Original Article

Perinatal and neurodevelopmental outcomes of fetal isolated ventriculomegaly: a systematic review and meta-analysis

Fahimah Ali[1#], Fiona Gurung[1#], Surabhi Nanda[1,2], Spyros Bakalis[1,2], Srividhya Sankaran[1,2], Tomoki Arichi[3,4], Kypros H. Nicolaides[1,5], Panicos Shangaris[1,2,5,6]^

[1]Department of Women and Children's Health, School of Life Course & Population Sciences, King's College London, St Thomas' Hospital, London, UK; [2]Department of Women and Children, Guy's and St Thomas' NHS Foundation Trust, London, UK; [3]Research Department of Early Life Imaging, School of Biomedical Engineering and Imaging Sciences, King's College London, London, UK; [4]Department of Paediatric Neurosciences, Evelina London Children's Hospital, Guy's and St Thomas' NHS Foundation Trust, London, UK; [5]Harris Birthright Research Centre for Fetal Medicine, King's College Hospital, London, UK; [6]Peter Gorer Department of Immunobiology, School of Immunology & Microbial Sciences, Faculty of Life Sciences and Medicine, King's College London, London, UK

Contributions: (I) Conception and design: P Shangaris, F Ali, F Gurung; (II) Administrative support: S Nanda, S Bakalis, S Sankaran, T Arichi, KH Nicolaides, P Shangaris; (III) Provision of study materials or patients: None; (IV) Collection and assembly of data: F Ali, F Gurung; (V) Data analysis and interpretation: F Ali, F Gurung; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

[#]These authors contributed equally to this work as co-first authors.

Correspondence to: Dr. Panicos Shangaris, MSc, AFHEA, MRCOG, PhD. Department of Women and Children's Health, School of Life Course & Population Sciences, King's College London, St Thomas' Hospital, London, UK; Department of Women and Children, Guy's and St Thomas' NHS Foundation Trust, London, UK; Peter Gorer Department of Immunobiology, School of Immunology & Microbial Sciences, Faculty of Life Sciences and Medicine, King's College London, London, UK; Immunoregulation Laboratory, Faculty of Life Sciences & Medicine, 5th Floor, Bermondsey Wing, Guy's Hospital, London SE1 9RT, UK. Email: panicos.shangaris@kcl.ac.uk.

Background: Isolated fetal ventriculomegaly can have a range of consequences, ranging from mild neurodevelopmental delay to perinatal death; the extent of these consequences often depend on the severity of ventriculomegaly. This systematic review and meta-analysis aims to investigate the impact of the degree of ventricular dilatation on the risk of neurodevelopmental delay and adverse perinatal outcomes in fetuses diagnosed with isolated fetal ventriculomegaly from gestational week 15 onwards.

Methods: PubMed, Embase, Scopus and the Cochrane Library were searched electronically to identify studies investigating the prognosis of mild and/or severe isolated fetal ventriculomegaly. Articles were included if they reported neurodevelopmental or perinatal outcomes in fetuses prenatally diagnosed with isolated fetal ventriculomegaly from week 15 of gestation and onwards. Studies were excluded if they reported on non-isolated ventriculomegaly (IVM), failed to specify the degree of ventriculomegaly, were non-English papers, animal studies or published outside of the 21-year period of interest. Study quality was assessed by two independent reviewers using a modified version of the Newcastle-Ottawa Quality Assessment Scale. Ventriculomegaly was defined as either mild or severe when ventricular diameter measured as 10–15 or >15 mm, respectively. Meta-analyses were conducted for adverse neurodevelopmental outcome, intrauterine fetal demise and infant mortality.

Results: Following the removal of duplicates, the search yielded 2,452 citations, of which 23 studies were included and 8 were eligible for meta-analysis. There were 767 and 347 cases of mild and severe isolated fetal ventriculomegaly, respectively. Adverse outcomes were consistently reported at a higher rate in severe cases than mild. The relative risks of adverse neurodevelopmental outcome, intrauterine fetal demise and infant mortality were 4.24 [95% confidence interval (CI): 2.46–7.30], 4.46 (95% CI: 1.64–12.11) and 6.02 (95% CI: 1.73–21.00), respectively, upon comparison of mild versus severe cases of isolated fetal ventriculomegaly.

Conclusions: The likelihood of adverse neurodevelopmental and perinatal outcomes, including

^ ORCID: 0000-0003-2750-8405.

intrauterine and infant mortality, is increased in severe isolated fetal ventriculomegaly compared to mild isolated fetal ventriculomegaly.

Keywords: Isolated ventriculomegaly (IVM); neurodevelopment delay; perinatal outcomes; second trimester

Submitted Nov 15, 2023. Accepted for publication Mar 21, 2024. Published online Apr 24, 2024.
doi: 10.21037/tp-23-548
View this article at: https://dx.doi.org/10.21037/tp-23-548

Introduction

Background

Fetal ventriculomegaly is defined as an excessive enlargement of the cerebral ventricles, typically detected at the mid-pregnancy scan (1,2). Viewed from an axial plane on the ultrasound scan (USS), a ventricular atrium width of ≥10 mm usually indicates ventriculomegaly (3,4). The prevalence is estimated to be 0.3–1.5 per 1,000 births, with a slightly higher incidence amongst males compared to female fetuses (5-9). Ventriculomegaly may be associated with other intracranial findings (e.g., agenesis of the Corpus Callosum, Dandy-Walker malformation, or aqueductal stenosis) or in the context of systemic conditions which also include extracranial anomalies (e.g., Spinal dysraphism, Trisomy 21, or infections) (1). In the absence of additional findings, ventriculomegaly is reported as isolated ventriculomegaly (IVM) (1). This may be further classified according to the degree of ventricular enlargement (2). There are two main classifications: mild (10–15 mm) or severe (>15 mm), and mild (10–12 mm), moderate (13–15 mm) or severe (>15 mm) (1,7,8,10,11). However, even within these two classifications, there are variations in the diagnostic thresholds.

Highlight box

Key findings

- This review found that infants with mild isolated fetal ventriculomegaly has better outcomes compared to severe cases, with higher risks of adverse neurodevelopmental outcomes, intrauterine fetal demise and infant mortality associated with severe ventriculomegaly.

What is known and what is new?

- The adverse outcomes of non-isolated fetal ventriculomegaly and severe fetal ventriculomegaly are well documented.
- This review provides a comprehensive synthesis of data comparing outcomes between mild and severe ventriculomegaly, specifically with numerical data through meta-analysis.

What is the implication, and what should change now?

