Thieme

Prenatal detection of mild fetal ventriculomegaly – a systematic review of the modern literature

Pränatale Diagnose der leichten fetalen Ventrikulomegalie – Eine systematische Übersicht über die aktuelle Literatur

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ABSTRACT

Introduction While mild fetal ventriculomegaly is frequently observed as an incidental and benign finding, it is also known to be linked with structural, genetic, and neurodevelopmental abnormalities. The objective of this study was to conduct a systematic review of the existing literature in order to evaluate the association between apparently isolated fetal mild ventriculomegaly with the presence of additional structural defects detected by fetal brain MRI, chromosomal or other genetic anomalies, and neurodevelopmental delay.

Methods This systematic review was designed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines. Modern literature was searched from January 1, 2011, to July 31, 2023.

Results 23 studies were included, comprising a total of 2590 patients. Nine studies assessed the association between fetal mild ventriculomegaly and neurodevelopmental impairment, including 536 cases, with normal neurodevelopmental outcomes ranging from 64% to 96.5%. Ten studies evaluated the additive value of fetal MRI, including 1266 fetuses, with the detection rate of additional brain defects that eventually altered the clinical management ranging from 0% to 19.5%. Seven studies investigated the association of mild ventriculomegaly with the presence of underlying chromosomal or genetic conditions, including 747 cases, with the rate ranging from 1.1% to 15.4%.

Conclusion The prevalence of aneuploidy and genetic abnormalities in ventriculomegaly, especially in isolated cases, is reported to be quite low and the incidence of neurodevelopmental delay appears to be similar to that of the general population in cases that are apparently and truly isolated.

ZUSAMMENFASSUNG

Einleitung Während eine leichte fetale Ventrikulomegalie häufig als zufälliger und gutartiger Befund beobachtet wird, ist auch bekannt, dass sie mit strukturellen, genetischen und neurologischen Entwicklungsanomalien einhergeht. Ziel dieser Studie war es, eine systematische Übersicht der vorhandenen Literatur vorzunehmen, um den Zusammenhang zwischen scheinbar isolierter fetaler leichter Ventrikulomegalie und dem Vorliegen zusätzlicher struktureller Defekte, die durch fetale Hirn-MRT nachgewiesen wurden, sowie chromosomaler oder anderer genetischer Anomalien und neurologischer Entwicklungsverzögerungen zu bewerten.

Methoden Diese systematische Übersichtsarbeit wurde gemäß den Leitlinien der „Preferred Reporting Items for Systematic Reviews and Meta-Analyses“ erstellt. Die aktuelle Lit-

eratur vom 1. Januar 2011 bis zum 31. Juli 2023 wurde durchsucht.

Ergebnisse Es wurden 23 Studien mit insgesamt 2590 Patienten eingeschlossen. Neun Studien untersuchten den Zusammenhang zwischen einer leichten fetalen Ventrikulomegalie und einer beeinträchtigten neurologischen Entwicklung, darunter 536 Fälle, bei denen 64 % bis 96,5 % ein normales Outcome der neurologischen Entwicklung zeigten. Zehn Studien untersuchten den additiven Wert der fetalen MRT bei 1266 Feten, wobei die Detektionsrate hinsichtlich zusätzlicher Hirndefekte, die letztendlich das klinische Management veränderten, zwischen 0 % und 19,5 % lag. Sieben Studien mit 747 eingeschlossenen Fällen untersuchten die Korrelation zwischen leichter Ventrikulomegalie mit dem Vorliegen chromosomaler oder genetischer Ursachen, wobei die Rate zwischen 1,1 % und 15,4 % lag.

Schlussfolgerungen Die Prävalenz von Aneuploidie und genetischen Anomalien bei Ventrikulomegalie, insbesondere bei isolierten Fällen, ist Berichten zufolge relativ gering. Die Inzidenz neurologischer Entwicklungsverzögerungen scheint sowohl bei scheinbaren als auch wirklich isolierten Fällen derjenigen der Allgemeinbevölkerung zu entsprechen.

Introduction

Ventriculomegaly (VM) is a condition defined by the enlargement of the cerebral ventricles in the fetus, which is frequently observed during prenatal ultrasound examinations. The diagnosis of ventriculomegaly often relies on reference ranges established by Cardoza et al. (1988), wherein the upper limit of fetal ventricular measurement remains constant throughout gestation [1]. Therefore, fetal ventriculomegaly discovered antenatally is commonly classified into two categories: mild, which refers to measurements ranging from 10 to 15 mm, and severe, which encompasses measurements exceeding 15 mm. Alternatively, it can also be classified as mild (10–12 mm), moderate (13–15 mm), or severe (> 15 mm) [2]. While mild fetal ventriculomegaly is frequently observed as an incidental and benign finding, it is also known to be linked with genetic, structural, and neurodevelopmental abnormalities. As such, the outcome of this condition can vary from normal to severe impairment. According to existing criteria, the estimated prevalence of mild ventriculomegaly is approximately 0.7 % [3]. In a clinical context, ventriculomegaly is considered to be isolated when there is no ultrasound evidence of accompanying anatomical deformities or markers of aneuploidy at the time of initial ultrasound assessment [3].

