abnormalities in 22% vs. 1% in the no-progression group (RR, 23.1; 95% CI, 3.66–145.94; $P < 0.0001$), 17% with neurodevelopmental delay vs. 4% in the no-progression group (RR, 4; 95% CI, 0.59–27.25; $P = 0.65$), and 71% misclassified cases vs. 4% in the no-progression group (RR, 16.2; 95% CI, 7.33–35.75; $P < 0.0001$). Overall, *in-utero* progression of ventricular dilatation is associated with adverse outcome in 44% vs. 7% in the no-progression group (RR, 6.32; 95% CI, 2.56–15.35; $P < 0.001$) (Table 3). Unfortunately the value of this analysis is limited because of the lack of complete details and full follow-up in the majority of the studies.

The most important prognostic factors in isolated mild VM are the association with other abnormalities not detected at first examination, and the progression of ventricular dilatation, both of which are retrospective diagnoses. Some authors have suggested that measurements in excess of 12 mm might be associated with worse prognosis, but there is no strong evidence supporting this opinion. Although male sex was previously thought to be associated with a slight improvement in prognosis, this effect was not significant in our pooled analysis. The presence of ventricular system asymmetry may be a prognostic factor, but this needs to be assessed in larger populations.

What postnatal management and type of follow-up are recommended?

Postnatal assessment by an expert pediatrician is aimed at identifying disorders that may have remained undetected prenatally[78,79]. Mercier *et al.* recommended long-term postnatal follow-up until at least 6 years of age in order to allow early identification of attention deficit and hyperactivity disorders as well as to assess educational success[75]. In an extensive review of neurodevelopmental outcome in children with a prenatal diagnosis of isolated mild VM, Wyldes and Watkinson concluded that follow-up should continue until development is established as normal, whereas referral for special educational intervention should be carried out promptly in cases of developmental delay[80] as this can improve the infants' outcome[81]. Standard tools for the evaluation of neurological performance should be adopted (such as Bayley scales, Griffiths scales or Schedule of Growing Skills)[82–84], which are able to identify different types of developmental delay. MRI after the age of 1 year to exclude lesions of the white matter that are not detectable during intrauterine or early postnatal life has also been suggested[7].

Postnatal assessment by an expert pediatrician is aimed at identifying disorders that may have remained undetected prenatally. Further postnatal follow-up should be planned according to the diagnosis at birth. Some authors suggest that long-term postnatal follow-up and MRI should be arranged, regardless of spontaneous resolution of the finding.

What are the limitations of the available studies?

There are many limitations of available studies on mild VM, and these will necessarily limit the value of such pooled analysis.

- Most studies identify cases retrospectively rather than reporting prospective cohorts.
- Many studies report on a small number of cases.
- There are many differences in the protocols for antenatal assessment of VM.
- Some studies include cases identified at a wide range of gestational ages.
- Many studies come from tertiary referral centers, and this predisposes to referral bias, with milder cases not being referred to such centers.
- Some studies started recruitment of patients in the late 1970s; technological limitations of the equipment available in those years may have resulted in an excess of false-negative diagnoses.
- In the majority of the studies only the distal hemisphere has been assessed, so information about the proximal one and cerebral asymmetry is lacking.
- MRI has been used in few studies.
- High rates of cases lost to follow-up.
- Use of subjective tests to assess the neurological development.
- Lack of distinction in the severity of neurodevelopmental delay.
- Lack of control groups to compare outcomes with those of the normal population.
- Wide age range of children at assessment (variable duration of follow-up).
- Lack of long-term follow-up.

When counseling, it is important to bear in mind the limitations of the available evidence. A large, collaborative, prospective study using a unified protocol for antenatal investigation and long-term objective postnatal follow-up is warranted.

CONCLUSION

Assessment of the cerebral ventricles remains part of the routine anomaly scan[1–4]. An atrial width of less than 10.0 mm is normal, whereas a measurement of 10.0–15.0 mm constitutes mild VM, which is isolated if there are no associated ultrasound abnormalities[10,11]. This finding is frequently associated with neural and extraneural anomalies, and so a careful evaluation of the fetal anatomy should be carried out using an expert ultrasound examination. Where available, fetal MRI is also indicated, although there is no consensus on the

optimal time for this examination. The likelihood ratio for trisomy 21 is about 9 and invasive testing for chromosomal analysis should be offered. Maternal serum CMV and *Toxoplasma* studies should be considered, and measurement of anti-HPA antibodies may be justified if there is a suspicion of ICH.

The rate of neurodevelopmental delay in infants with a prenatal diagnosis of isolated mild VM is about 11%, and it is unclear whether this is increased over that in the general population. The most important prognostic factors in isolated mild VM are the association with other abnormalities undetected at the time of the first diagnosis (about 13% of cases) and progression of the ventricular dilatation (about 16% of cases). Therefore, follow-up sonograms and/or MRI in the third trimester should be considered.

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