- The implications of these findings indicate that infants with mild isolated ventriculomegaly have better outcomes compared to those with severe cases. Clinicans can use the severity of ventriculomegaly, whilst in-utero, as a prognostic indicator to stratify patients into low and high-risk categories. Those with severe cases may require closer monitoring and more intensive interventions.

Rationale and knowledge gap

Assessment of the cerebral ventricles is an essential part of the routine pregnancy scan as it can be the first sign of abnormal brain development and poor perinatal and neurodevelopmental outcomes (11-13). In non-IVM, fetal outcomes are often related to the associated findings. Difficulties arise with IVM, where there are still uncertainties in the prognosis of affected fetuses. It is further complicated by the potential identification of other anomalies postnatally, in which case the IVM was not truly isolated and tends to be associated with a worse prognosis (14). There is a prevailing consensus indicating that the prognosis of IVM tends to be more favorable compared to non-IVM cases. Moreover, individual studies highlight the bleak prognosis associated with severe ventriculomegaly. Nevertheless, the existing literature lacks comprehensive synthesis of the available data on mild versus severe ventriculomegaly, thereby limiting our ability to quantify the relative risk of adverse outcomes (1,2,10,15,16).

A broad spectrum of outcomes have been reported for IVM, ranging from normal development to adverse perinatal outcomes (intrauterine fetal demise, infant death) and neurodevelopmental delay or disorders (hearing impairments, autism, cerebral palsy) (2,5,7,8,10,12). In general, however, previous papers suggest the majority of children with IVM have normal neurodevelopmental and perinatal outcomes, particularly in mild cases, where it has been reported that rates of abnormal neurodevelopment are similar to that of the general population (7,8,12,14,17). Several cohort studies and case-series have been conducted

investigating the differential outcomes associated with mild and severe ventriculomegaly; results from these studies appear to indicate a poorer prognosis for severe cases, with an association to varying degrees of neurodevelopmental outcome, as well as adverse perinatal outcomes (10,15,16,18). There appears to be a lack of systematic reviews and meta-analyses synthesising this data in order to create a stronger evidence base to support this correlation. The most up-to-date systematic reviews on isolated fetal ventriculomegaly fail to report on the differential outcomes in mild versus severe cases, which is fundamental for purpose of counselling (14). Thus, a comprehensive analysis on the impact of the degree of ventriculomegaly on the formerly stated outcomes is necessary, to fill a crucial gap in the existing literature.

Objective

Parents opt for termination of pregnancy in 3.5% of mild IVM cases and up to 52% in severe IVM cases (16). One study reports mortality to be as high as 40% in severe IVM (18). However, links between the degree of ventriculomegaly and neurodevelopmental outcome are less clear, with some papers suggesting that the degree of ventricular dilatation may contribute to the prognosis and outcomes of affected infants, whilst others report that is not important (1,2,10,15,16). Providing parents with accurate information on the prognosis of IVM is important to ensure that informed decisions can be made, depending on the degree of the IVM. Hence, the primary aim of this report is to undertake a systematic review and meta-analysis on the impact of the degree of fetal IVM on neurodevelopment and perinatal outcomes in affected fetuses, diagnosed prenatally at the anomaly scan. We hope that this information will aid clinicians in the counselling process for varying degrees of isolated fetal ventriculomegaly diagnosed at the anomaly scan. We present this article in accordance with the PRISMA reporting checklist (available at https://tp.amegroups.com/article/view/10.21037/tp-23-548/rc).

Methods

Search strategy

We created a protocol and registered it on Prospero (Registration No. CRD42021239300). In February 2021, two reviewers searched electronically on four medical research databases (PubMed, the Cochrane Library, Embase, and Scopus) using a combination of keywords, relevant medical subject heading (MeSH) terms and word variants for "ventriculomegaly", "perinatal outcome" and "neurodevelopment" (see Appendix 1). The search was limited to manuscripts published in the last 21 years only (1st February 2000 to 1st of February 2021). Data from studies prior to 2000 may be outdated, given the use of more advanced technology and techniques, such as magnetic resonance imaging (MRI). Furthermore, the electronic database search was conducted in February 2021, limiting us to manuscripts published up to 1st February 2021 at the latest. Additionally, we searched manually from the references of the included articles and previous reviews identified further relevant studies.

Eligibility criteria

Animal studies were excluded, as well as systematic and literature reviews, as this review solely included primary research. Eligible studies included cohort studies, case-control studies, case series, and randomised controlled trials on human subjects. Case reports and grey literature (e.g., conference abstracts, dissertations, etc.) also did not fulfil the eligibility criteria, so were excluded. We excluded non-English papers.

Participants were included if they were diagnosed with mild or severe IVM at 15 weeks of gestation or later; cases with non-IVM were excluded from analysis. Studies lacking clarity on the gestational age at diagnosis and not specifying that diagnosis was made prenatally were excluded. For the purpose of this review, we defined mild ventriculomegaly as a lateral atrium width of ≥10 and <15 mm, and severe ventriculomegaly as a lateral atrium width of ≥15 mm. We chose to classify ventriculomegaly as mild or severe, as studies have reported there to be little significant difference between mild and moderate ventriculomegaly (19,20). For our review, ventriculomegaly cases were categorised as isolated if, at the time of the initial diagnosis, there was an absence of other abnormalities; as such, cases of severe ventriculomegaly that progressed to hydrocephalus were included, as these cases were considered 'apparently' isolated at the time of diagnosis. Studies were excluded if they did not discriminate between the different degrees of ventriculomegaly or if measurements of the lateral atrium were not given.

The primary outcome of this review was presence or absence of neurodevelopmental delay in infants to school-age children, depending on the duration of follow-up. This was defined as any delay in the attainment of neurodevelopmental milestones in one or more of the

developmental domains (motor, cognitive, language and social) or the presence of a neurological disorder. Such neurological disorders included hearing impairment, intellectual disability, autism spectrum disorder, cerebral palsy and seizure disorder (19). Given the heterogeneity in the assessment of neurodevelopmental delay across the included studies, analysis of the severity of neurodevelopmental abnormality was not included as part of this review. Additionally, for the purpose of analysing data on neurodevelopmental delay, only the cases which were adequately followed up were included; thus, any cases which were lost to follow up, terminated or died before assessment of neurodevelopmental outcome could be made were excluded from analysis. The secondary outcomes of this review were intrauterine and infant mortality. We defined intrauterine fetal demise as death in utero, including miscarriage and stillbirth, and infant mortality was defined as death in the first year postnatally.