The presence of fetal ventriculomegaly has been observed to have varying associations with chromosomal and structural abnormalities, as well as fetal infections. Even when occurring in isolation, it is believed to be connected to aberrant neurodevelopmental outcomes [3, 4]. While the latter condition is well acknowledged in cases of severe ventriculomegaly, the existing research on isolated mild ventriculomegaly presents inconsistent findings about the prevalence of neurodevelopmental delay, ranging from 0 % to 40 % [5]. The objective of this study was to conduct a systematic review of the existing literature in order to evaluate the association between apparently isolated mild fetal ventriculomegaly with the presence of additional structural defects detected by fetal brain MRI, chromosomal or other genetic anomalies, and neurodevelopmental delay.

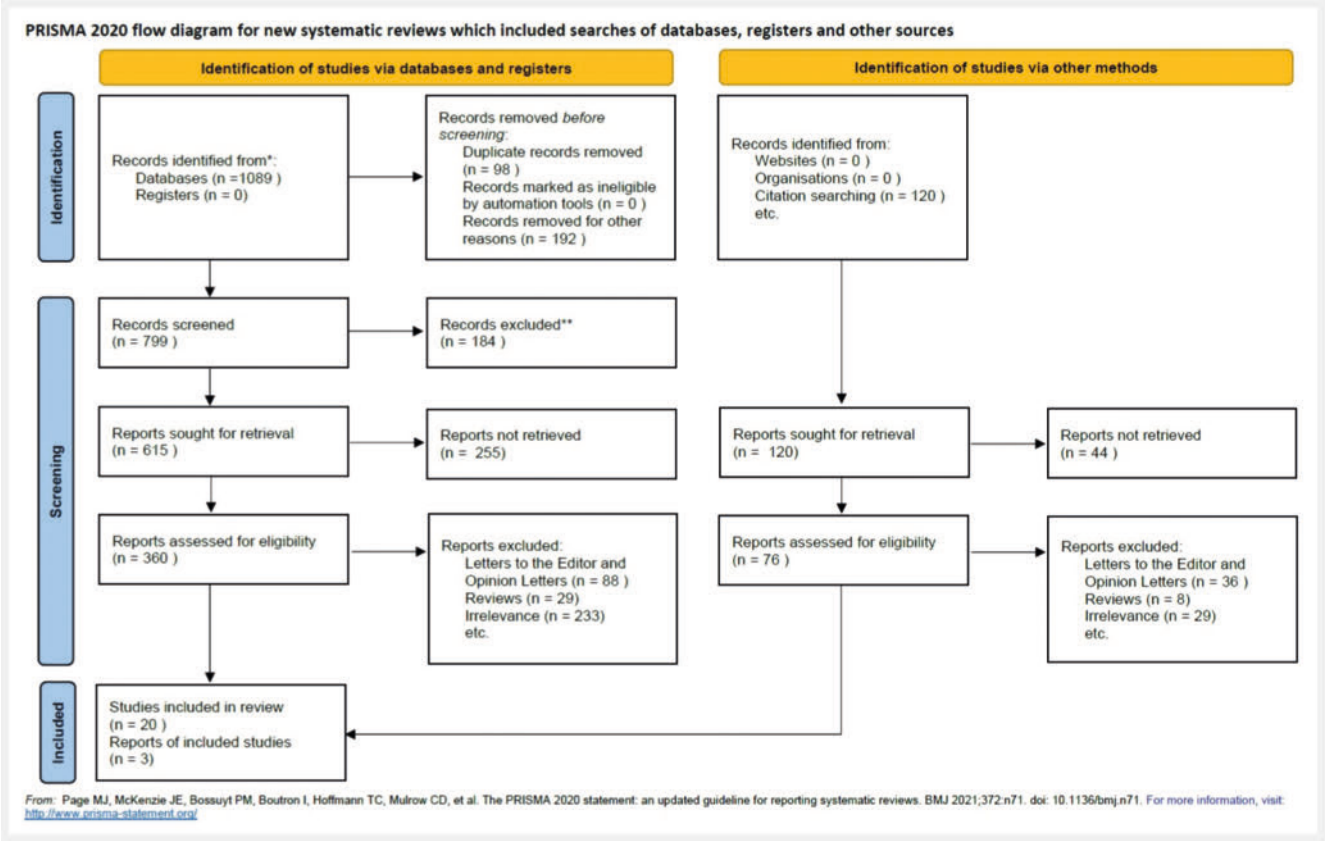
Subjects and Methods

Study design, literature search, and data collection

This systematic review was designed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [6]. This review was registered in the PROSPERO international database for systematic reviews. The databases MEDLINE, Scopus, Cochrane Central Register of Controlled Trials (CENTRAL), and Clinicaltrials.gov were searched from January 1, 2011, to July 31, 2023. Google Scholar and the reference lists of the included studies ('snowball' method) were also screened to identify potential additional articles that were not recognized by the primary literature search. The search was based on the following key terms and their combinations: 'mild ventriculomegaly', 'fetal ventriculomegaly', 'dilatation', 'fetal ventricular system', 'atrial width', 'isolated', 'non-isolated', 'abnormalities', 'chromosomal', 'genetic', 'neurodevelopment', 'delay'. The search was restricted to English language records only.