Study selection and data extraction

Two independent reviewers (F.A. and F.G.) were involved in study selection and data extraction. Initially, the search results were imported to EndNote X9.3.3 (Bld 15659) [2020] for duplicate removal. The remaining studies were imported to Rayyan (QCRI, 2021), where a second duplicate search was carried out. Using Rayyan, studies were categorised as 'include', 'exclude' or 'maybe' following title and abstract screening. Conflicts and uncertainties were resolved following discussion between the two reviewers. Full-text articles were retrieved and saved on Mendeley. The studies were included or excluded according to our criteria. Reasons for exclusion included the following: the gestational age at diagnosis was not specified or clear, the study included cases of non-IVM which were not distinguishable from IVM, the extent of ventriculomegaly was not specified or findings were reported without discriminating between the different degrees of ventriculomegaly. For studies which were categorised as 'maybe' by either reviewer and for which there were conflicting decisions, a consensus was reached between the two reviewers or through consultation with the third reviewer (P.S.).

The relevant data sets were extracted and noted on a data extraction template from Cochrane and tables were created to separate study data related to mild IVM and severe IVM. Baseline and study characteristics were collected for each study. The baseline characteristics we included were maternal age in years (median, mean, or range), gestational age at delivery in weeks (mean, median or range), birth weight in grams (mean, median or range), male to female ratio, ethnicity, and socioeconomic status. Study characteristics included the study design and period, gestational age at diagnosis in weeks, no. of cases of IVM, definitions of mild and severe IVM, and time of neurodevelopmental follow-up. For our outcomes, we extracted data on the number of cases of mild and severe IVM with normal and adverse neurodevelopmental outcomes, and the number of intrauterine and infant deaths. Terminated pregnancies and cases lost to follow-up were excluded from the total. Only live-born cases were included for the neurodevelopmental outcome. Where possible, we also kept notes on whether karyotyping and congenital infection screening were carried out, MRI scans, the progression of the IVM in utero, and the proportion of terminated pregnancies.

Assessment of bias

Included studies were assessed independently by the previously mentioned reviewers for their quality using the Newcastle-Ottawa scale (NOS). We modified the NOS to suit our review by removing an item from the selection criteria (selection of non-exposed cohort) and changing the comparability section to baseline characteristics as most of our papers did not have a control or a non-exposed cohort. The selection component was based on whether the cohorts selected were representative of the target population, what source was used to find potential participants with the exposure, and whether the study ensures that the outcome of interest had not already happened. The comparability component was based on whether the study reported on baseline characteristics such as sex, maternal age, gestational age at diagnosis, ethnicity, and socioeconomic status. The outcome section was based on how the study assessed their outcomes of interest, the duration, and completeness of follow-up data. A maximum of one star can be given to each item, except for comparability where the maximum is two stars (20). Based on the number of stars under each of the three components, we assessed the studies as having a good, fair, or poor quality. Studies of poor quality were excluded from the meta-analysis but included in the qualitative synthesis.

Statistical analyses/data synthesis

Meta-analysis was only implemented for studies that

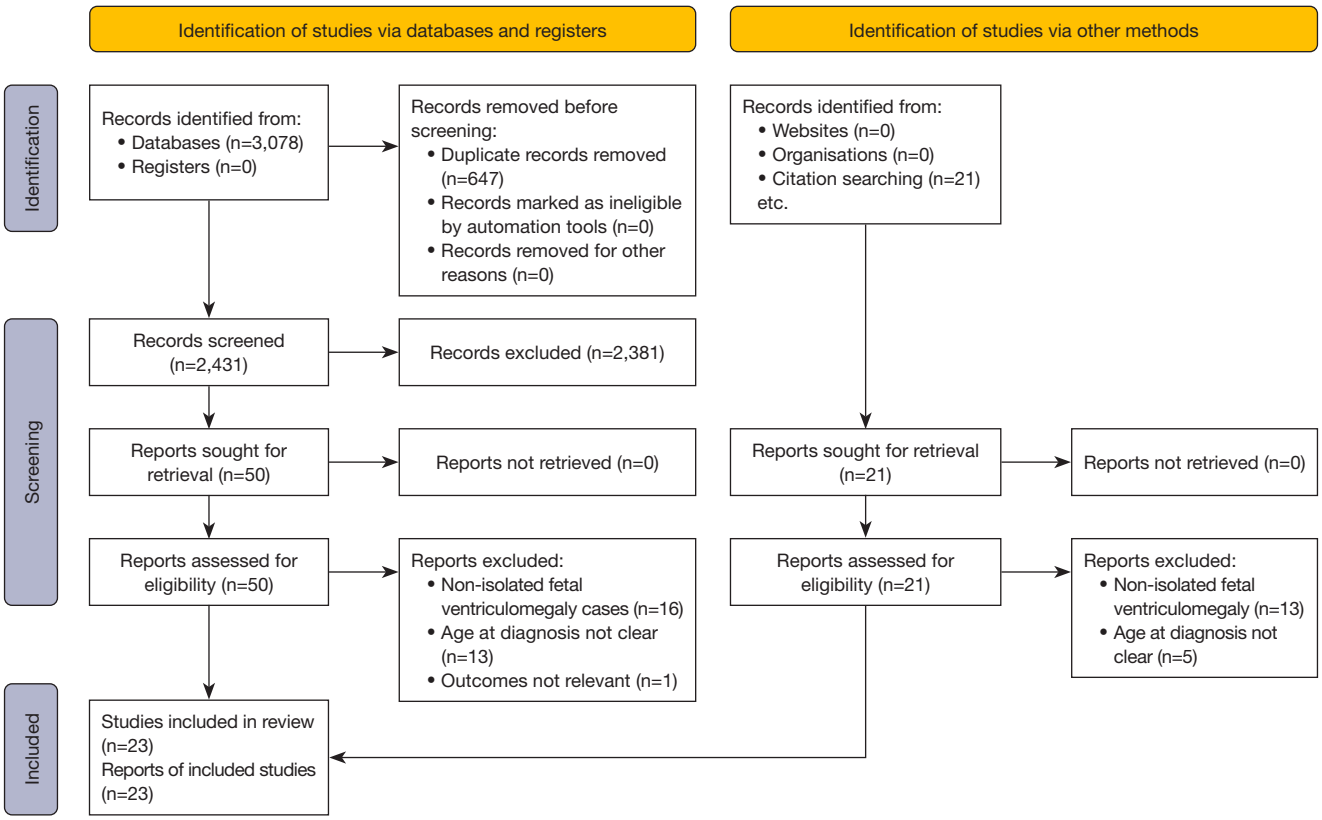

Figure 1 PRISMA flow diagram summarising the inclusion of studies on the prognosis of mild or severe cases of isolated fetal ventriculomegaly.

reported outcomes for both mild and severe cases of IVM; hence, any studies which failed to report on outcomes for both mild and severe ventriculomegaly could not be included in meta-analysis. Additionally, the number of studies included for meta-analysis for each outcome was dependent on whether the included studies reported on them. This resulted in variation between the number of studies available for each analysis. We used the software RevMan to create forest plots for the following outcomes: adverse neurodevelopmental outcomes (presence of neurodevelopmental delay or disorder), intrauterine death, and infant mortality. For adverse neurodevelopmental outcomes, only live-born cases of mild and severe IVM were included. Cases lost to follow-up were excluded. For intrauterine fetal demise and infant mortality, terminated pregnancies were excluded. For all three outcomes, we produced forest plots that used the Mantel-Haenszel statistical method and risk ratio for direct comparison of risks between mild and severe IVM. A random effects model, rather than a fixed effect model, was used. The forest plots produced by RevMan also generated values for Chi^2 and I^2. We used the Chi^2 value together with its P value to assess whether heterogeneity was present and the I^2 value was used to assess the importance of the between-study heterogeneity if present. A P value of <0.05 for the Chi^2 value was considered significant to reject the null hypothesis assuming no heterogeneity between the studies.

Results

Study selection

As demonstrated in *Figure 1*, 3,078 citations were identified through the electronic database search, in addition to 21 articles identified through hand-searching. Following the removal of duplicates, the number of studies eligible for title and abstract screening was 2,452. Of these, a total of 2,381 studies were excluded, resulting in 71 studies which were suitable for full-text screening. The process of full-text screening resulted in the exclusion of 48 studies which

did not meet the inclusion criteria. Ultimately, a total of 23 citations were eligible for inclusion, with eight of these studies meeting the criteria for our meta-analysis (5,7,8,10,12,15-18,21-34).

Study characteristics

The characteristics of the included studies are summarised in *Table 1*. There was moderate variation in the countries of origin, with the majority being high income settings. Although a handful of the papers describe their study design as 'case-series', based on definitions described by Dekkers *et al.* (35), nineteen were retrospective cohort studies, two were prospective cohort studies and one was defined as both a prospective and retrospective cohort study.

For majority of the studies, we obtained the gestational age at which diagnosis of isolated fetal ventriculomegaly was made. For two of the studies (23,31), this information was unclear or unreported and attempts were made to contact two authors to obtain the missing data, however, we failed to obtain any responses. There was a variability in the sample sizes, ranging from 19 to 159 subjects across the included studies.

The definitions of mild and severe ventriculomegaly as well as IVM are also reported in *Table 1*. In studies where 'moderate' ventriculomegaly was used as a category of severity, we grouped 'mild' and 'moderate' cases into one category. Overall, there seemed to be a consensus among the papers, defining IVM as 'the absence of associated abnormalities, a normal karyotype and negative infection screening'. Where neurodevelopmental delay was assessed, there was a variation in the period of follow-up, with majority of studies following infants for at least two years, with a range of 1 month to 14.6 years. A handful of the studies used assessment tools for neurologic and neurodevelopmental evaluation, including the Cognitive Adaptive Test/Clinical Linguistic and Auditory Milestone Scale (CAT/CLAMS), Griffith mental developmental scale, modified Amiel-Tison assessment, Battelle Developmental Inventory Screening Test (BDIST), strengths and difficulties questionnaire (SDQ) and the Bayley scales of infant and toddler development (8,16,21,23-25,29,32). The various methods of assessment employed in the papers reporting neurodevelopmental outcomes have been summarised in *Table 2*.

Numerous studies collected data on neurodevelopmental outcome using self-reported methods, including structured interviews and questionnaires (8,10,23,27,28,30,31,33) or by means of data collection through secure records (12,18,23,27). Self-reported methods were used to collect information on the achievement of developmental milestones, social skills and emotional-behavioural outcomes. Information on the diagnoses of specific impairments such as cerebral palsy, epilepsy and autism spectrum disorder were obtained via records or neurologic assessment.

Where possible, we summarised the baseline characteristics of the study populations in *Table 3*; it must be noted that in many instances there appeared to be missing data. All, but five studies, provide maternal age, with a range of 19 to 46 years. Furthermore, where it was reported, the average gestational age at delivery appeared to range from 22.2 to 42 weeks, however this was not always clear. Birthweight was scarcely reported, ranging from an average of 2,200 to 3,493.9 g. Interestingly, where the number of males and females were reported, it appears that males consistently outnumbered females in majority of the papers. Ethnicity was only reported in one study and socioeconomic status was reported in three.

Risk of bias of included studies

Quality assessment of the papers, using our modified NOS, was completed and majority of the included studies were of a 'fair' or 'good' quality. Moderate heterogeneity between the studies can be observed, particularly for baseline characteristics and outcome. Common areas of shortfall included the absence of specific baseline characteristics, which could influence outcomes. Another area of weakness falls within the assessment of outcome. As such, the use of self-report measures resulted in one or two stars. Alternatively, selection was strong throughout the bulk of the included studies. Patients with ventriculomegaly were usually identified from secure hospital records or databases. Two stars were awarded for selection in three papers, as patients were selected from tertiary hospitals, which may affect the representativeness of the sample.

Synthesis of results

Qualitative synthesis of outcomes for mild IVM

Outcomes were reported for 767 cases of mild isolated fetal ventriculomegaly across nineteen studies (5,7,8,10,12,15,16,18,21-25,28-31,33,34). Among these subjects, 578 surviving infants were assessed for

Table 1 Study characteristics of the 23 included papers on the prognosis of mild and/or severe isolated fetal VM