Study selection was planned to be performed in three consecutive stages. First, the titles and/or abstracts of all electronic articles were screened to assess their potential eligibility, and subsequently, the full text of all articles that met or were presumed to meet the prespecified eligibility criteria was retrieved. Finally, the full text was assessed and all studies reporting the association of mild fetal ventriculomegaly with the presence of additional brain and extracerebral abnormalities identified by fetal brain MRI, chromosomal or other genetic abnormalities, as well as neurodevelopmental impairment were considered eligible for inclusion. RCTs and prospective or retrospective observational cohort studies were included. Case-control studies, small case series (involving fewer than 10 patients), case reports, posters, letters to the editor, and animal and *in-vitro* studies were excluded. Study selection was conducted independently by two authors, and any discrepancies regarding the inclusion and exclusion of studies were resolved by consensus. The search strategy is depicted in ▶ **Fig. 1.**

Ventriculomegaly was characterized by an atrial width greater than 10 mm, involving either one (unilateral) or both (bilateral) sides of the brain. Isolated ventriculomegaly was characterized by the absence of any further brain or extracerebral ultrasound abnormalities at the time of the assessment. Some studies have classed ventriculomegaly as mild when the width of the atrium is between 10 and 15 mm, while others have classified it as such



▶ **Fig. 1** Search strategy according to the PRISMA 2020 flow diagram.

when ventricular dilatation ranges from 10 to 12 mm or 13 mm. Fetal MRI was offered in some studies after a targeted neurosonography examination was performed while in others it was performed after a basic fetal brain assessment. In several studies, conventional karyotypic analysis was performed while in others both karyotype and chromosomal microarray analysis (CMA) was offered.

Data extraction

The following data were extracted from each of the included studies: name of first author, year of publication, study design, sample size, eligibility criteria, exclusion criteria, incidence of associated structural deformities (where applied), incidence of associated chromosomal and other genetic abnormalities (where applied) and rate of neurodevelopmental delay (where applied). Data extraction was conducted independently by two researchers and any disagreement was resolved by consensus or by discussion with the other authors.

Quality Assessment

The methodological quality of the included studies was assessed by two independent reviewers using the QUADAS-2 (Quality Assessment of Diagnostic Accuracy Studies-2) tool that evaluates the technique of patient selection, the indexed test, the reference standard to that test, and the flow and timing of the test/study **(Supplementary Table 1)**.

Results

Study selection and characteristics

A flowchart summarizing the study selection is shown in ▶ **Fig. 1**. Overall, of 1089 records identified through the electronic database search and other sources, 23 were deemed potentially eligible and retrieved in full text for further evaluation, comprising a total of 2590 patients [7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29]. Among these, 13 studies were retrospective cohort studies and 8 were prospective. There was also 1 nationwide registry-based study and 1 case series. Nine studies assessed the association between mild fetal ventriculomegaly and neurodevelopmental impairment (examined through different developmental scales) [7, 8, 9, 10, 11, 12, 13, 14, 15], seven studies focused on the correlation between mild VM and the presence of underlying chromosomal or other genetic conditions [15, 16, 17, 18, 19, 20, 21], and ten studies evaluated the additive value of fetal MRI in the diagnosis of additional structural defects missed by ultrasound [13, 14, 16, 22, 23, 24, 25, 26, 27, 28, 29].

Mild ventriculomegaly was defined as a ventricular width of 10–12 mm or 10–15 mm in 13 (57 %) and 10 (43 %) studies, respectively, including a total of 1373 and 1217 patients, respectively.

Out of the 9 studies that assessed the neurodevelopmental impairment in mild VM, six studies (66.7 %) included only apparently

isolated cases during the first assessment while three (33.3%) assessed non-isolated cases, as well. In 8 studies (88%), karyotype investigation, infection screening, and fetal brain MRI were additionally offered in the event of mild VM while in one study (12%) only fetal MRI was provided. Furthermore, in only 3 (33.3%) of those studies the length of follow-up was documented, and 5 different developmental screening tools were used.

In 6 out of 10 (60%) included studies that assessed the value of fetal brain MRI in the detection of structural brain defects, multiplanar neurosonography was offered prior to the brain MRI examination.

Out of the 7 included studies that investigated the association of mild VM with the presence of chromosomal or other genetic conditions, 5 studies (71%) implemented both conventional karyotype investigation and chromosomal microarray analysis (CMA) while two (29%) provided only conventional karyotype analysis.

The characteristics of the included studies are depicted in ▶ **Table 1**, ▶ **Table 2**, and ▶ **Table 3**.