Paper	Country	Study design	Study period	Gestational age at diagnosis (weeks)	Fetuses with isolated ventriculomegaly (n)	Definitions of mild and severe VM	Definition of isolated VM	Time of neurodevelopmental follow-up
Graham *et al.* [2001], (25)	USA	Retrospective cohort	1994–1999 (5 yrs)	Implied 18–22	28	Mild: ventricular measurement of 10–15 mm, severe: >15 mm	Not given	Birth—4 yrs
Mercier *et al.* [2001], (7)	France	Retrospective cohort	1992–1998 (6 yrs)	18–37.5	26	Mild: ventricular atrial diameter of 10–15 mm at the time of initial diagnosis	Not given. Implied: cases with cerebral or extracerebral malformations (corpus callosum agenesis, porencephaly, Dandy Walker syndrome, holoprosencephaly, myelomeningocele, renal hydronephrosis), cerebral calcifications, abnormal antenatal karyotyping excluded	Mean 28 m. Range, 3 m–6 yrs
Leitner *et al.* [2004], (30)	Israel	Retrospective cohort	1994–1999 (5 yrs)	15–41	57	Dilation of the lateral ventricles of 10 to 12 mm	No other central nervous system anomalies present	3 m–3 yrs
Signorelli *et al.* [2004], (8)	Italy	Retrospective and prospective cohort	1992–2001 (9 yrs)	20–32	60	Mild: a transverse diameter of the ventricular atrium of ≥10 mm (4 standard deviations above the average of 7.6±0.6 mm between 15 and 40 gestational weeks) and ≤15 mm (study only considered 10–12 mm)	VM without any other identifiable anomaly (negative TORCH screening, associated anomalies, normal karyotype)	Prospective follow up 18 m. Retrospective follow up 3–10 yrs
Gaglioti *et al.* [2005], (10)	Italy	Retrospective cohort	1990–2000 (10 yrs)	15–39	78	The diameter of one or both lateral ventricles ≥10 mm	Not defined	2–12 yrs
Breeze *et al.* [2005], (21)	England	Prospective cohort	2001–2003 (2 yrs)	19–33	30	Mild: atrium of the lateral ventricle measured 10–15 mm	No other abnormalities, such as spina bifida	4 m
Kennelly *et al.* [2009], (27)	Ireland	Retrospective cohort	2000–2008 (8 yrs)	19–40 (GA at referral)	19	Mild: a ventricular width of 10–15 mm	The absence of associated cranial or extra-cranial abnormalities	10 m–6 yrs
Leitner *et al.* [2009], (31)	Israel	Retrospective cohort	1999–2002 (3 yrs)	24–36 (confirmation by MRI) US diagnosis may be done earlier. Emailed author to ascertain when US diagnosis was made—no reply	109	Mild: atrial width between 10 and 15 mm	Normal karyotype and serology for TORCH	Median: 4.4 yrs. Range, 3.08–5.96 yrs
Weichert *et al.* [2010], (15)	Germany	Retrospective cohort	1993–2007 (14 yrs)	12+4 to 38+4	47	Mild: 10–14.9 mm, severe ≥15 mm	Absence of associated structural malformations and/or chromosomal defects at the time of initial presentation.	Mean: 41.5 m. Range, 1–151 m
Madazli *et al.* [2011], (33)	Turkey	Retrospective cohort	2000–2008 (8 yrs)	15–39	23	Mild: 10 to 14.9 mm, severe ≥15 mm	No associated malformations	Median: 4.4 yrs. Range, 1–10 yrs

Table 1 (*continued*)

Table 1 (*continued*)

Paper	Country	Study design	Study period	Gestational age at diagnosis (weeks)	Fetuses with isolated ventriculomegaly (n)	Definitions of mild and severe VM	Definition of isolated VM	Time of neurodevelopmental follow-up
Sethna *et al.* [2011], (5)	England	Prospective cohort	1994–2008 (14 yrs)	18–24	159	Mild: lateral width of 10 and <15 mm	No associated anomalies identified by a specialist and no infection or karyotype abnormality detected	NA
Gómez-Arriaga *et al.* [2012], (24)	Spain	Retrospective cohort	2002–2008 (6 yrs)	19–33	18	Mild: a transverse diameter of one or both ventricular atria between >10.0 mm and equal to or less than 12.0 mm	Absence of associated anomalies	Mean: 4.9 yrs. Range, 1–8 yrs
Hannon *et al.* [2012], (26)	UK	Retrospective cohort	1994–2008 (14 yrs)	20–31	79	Severe ventriculomegaly, defined as a lateral atrium width of 15 mm or greater at any week of gestation	Prenatally isolated cases of severe ventriculomegaly were defined as those with no additional complications	NA
Kutuk *et al.* [2013], (29)	Turkey	Retrospective cohort	2006–2010 (4 yrs)	17–34	25	Mild VM was defined as the diameter of one or both lateral ventricles ≥10 and ≤12 mm	VM was defined as isolated when prenatal and postnatal evaluation revealed no other cranial or extracranial malformation, perinatal infection, or karyotype abnormalities	Mean: 45.9 m. Range, 24–77 m
Tugcu *et al.* [2014], (34)	Turkey	Retrospective cohort	2006–2013 (7 yrs)	16–37	21	Mild: 10–15 mm; severe: >15 mm	If there are not any intracranial or extracranial abnormalities, it is termed as “isolated” severe VM	NA
Chu *et al.* [2016], (18)	China	Retrospective cohort	2004–2013 (9 yrs)	18–36	66	Mild: 10–12 mm; moderate: 13–15 mm; severe: >15 mm	The fetuses were also classified as “Isolated Ventriculomegaly” (IVM) if no associated anomaly was detected at the initial ultrasonography with negative findings in TORCH screening and karyotype examinations	1 m–9 yrs
Gezer *et al.* [2016], (23)	Turkey	Retrospective cohort	2007–2009 (2 yrs)	Unspecified—emailed author no reply	20	VM was defined as mild when the dimension of the atrium of lateral ventricle was between 10 to 15 mm and severe when it was above 15 mm	No definition given	6–24 m
Kumar *et al.* [2020], (28)	India	Prospective cohort	2010–2018 (8 yrs)	Range not given. Mean: 30.8±6.7	115	It was mild if it measured less than 15 mm, severe, if more than 15 mm	Ventriculomegaly was considered isolated if no ultrasound evidence of associated structural malformations were observed either on ultrasound or after birth	2 yrs

Table 1 (*continued*)

Table 1 (*continued*)