All studies were evaluated qualitatively.

Mild fetal ventriculomegaly and neurodevelopmental impairment

Nine studies assessed the association between mild fetal ventriculomegaly and neurodevelopmental impairment [7, 8, 9, 10, 11, 12, 13, 14, 15] including a total of 536 cases (▶ **Table 1**). Out of those 536 cases, 311 fetuses (58.1%) had no additional findings after a thorough investigation that included karyotype assessment, infection screening, and fetal brain MRI and, as such, they were categorized as apparently isolated cases during their initial prenatal visit. Normal neurodevelopmental outcomes range from 64% to 96.4% among different studies with 486 infants out of the 536 included (90.6%) being reportedly within the established normal range, while 50 out of the 536 infants included (9.4%), developed a mild or severe form of neurodevelopmental impairment. One study [14] reported the detection of additional findings as gestation progressed (a case of periventricular hemorrhage, a case of renal hypoplasia, heart chamber disproportion, fetal growth restriction (FGR), and a case of FGR and CMV infection) while 6 studies [7, 8, 9, 10, 11, 13] included additional postnatal findings in prenatally detected isolated mild VM. A total of 8 infants (8/50, 16%) were diagnosed with severe additional structural defects that were missed prenatally. Six of the included studies reported the developmental screening tool that was used to assess the neurodevelopment of the infants with 2 of those implementing the Griffith test [9, 13], two of them the Battelle Developmental Inventory Screening Test (BDIST) [11, 12], one used the Age and Stage Questionnaires Third Edition (ASQ-3) [7], and one either the ASQ-3 or the Bayley Scales of Infant and Toddler Development – Third Edition (BSID3) [8]. Seven of the 9 studies reported the nature of neurodevelopmental impairment [9, 10, 11, 12, 13, 14, 15] including conditions ranging from mild forms of speech delay and hearing difficulties to extremely severe ones such as autism spectrum disorder and severe intellectual impairment.

The additive value of fetal brain MRI in mild ventriculomegaly

Ten studies evaluated the additive value of fetal MRI in the diagnosis of clinically important additional structural defects , missed by ultrasound, with their detection eventually altering the management of the pregnancy and the counseling of the couple [13, 14, 22, 23, 24, 25, 26, 27, 28, 29] (▶ **Table 2**). Seven of the included studies investigated the brain anatomy by using multiplanar assessment techniques, while thorough brain assessment was not performed in the remaining 3 studies. A total of 1266 fetuses with mild VM had a fetal brain MRI with 946 of those (74.7%) having been previously assessed using multiplanar ultrasound methods. The detection rate of additional brain defects with fetal MRI that eventually altered the clinical management and outcome ranged from 0% to 19.5% with a mean of 12.3% (156/1266 cases). The mean detection rate was similar (120/946, 12.7%) in the studies that evaluated brain anatomy using multiplanar sonographic techniques.

Mild fetal ventriculomegaly and genetic and karyotypic abnormalities

Seven studies investigated the association between mild VM and the presence of underlying chromosomal or other genetic anomalies [15, 16, 17, 18, 19, 20, 21], including a total of 747 cases (▶ **Table 3**). In 5 out of the 7 included studies, both conventional karyotype and CMA were offered while in 2 studies the investigators offered only the standard karyotypic assessment. Five of the studies included only isolated cases of mild VM while in the remaining 2 the group under investigation included both isolated and non-isolated mild VM cases (fetuses with additional structural defects were considered non-isolated cases). The rate of chromosomal or other genetic anomalies ranged from 1.1% to 15.4% with a total of 50 fetuses being affected by underlying genetic aberrations based on the studies under investigation (50/777, 6.4%). In isolated mild VM cases after a thorough ultrasound assessment, this rate appeared to be even lower at 3.6% (19/527 fetuses).

Discussion

Mild ventriculomegaly and neurodevelopmental impairment

Within the existing body of literature, there is a scarcity of extensive, long-term investigations that specifically examine minor neurodevelopmental abnormalities, such as attention deficit disorders, behavioral problems, and learning disabilities [12, 30, 31]. Moreover, the limited studies available present conflicting findings. Although a number of studies documented impairment in attention and working memory, such issues do not appear to diminish overall cognitive capacities, but they may potentially impact academic achievement in the future [32]. It is important to highlight that there is considerable variability in the documented prevalence of neurodevelopmental delay [33]. However, aggregated findings from prior reviews indicate an estimated range of ap-

▶ **Table 1** Included studies investigating the association between mild fetal ventriculomegaly and neurodevelopmental impairment. Abbreviations: CMA: Chromosomal Microarray Analysis, TORCH: Toxoplasma, Other, Rubella, Cytomegalovirus, Herpes, MRI: Magnetic Resonance Imaging, NS: Not stated.