Paper	Country	Study design	Study period	Gestational age at diagnosis (weeks)	Fetuses with isolated ventriculomegaly (n)	Definitions of mild and severe VM	Definition of isolated VM	Time of neurodevelopmental follow-up
Winkler *et al.* [2018], (16)	Switzerland	Retrospective cohort	1999–2011 (12 yrs)	18–35	55	Mild: 10–11.9 mm; moderate: 12–14.9 mm; severe: ≥15 mm	No definition given but exclusion criteria: prenatal diagnosis of aneuploidy, intrauterine infection, myelomeningocele, structural cerebral anomaly or structural extracerebral malformation	Median: 7.2 yrs. Range, 2.1–14.6 yrs
Ge *et al.* [2021], (17)	USA	Retrospective cohort	2008–2015 (7 yrs)	18.3–39.6	26	Severe VM defined as a maximum atrial width of the lateral ventricle ≥15 mm	When other cranial or extracranial ultrasound abnormalities are not identified	Not assessed
Doğan Durdağ *et al.* [2019], (22)	Turkey	Retrospective cohort	2011–2017 (6 yrs)	18–35	56	Mild: 10–<12 mm; moderate: ≥12–<15 mm; severe: ≥15 mm	Lacking any accompanying cranial and/or extracranial anomalies on imaging, infection or chromosomal abnormality were evaluated as isolated ventriculomegaly	1–6 yrs
Thorup *et al.* [2019], (12)	Denmark	Retrospective cohort	2008–2014 (6 yrs)	18–22	133	Mild: 10–15 mm lateral ventricular diameter	No sonographic evidence of an associated structural abnormality detected on the second-trimester anomaly scan (18–22 weeks' gestation). Cases with abnormal MRI, TORCH, thrombocyte antibodies, fetal karyotype or CMA before 22 weeks were excluded and the included cases were therefore presumed to be isolated	2–7 yrs
Litwinska *et al.* [2019], (32)	Poland	Retrospective cohort	2010–2015 (5 yrs)	Didn't specify GA at diagnosis, but shunt was inserted median 25 weeks (20–33 weeks)	44	Severe: lateral ventricular width >20 mm	Absence of other major abnormalities, normal karyotype, and negative maternal infection screen	2 yrs

VM, ventriculomegaly; yrs, years; GA, gestational age; MRI, magnetic resonance imaging; US, ultrasound; TORCH, toxoplasmosis, others (syphilis, hepatitis B), rubella, cytomegalovirus, herpes simplex; m, months; CMA, chromosomal microarray; N/A, not applicable.

Table 2 A table summarising the tools by which neurodevelopment was assessed

Paper	Specific tests and methods of assessment
Graham *et al.* [2001], (25)	CAT/CLAMS
Mercier *et al.* [2001], (7)	No explanation of method of assessment
Leitner *et al.* [2004], (30)	Telephone interview with parents, conducted by two senior pediatric neurologists
Signorelli *et al.* [2004], (8)	Griffith scale, interviews with parents and gathering of anamnestic data regarding every development area
Gaglioti *et al.* [2005], (10)	Structured interviews with parents
Breeze *et al.* [2005], (21)	Modified Amiel-Tison Technique and assessment of neurodevelopmental milestones
Kennelly *et al.* [2009], (27)	Records and telephone interview using detailed structured questionnaire
Leitner *et al.* [2009], (31)	Examination of physical and neurologic status and special tests of brain maturation. Cognitive outcome evaluated by developmental psychologist, using K-ABC. Parents completed questionnaires
Weichert *et al.* [2010], (15)	Neuropediatric assessment
Madazli *et al.* [2011], (33)	Telephone interviews with the parents
Gómez-Arriaga *et al.* [2012], (24)	BDIST: mean and SDs in each domain calculated to classify patients either as normal, borderline, mild retardation or severe retardation
Kutuk *et al.* [2013], (29)	Data obtained via telephone interview and assessed using BDIST
Chu *et al.* [2016], (18)	Reported specific neurodevelopmental outcomes including hearing loss, strabismus and hearing loss, optic nerve abnormalities and mental retardation
Gezer *et al.* [2016], (23)	Denver Developmental Screening Test, audiometric test, weight, height and head circumference. Unable to be followed up: parental questionnaire via phone call and collection of patient files
Kumar *et al.* [2020], (28)	Questionnaire about developmental milestones
Winkler *et al.* [2018], (16)	SDQ score
Doğan Durdağ *et al.* [2019], (22)	This paper did not define what neurodevelopmental delay is nor did they differentiate between mild and severe neurodevelopmental outcomes
Thorup *et al.* [2019], (12)	ICD diagnoses of: intellectual disability, cerebral palsy, epilepsy, impaired psychomotor development or ASDs
Litwinska *et al.* [2019], (32)	Bayley scale

CAT/CLAMS, the Cognitive Adaptive Test/Clinical Linguistic and Auditory Milestone Scale; K-ABC, The Kaufman Assessment Battery for Children; BDIST, the Battelle Developmental Inventory Screening Test; SD, standard deviation; SDQ, strengths and difficulties questionnaire; ICD, International Classification of Diseases; ASD, autism spectrum disorder.

neurodevelopmental delay in seventeen studies, of which 64 (11.1%) had adverse neurodevelopmental outcomes. Across the fourteen studies reporting on the rate of intrauterine fetal demise, 13 (2.0%) of 648 infants died in utero. In addition, for infant mortality, there were 9 (1.6%) infants who died in the perinatal period out of 560 subjects across twelve studies.

Few studies reported the number of preterm births and low birth weight infants as outcomes in mild IVM. Across the three studies reporting on the number of preterm births, the rate at which this outcome occurred was 10 (14.3%) out of 70 births (7,24,29). One studied reported the number of low-birth-weight infants, which was 0 out of 27 infants with mild IVM (29). These outcomes are summarised in *Table 4*.

Qualitative synthesis of outcomes for severe IVM

Thirteen papers reported outcomes for severe isolated fetal ventriculomegaly, corresponding to 347 cases (10,15-18,22,23,25-28,32,33). Neurodevelopmental outcomes were reported in eleven studies and adverse neurodevelopment was observed in 73 (58.4%) of 125

Table 3 Summary of the baseline characteristics of the study populations from the 23 included studies