Year	Study	Type of study	Inclusion criteria	Exclusion criteria	No. of cases	Mild ventriculomegaly definition (mm)	Additional defects	Assessments offered	Length of follow-up	Mode of follow-up	Normal outcome (%)
2021	Sun et al.	Prospective Cohort Study	Transverse diameter of one or both ventricular atria between 10.0 and 15.0 mm	Preterm labor <36 weeks, presence of additional defects on US or MRI, presence of chromosomal abnormalities on karyotype or CMA, presence of congenital infections, no informed consent provided, patients lost to follow-up	60	10–12	Isolated	Karyotype, TORCH screening, MRI	NS	Age and Stage Questionnaires Third Edition (ASQ-3)	55/60 (91.7)
2021	Lok et al.	Retrospective Cohort Analysis	Transverse diameter of one or both ventricular atria of more than 10.0 mm	Incomplete data, not delivered in the unit, no informed consent provided	84	10–11.9	Isolated and non-isolated	Karyotype, TORCH screening, MRI	NS	NS	28/31 (90.3)
2022	Griffith et al.	Prospective Cohort Study	Transverse diameter of one or both ventricular atria between 10.0 and 12.0 mm	No informed consent provided, Contraindications for fetal MRI	42	10–12	Isolated	MRI	NS	Bayley Scales of Infant and Toddler Development – Third Edition (BSID3) or Ages and Stages Questionnaire third Edition (ASQ3)	35/42 (83)

▶ **Table 1** (Continuation)

Year	Study	Type of study	Inclusion criteria	Exclusion criteria	No. of cases	Mild ventriculomegaly definition (mm)	Additional defects	Assessments offered	Length of follow-up	Mode of follow-up	Normal outcome (%)
2018	Scelsa et al.	Case Series	Transverse diameter of one or both ventricular atria between 10.0 and 15.0 mm	Presence of additional defects on US or MRI, presence of chromosomal abnormalities on karyotype or CMA, presence of congenital infections, progression of ventriculomegaly or aqueductal stenosis, no informed consent provided	59	10–15	Isolated	Karyotype, TORCH screening, MRI	NS	Griffith test	55/59 (93.3)
2018	Thorup et al.	Nationwide registry-based study	Transverse diameter of one or both ventricular atria between 10.0 and 15.0 mm	Presence of additional defects on US or MRI, presence of chromosomal abnormalities on karyotype or CMA, presence of congenital infections, presence of thrombocyte antibodies, no informed consent provided	122	10–15	Isolated	Karyotype, TORCH screening, MRI	2–7 years	NS	101/107 (94.4)
2011	Gómez-Arriaga et al	Retrospective Cohort Study	Transverse diameter of one or both ventricular atria between 10.0 and 12.0 mm	Presence of additional defects on US or MRI, presence of chromosomal abnormalities, presence of congenital infections, terminated pregnancies stillbirths, patients lost to follow-up, no informed consent provided	18	10–12	Isolated	Karyotype, TORCH screening, MRI	NS	Battelle Developmental Inventory Screening Test (BDIST)	13/18 (72)

▶ **Table 1** (Continuation)

Year	Study	Type of study	Inclusion criteria	Exclusion criteria	No. of cases	Mild ventriculomegaly definition (mm)	Additional defects	Assessments offered	Length of follow-up	Mode of follow-up	Normal outcome (%)
2013	Kutuk et al.	Retrospective Cohort Study	Transverse diameter of one or both ventricular atria between 10.0 and 12.0 mm	Presence of additional defects on US or MRI, progression to transverse diameter of one or both ventricular atria more than 15 mm, presence of chromosomal abnormalities, presence of congenital infections, patients lost to follow-up, no informed consent provided	25	10–12	Isolated	Karyotype, TORCH screening, MRI	NS	Battelle Developmental Inventory Screening Test (BDIST)	16/25 (64)
2014	Pasquini et al.	Retrospective Cohort Study	Transverse diameter of one or both ventricular atria between 10.0 and 15.0 mm	Transverse diameter of one or both ventricular atria more than 15 mm, incomplete maternal serologic evaluation for infections, patients lost to follow-up, no informed consent provided	141	10–15	Isolated and non-isolated	Karyotype, TORCH screening, MRI	10–60 months	NS	135/140 (96.4)
2016	Tonni et al.	Prospective cohort study	Transverse diameter of one or both ventricular atria between 10.0 and 15.0 mm	No informed consent provided	54	10–15	Isolated and non-isolated	Karyotype, TORCH screening, MRI	12–48 months	Griffith test	48/54 (88.8)

▶ **Table 2** Included studies investigating the additive value of fetal brain MRI in mild ventriculomegaly. Abbreviations: iuMR: Intrauterine Magnetic Resonance.

Year	Study	Type of study	Inclusion criteria	Exclusion criteria	No. of cases	Mild ventriculomegaly definition (mm)	Multiplanar neurosonography assessment	No. of additional defects (%)
2017	Griffiths et al.	Prospective cohort study	Pregnant women aged ≥16 years fetus with VM detected by USS	Contraindications to iuMR, no informed consent provided	244	10–12	Not performed	14/244 (5.7 %)
2017	Lavongtheung et al.	Retrospective Cohort Study	Transverse diameter of one or both ventricular atria between 10.0 and 12.0 mm	Presence of chromosomal abnormalities on karyotype, presence of congenital infections, no contraindications to iuMR, no informed consent provided	12	10–12	Not performed	0/12 (0 %)
2017	Mehlhorn et al.	Retrospective Cohort Study	Transverse diameter of one or both ventricular atria between 10.0 and 15.0 mm	Presence of chromosomal abnormalities on karyotype, presence of congenital infections, no contraindications to iuMR, no informed consent provided	24	10–15	Not performed	3/24 (12.5 %)
2016	Tonni et al.	Prospective cohort study	Transverse diameter of one or both ventricular atria between 10.0 and 15.0 mm	Contraindications to iuMR, no informed consent provided	54	10–15	Performed	7/54 (13 %)
2015	Baffero et al.	Retrospective Cohort Study	Transverse diameter of one or both ventricular atria between 10.0 and 15.0 mm	Presence of additional defects on US, presence of chromosomal abnormalities on karyotype, presence of congenital infections	118	10–15	Performed	6/118 (5 %)
2015	Kandula et al.	Prospective cohort study	Transverse diameter of one or both ventricular atria between 10.0 and 12.0 mm	Contraindications to iuMR, no informed consent provided	40	10–12	Not performed	5/40 (12.5 %)
2014	Pasquini et al.	Retrospective Cohort Study	Transverse diameter of one or both ventricular atria between 10.0 and 15.0 mm	Transverse diameter of one or both ventricular atria more than 15 mm, incomplete maternal serologic evaluation for infections, patients lost to follow-up, no informed consent provided	132	10–15	Performed	7/132 (5.3 %)
2012	Parazzini et al.	Retrospective Cohort Study	Transverse diameter of one or both ventricular atria between 10.0 and 12.0 mm	MCDA pregnancies, previous abnormal pregnancies, parents' consanguinity	179	10–12	Performed	35/179 (19.5 %)

▲ **Table 2** (Continuation)

Year	Study	Type of study	Inclusion criteria	Exclusion criteria	No. of cases	Mild ventriculomegaly definition (mm)	Multiplanar neurosonography assessment	No. of additional defects (%)
2012	Miguelote et al.	Prospective cohort study	Transverse diameter of one or both ventricular atria between 10.0 and 15.0 mm	Presence of chromosomal abnormalities on karyotype	18	10–15	Performed	0/18 (0%)
2020	ENSO Working Group	Multicenter, retrospective, cohort study	Transverse diameter of one or both ventricular atria between 10.0 and 15.0 mm	Transverse diameter of one or both ventricular atria more than 15 mm, presence of additional defects on US, presence of chromosomal abnormalities, presence of congenital infections no informed consent provided	445	10–12	Performed	79/445 (17.7%)

proximately 10.9% to 12% [5, 34]. The present study findings indicate a reduced prevalence of neurodevelopmental delay, specifically at a rate of 11.6% (36/311), in isolated cases following a thorough investigation.

The observed disparity could perhaps be attributed to advancements in contemporary understanding of the connections between ventriculomegaly and enhanced prenatal detection of related anomalies, including agenesis of corpus callosum and posterior fossa abnormalities [35]. The decreased incidence of neurodevelopmental delay may additionally be attributed to the elimination of patients who exhibited accompanying abnormalities on postnatal imaging. However, the recorded number exceeded the predicted range of 2–3% for childhood impairment in the general population as determined by epidemiological studies [36, 37]. Nevertheless, there have been case-control studies that indicate a greater prevalence (10%) of neurodevelopmental delay in term fetuses that are anatomically normal and appropriate for their gestational age [38]. Furthermore, it can be highlighted that the systematic use of postnatal imaging in all instances would result in a higher proportion of related anomalies, thereby redefining the truly isolated group of mild VM, leading to a further reduction in the prevalence of neurodevelopmental delay.

The additive value of fetal brain MRI in mild ventriculomegaly

When considering mild VM, the additive value of fetal MRI becomes particularly relevant. While most studies have emphasized the role of MRI in assessing severe and intermediate VM, there is a debate regarding its role in mild VM.

The accuracy of ultrasound in detecting mild VM can be highly dependent on the experience of the sonographer. In some situations, access to neurosonography and advanced ultrasound equipment may be limited, making MRI a more reliable option.

Fetal position and movements may obstruct the view of certain structures during ultrasound, while MRI is less affected by these factors and can provide more consistent imaging.

In cases where mild VM is suspected but not definitively confirmed on ultrasound, MRI can be used to provide a more conclusive diagnosis.

MRI can confirm the presence of mild VM and reveal other associated brain abnormalities that can be missed on neurosonography alone in about 5% of cases.

The excellent tissue contrast of MRI makes this imaging technique ideal for the detection of cortical malformations, such as polymicrogyria, lissencephaly, schizencephaly, heterotopia, cerebellar hypoplasia, and corpus callosum agenesis.