Paper	Maternal age in years, median/mean [range]	Gestational age at delivery in weeks, median/mean [range]	Birth weight in grams, median/mean [range]	Infant sex, M:F given as 1:(F)	Ethnicity, n [%]	Socioeconomic status[†]
Graham *et al.* [2001], (25)	NR	NR	NR	1:0.67	NR	NR
Mercier *et al.* [2001], (7)	Mean: 28 [19–40]	No average. 23 term, 3 preterm	NR	1:0.24	NR	NR
Leitner *et al.* [2004], (30)	NR	NR	NR	NR	NR	NR
Signorelli *et al.* [2004], (8)	Mean: 29.6	NR	3,250	1:0.81	NR	NR
Gaglioti *et al.* [2005], (10)	NR	NR	NR	Groups B and C ratio close to 1. Group A—1:0.63	NR	NR
Breeze *et al.* [2005], (21)	NR	NR	NR	NR	NR	NR
Kennelly *et al.* [2009], (27)	Median: 30	Mean: 38.5 [33–42]; 1 born preterm	Mean: 3,469 [2,360–4,960]	1:0.7 (59% M)	NR	NR
Leitner *et al.* [2009], (31)	NR	NR	NR	1:0.62	NR	Maternal and paternal education, and economic status given. No significant differences
Weichert *et al.* [2010], (15)	Mean: 28.7 [18–45]	Mild: 37+0, severe: 36+6	Mild: 3,065, severe: 3,345	1:0.81	NR	NR
Madazli *et al.* [2011], (33)	Mean: 26.8±5 [17–40]	NR	NR	NR	NR	NR
Sethna *et al.* [2011], (5)	Median: 27 [15–46]	Median: 39 [31–42]	Median: 3,300	1:0.78	NR	NR
Gómez-Arriaga *et al.* [2012], (24)	Mean: 29 [20–38]	Mean: 38 [34–41]; 4 preterm births (22.2)	NR	1:0.64	NR	NR
Hannon *et al.* [2012], (26)	Median: 27 [17–42]	Median: 37 [27–41]	Median: 2,900	1:0.94	NR	NR
Kutuk *et al.* [2013], (29)	Mean: 26.28 [18–39]	Mean: 38.64 [36–41]	Mean: 3,302.8 [2,800–3,900]	1:0.79	NR	NR
Tugcu *et al.* [2014], (34)	Mean: 28.58 [17–41]	NR	NR	1:0.90	NR	NR
Chu *et al.* [2016], (18)	Mean: 28 [19–44]	NR	NR	NR	NR	NR
Gezer *et al.* [2016], (23)	NR	NR	NR	NR	NR	NR
Kumar *et al.* [2020], (28)	Mean: 25.1±3.67 (18 to >38)	No mean or range given. Majority in the >37 category	Mean: 2,200±4,200	1:1	NR	Low: 76 (28.9%), middle: 156 (59.3%), high: 31 (11.8%)

Table 3 (*continued*)

Table 3 (*continued*)

Paper	Maternal age in years, median/ mean [range]	Gestational age at delivery in weeks, median/mean [range]	Birth weight in grams, median/ mean [range]	Infant sex, M:F given as 1:(F)	Ethnicity, n [%]	Socioeconomic status†
Winkler *et al.* [2018], (16)	Mean: 33.4 [22–45]	Mean: 38 [29–41]	Mean: 3,010 [1,025–4,050]	NR	NR	Mean: 4.85 [2–11]‡
Ge *et al.* [2021], (17)	18–43	Accelerator: 34.7±2.7. Plateau: 37.1±2.5*	NR	1:0.63	Caucasian: 20 [77]. Non-Caucasian: 6 [23]	NR
Doğan Durdağ *et al.* [2019], (22)	Mean: 29.02	NR	NR	NR	NR	NR
Thorup *et al.* [2019], (12)	Mean: 29.7±4.9	Median: 40.3	Mean: 3,493.9 [3,364.9–3,622.8]	1:0.44	NR	NR
Litwinska *et al.* [2019], (32)	NR	Median: 37 [28–39]	Median: 2,690 [1,350–3,770]	NR	NR	NR

*, study population was split into two groups, accelerator or plateau, and gestational age at delivery was reported separately for these; †, three studies reported socioeconomic status. Leitner *et al.* did not publish specific data on socioeconomic status, however, they reported no key differences within the cohort. Kumar *et al.* reported the number and percentage of low-, middle- and high-income participants within the study population. Winkler *et al.* reported a mean and range for socioeconomic status, measured using a 6-point scale according to paternal occupation and maternal education; ‡, mean and range for socioeconomic status as reported by Winkler *et al*. 2018, measured using a 6-point scale according to paternal occupation and maternal education. M, male; F, female; NR, not reported.

surviving infants. Furthermore, across eleven studies 74 (24.3%) out of 304 infants died in utero. To add to this, thirteen studies reported infant mortality; across these papers 36 (17.1%) infants out of 211 died postnatally.

Again, there was little data on the rates of preterm births and low birth weight infants across the studies. Two studies investigated the number of preterm births, resulting in 14 (33.3%) premature infants out of 42 livebirths with severe isolated fetal ventriculomegaly (27,32). As for the number of low-birth-weight infants, one study reported zero low birth weight infants out of a total of 12 livebirths (27). These outcomes are summarised in *Table 5*.

Quantitative synthesis—meta-analysis

Meta-analysis was used to compare the risk of neurodevelopmental delay, intrauterine fetal demise and infant mortality in fetuses with mild versus severe isolated fetal ventriculomegaly. These findings are summarised in *Table 6*.

Eight studies were included to assess the neurodevelopmental outcomes (*Figure 2*) in 331 infants with mild versus severe isolated fetal ventriculomegaly (10,15,16,18,22,25,28,33). The number of infants diagnosed with mild and severe IVM was 249 (75.2%) and 82 (24.8%), respectively. Among the 249 cases of mild IVM, there were 21 (8.43%) cases of neurodevelopmental delay. Contrastingly, there were 37 (45.1%) cases of neurodevelopmental delay among the 82 cases of severe IVM. Subjects with severe isolated fetal ventriculomegaly had 4.24 [95% confidence interval (CI): 2.46–7.30] times the risk of developing neurodevelopmental delay compared to those with mild isolated fetal ventriculomegaly. In addition, the χ^2 test for heterogeneity was non-significant, with a P value of >0.05 and the I^2 value was 0%. This suggests that there is little between-study variability.

Six studies (*Figure 3*) were used to investigate the risk of intrauterine fetal demise in mild *vs.* severe cases of fetal ventriculomegaly (10,16,22,25,28,33). Among the 324 fetuses, the number of fetuses diagnosed with mild and severe isolated fetal ventriculomegaly was 186 (57.4%) and 138 (42.6%), respectively. Of those with mild ventriculomegaly, there were 5 (2.69%) cases of intrauterine fetal demise. There were 64 (46.4%) cases of intrauterine fetal demise in those with severe ventriculomegaly. Thus, for subjects with severe isolated fetal ventriculomegaly there was a relative risk of 4.46 (95% CI: 1.64–12.11) of intrauterine fetal demise compared to those with mild isolated fetal ventriculomegaly. Moreover, the χ^2 test for heterogeneity was non-significant, with a P value >0.05 and the I^2 value was 0%. Again, this indicates a lack of heterogeneity between the studies.