Multiple studies have shown encouraging results regarding the use of MRI. In the study by Tonni et al., the performance of fetal MRI provided crucial information in 13% (7/54) of the included fetuses that significantly influenced the counseling process, antenatal management decisions, and the care planning undertaken by the multidisciplinary team. Subsequent postnatal assessments identified 6 cases (accounting for 11.1% of the total) with adverse neurodevelopmental outcomes [13].

▶ **Table 3** Included studies investigating the association between mild fetal ventriculomegaly and genetic and karyotypic abnormalities. Abbreviations: CMA: Chromosomal Microarray Analysis, NIPT: Noninvasive Prenatal Testing, IVM: isolated mild ventriculomegaly, n-IVM: non-isolated mild ventriculomegaly.

Year	Study	Type of study	Inclusion criteria	Exclusion criteria	No. of cases	Mild ventriculomegaly definition	Mode of assessment	Additional defects	No. (%)
2021	Lok et al.	Retrospective Cohort Analysis	Transverse diameter of one or both ventricular atria of more than 10.0 mm	Incomplete data, not delivered in the unit, no informed consent provided	84	10–11.9	Karyotype, CMA	Isolated and non-isolated	IVM: 3/55 (5.4%)
2022	Ryan et al.	Prospective Observational Study	Transverse diameter of one or both ventricular atria between 10.0 and 15.0 mm	Transverse diameter of one or both ventricular atria more than 15 mm, presence of additional defects, incomplete data, no informed consent provided	213	10–12	NIPT, Karyotype, CMA	Isolated and non-isolated	14/91 (15.4%)
2020	Huang et al	Retrospective Cohort Study	Transverse diameter of one or both ventricular atria between 10.0 and 15.0 mm, presence or absence of additional defects on US or MRI, singleton pregnancy, consent to invasive diagnostic procedure	Transverse diameter of one or both ventricular atria more than 15 mm, multiple pregnancy, abnormal family history, declined invasive diagnostic procedure, incomplete data, no informed consent provided	334	10–15	Karyotype, CMA	Isolated and non-isolated	IVM: 2/175 (1.1%) n-IVM: 17/159 (10.7%)
2019	Hong -Lei Duan et al.	Retrospective Cohort Study	Transverse diameter of one or both ventricular atria between 10.0 and 15.0 mm	Transverse diameter of one or both ventricular atria more than 15 mm, presence of additional defects on MRI, incomplete data, no informed consent provided	101	10–15	Karyotype, CMA	Isolated	6/101 (6%)
2014	Gezer et al.	Retrospective Cohort Study	Transverse diameter of one or both ventricular atria between 10.0 and 15.0 mm	Transverse diameter of one or both ventricular atria more than 15 mm, incomplete data, no informed consent provided	96	10–15	Karyotype, CMA	Isolated	3/35 (8.6%)

▲ **Table 3** (Continuation)

Year	Study	Type of study	Inclusion criteria	Exclusion criteria	No. of cases	Mild ventriculomegaly definition	Mode of assessment	Additional defects	No. (%)
2015	Bijamia-Mahay et al.	Retrospective Cohort Study	Transverse diameter of one or both ventricular atria between 10.0 and 12.0 mm	Incomplete data, no informed consent provided	30	10–12	Karyotype	Isolated	1/30 (3.3 %)
2011	Sethna et al.	Prospective Cohort	Transverse diameter of one or both ventricular atria between 10.0 and 12.0 mm	Incomplete data, no informed consent provided	131	10–12	Karyotype	Isolated	4/131 (3.4 %)

In the study by Salomon et al., MRI that was performed in fetuses with isolated mild VM revealed additional anomalies in 5 % of the cases that were not visible during ultrasound assessment [39].

Similarly, in the study by Melhorn et al., MRI was able to provide additional information for 12.5 % of cases with fetuses with isolated mild VM, identifying colpocephaly, parenchymal atrophy, and decreased gyration of the fetal cerebral cortex [24].

In the study by Levine et al., MRI found additional anomalies in 13.5 % of fetuses, identifying porencephaly, polymicrogyria, schizencephaly, subependymal hemorrhage, spinal meningocele, encephalocele, congenital infarction and septo-optic dysplasia, which changed the final patient management [40].

According to Quahba et al., MRI was able to diagnose additional brain abnormalities in 15 out of 167 fetuses, including cortical malformations, absence of the septum pellucidum, agenesis of the cerebellar vermis not detected by ultrasound [41].

Valsky et al. highlighted the crucial role of fetal MRI, particularly in obese patients, where it differentiated severe ventriculomegaly from an initial diagnosis of mild VM by ultrasound and identified Germinal matrix hemorrhage in two additional cases [42].

In contrast, in the Parrazzini study, MRI revealed clinically relevant information in only 2 out of 197 patients, one with bilateral frontal schizencephaly with agenesis of the septum pellucidum and one with isolated agenesis of the septum pellucidum. Furthermore, in 9 cases, MRI reversed the ultrasonographic diagnosis of VM to normal-sized ventricles, favorably impacting counselling [27].

These findings emphasize the importance of MRI in the evaluation of mild VM, as it may identify previously undetected brain abnormalities and affect counselling and decision-making for both healthcare practitioners and expecting parents. The increased diagnostic specificity of MRI allows for more accurate postnatal outcome counselling, resulting in better-informed decisions by patients and those providing medical care to pregnant women and fetuses.

Mild ventriculomegaly and genetic and karyotypic abnormalities

The findings from the 7 included studies, investigating the association of mild ventriculomegaly (VM) with underlying chromosomal and other genetic anomalies, provide important insight into the prevalence and implications of such conditions in prenatal cases. The results shed light on the rates of chromosomal and other genetic anomalies in fetuses with mild VM. It is worth mentioning that in the majority of the studies, both conventional karyotype and chromosomal microarray analysis (CMA) were offered as diagnostic tools, highlighting the evolving landscape of genetic testing in prenatal care, with CMA offering new options regarding the identification of genetic abnormalities.

Moreover, current literature reports both isolated and non-isolated mild VM cases. The inclusion of non-isolated cases, where additional structural defects were identified, introduces an important distinction as these cases tend to be associated with a higher risk of genetic abnormalities. The overall rate of chromosomal and other genetic anomalies in these studies underscores the significance of genetic assessment in cases of mild VM, as these conditions can have a substantial impact on fetal and neonatal out-

comes. Interestingly, in the subgroup of isolated mild VM cases, the rate of genetic abnormalities appeared to be even lower. This finding suggests that in cases where mild VM is the sole identified anomaly, following a thorough ultrasound assessment, the likelihood of underlying genetic abnormalities is relatively reduced.

The aforementioned data emphasizes the importance of offering comprehensive genetic assessment, including CMA, to fetuses with mild VM identified, especially when additional structural anomalies are present. The relatively lower rate of genetic aberrations in isolated mild VM cases suggests that they may have a more favorable prognosis, although genetic evaluation remains an essential aspect of prenatal care for all cases of mild VM.

Strengths and Limitations

The main strength of the review lies on the fact that an extensive search strategy was applied in an effort to include all the available literature of the issue under review with our review comprising a sample size based on a total of 23 studies and 2644 cases. The credibility of evidence was also evaluated, proposing a high quality of evidence. Furthermore, it should be highlighted that the authors of the majority of the included studies offered a thorough and analytic investigation of ventriculomegaly by implementing a wide range of further diagnostic tools such as karyotype, chromosomal microarray analysis, TORCH screening, and fetal MRI in order for the fetal assessment to be complete.

We acknowledge that the present systematic review has several limitations including retrospective design, small sample size, studies that included both isolated and non-isolated ventriculomegaly cases, lack of stratification of the results according to the laterality or the progression of the dilatation, and the utilization of different tests to assess neurodevelopment. Among the included studies, 13 studies were retrospective cohorts, 2 of the included studies assessed both isolated and non-isolated cases and 5 different developmental screening tools were used. Furthermore, even though there are guidelines for performing fetal neurosonography, the expertise of examiner and the center affects the diagnostic interpretation of ultrasound images, making it challenging to standardize. It should be further stressed that there is an ongoing debate regarding the best time to evaluate neurodevelopmental outcomes, because certain problems could not be noticeable until a child reaches school age. However, we may point out that extending the follow-up period makes it more likely that confounding variables, such as socioeconomic or environmental factors, will skew the results and make it impossible to determine whether a disability is a direct result of the mild ventriculomegaly or other factors. It should be underlined that the majority of the studies in the review did not distinguish between neurodevelopmental disabilities that were mild, moderate, or severe, which represents an additional limitation. While the effect of mild delay on quality of life is arguable, we could contend that the effect of severe delay is much more pronounced. Therefore, it appears that distinguishing between “neurodevelopmental delay” and “neurological disability” is essential. In light of this, research on the prevalence of neurodevelopmental impairment rather than neurodevelopmental delay may prove more beneficial for clinical counseling in the future.

Conclusion

The prevalence of aneuploidy and genetic abnormalities in ventriculomegaly, especially in isolated cases, is reported to be quite low and the incidence of neurodevelopmental delay appears to be similar to that of the general population in cases that are apparently and truly isolated. Furthermore, the detection rate of additional abnormalities missed by ultrasound by means of fetal brain MRI is reported to be roughly 12 %, a rate which appears to be similar after either standard or multiplanar extended neurosonography techniques have been previously used. Due to the vast heterogeneity of the published studies regarding neurodevelopmental outcomes, large multicenter prospective studies that implement the same developmental screening tests and their follow-up periods extend through school age are required in order to determine the true likelihood of neurodevelopmental delay in fetuses with unilateral ventriculomegaly and other risk factors that may affect their postnatal prognosis and, as such, the subsequent consultation.

Conflict of Interest

The authors declare that they have no conflict of interest.

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