Table 4 A table summarising the neurodevelopmental and perinatal outcomes for mild isolated fetal ventriculomegaly, reported across a total of 19 studies

Paper	Mild isolated ventriculomegaly (n)	Neurodevelopmental delay (n/survivors)	Intrauterine death (n/total)	Infant mortality (n/livebirths)	Preterm birth <37 weeks (n/livebirths)	LBW, <2,500 g (n/livebirths)
Graham *et al.* [2001], (25)	19	2/19	0/19	0/19	–	–
Mercier *et al.* [2001], (7)	22	4/22	–	–	3/25	–
Leitner *et al.* [2004], (30)	37	9/37	–	–	–	–
Signorelli *et al.* [2004], (8)	60	0/60	0/60	0/60	–	–
Gaglioti *et al.* [2005], (10)	53	5/51	1/53	1/52	–	–
Breeze *et al.* [2005], (21)	21	4/21	0/21	–	–	–
Leitner *et al.* [2009], (31)	28	6/28	–	–	–	–
Weichert *et al.* [2010], (15)	14	1/14	–	–	–	–
Madazli *et al.* [2011], (33)	9	1/7	0/9	1/9	–	–
Sethna *et al.* [2011], (5)	136	–	4/136	4/132	–	–
Gómez-Arriaga *et al.* [2012], (24)	18	4/18	–	–	4/18	–
Kutuk *et al.* [2013], (29)	28	9/25	1/28	1/27	3/27	0/27
Tugcu *et al.* [2014], (34)	21	–	0/21	0/21	–	–
Chu *et al.* [2016], (18)	58	2/58	0/58	0/58	–	–
Gezer *et al.* [2016], (23)	11	1/11	0/11	0/11	–	–
Kumar *et al.* [2020], (28)	20	1/18	2/20	0/18	–	–
Winkler *et al.* [2018]*, (16)	30	Motor: 5/28; visual: 5/28; hearing: 2/29; epilepsy: 3/28; learning problems: 5/28; emotional/ behavioural: 2/28	1/30	0/29	–	–
Doğan Durdağ *et al.* [2019], (22)	55	4/54	1/55	–	–	–
Thorup *et al.* [2019], (12)	127	6/107	3/127	2/124	–	–
Total (%)	767	64/578 (11.1)	13/648 (2.0)	9/560 (1.6)	10/70 (14.3) inadequate data	Inadequate data

*, neurodevelopmental outcomes for this study were reported as separate categories; the author was contacted to obtain the raw data and overall rate of adverse neurodevelopmental outcome; however, a response was not obtained. So, for the purpose of qualitative and quantitative synthesis of results, rates of motor impairment were used. LBW, low birthweight.

Seven studies were included for meta-analysis to compare the rate of infant mortality in mild versus severe isolated fetal ventriculomegaly (10,15,16,18,25,28,33) (*Figure 4*). Of the 300 included infants, the number of subjects with mild and severe isolated fetal ventriculomegaly was 200 (66.6%) and 100 (33.3%), respectively. Infant mortality occurred in 3 (1.5%) of the subjects with mild ventriculomegaly and 20 (20%) of those with severe ventriculomegaly. Overall, the risk of infant mortality in those with severe isolated fetal ventriculomegaly was 6.02 (95% CI: 1.73–21.00) times the risk in subjects with mild isolated fetal ventriculomegaly. As for heterogeneity, the I^2 statistic was 19%, suggesting very little heterogeneity. The P value was >0.05 for the χ^2 test and therefore non-significant, suggesting that any between-study variability observed was due to chance.

The remaining perinatal outcomes which we aimed

Table 5 A table summarising the neurodevelopmental and perinatal outcomes for severe cases of isolated fetal ventriculomegaly, reported across a total of 13 studies

Paper	Severe isolated ventriculomegaly (n)	Neurodevelopmental delay (n/survivors)	Intrauterine death (n/total)	Infant mortality (n/live-births)	Preterm birth <37 weeks (n/live-births)	LBW, <2,500 g (n/live-births)
Graham *et al.* [2001], (25)	9	8/9	0/9	0/9	–	–
Gaglioti *et al.* [2005], (10)	11	3/8	0/11	3/11	–	–
Kennelly *et al.* [2009], (27)	17	9/10	5/17	2/12	1/12	0/12
Weichert *et al.* [2010], (15)	19	13/19	–	0/19	–	–
Madazli *et al.* [2011], (33)	6	1/2	1/6	3/5	–	–
Hannon *et al.* [2012], (26)	38	–	1/38	6/37	–	–
Chu *et al.* [2016], (18)	58	2/8	0/58	0/8	–	–
Gezer *et al.* [2016], (23)	9	2/6	1/9	2/8	–	–
Kumar *et al.* [2020], (28)	95	4/21	63/95	11/32	–	–
Winkler *et al.* [2018]*, (16)	16	Motor: 6/14; visual: 5/14; hearing: 0/14; epilepsy: 4/14; learning problems: 5/14; emotional/ behavioural: 2/11	0/16	3/16	–	–
Ge *et al.* [2021], (17)	24	–	–	3/24	–	–
Doğan Durdağ *et al.* [2019], (22)	1	0/1	0/1	–	–	–
Litwinska *et al.* [2019], (32)	44	25/27	3/44	3/30	13/30	–
Total (%)	347	73/125 (58.4)	74/304 (24.3)	36/211 (17.1)	14/42 (33.3) inadequate data	Inadequate data

A table summarising the neurodevelopmental and perinatal outcomes for severe cases of isolated fetal ventriculomegaly, reported across a total of 13 studies. *, neurodevelopmental outcomes for this study were reported as separate categories; the author was contacted to obtain the raw data and overall rate of adverse neurodevelopmental outcome; however, a response was not obtained. So, for the purpose of qualitative and quantitative synthesis of results, rates of motor impairment were used. LBW, low birthweight.

Table 6 Summary of findings—relative effects are demonstrated using RRs and absolute effects are demonstrated using RDs, with confidence intervals given in both instances

Outcomes	Number of infants [studies]	Relative effects		Absolute effects	
		RR	95% CI	RD	95% CI
Neurodevelopmental delay	331 [8]	4.24	2.46 to 7.30	0.35	0.14 to 0.55
Intrauterine fetal demise	324 [6]	4.46	1.64 to 12.11	0.12	–0.12 to 0.36
Neonatal and postnatal deaths	300 [7]	6.02	1.73 to 21.00	0.13	–0.01 to 0.28

RR, risk ratio; RD, risk difference; CI, confidence interval.

to investigate were preterm birth, low birthweight and admission to neonatal intensive care unit (NICU). Among our included studies, the data for these remaining outcomes was scarce. As a result, meta-analysis for these outcomes was not possible.

Discussion

Key findings

This systematic review and meta-analysis reports on the impact of the degree of isolated fetal ventriculomegaly

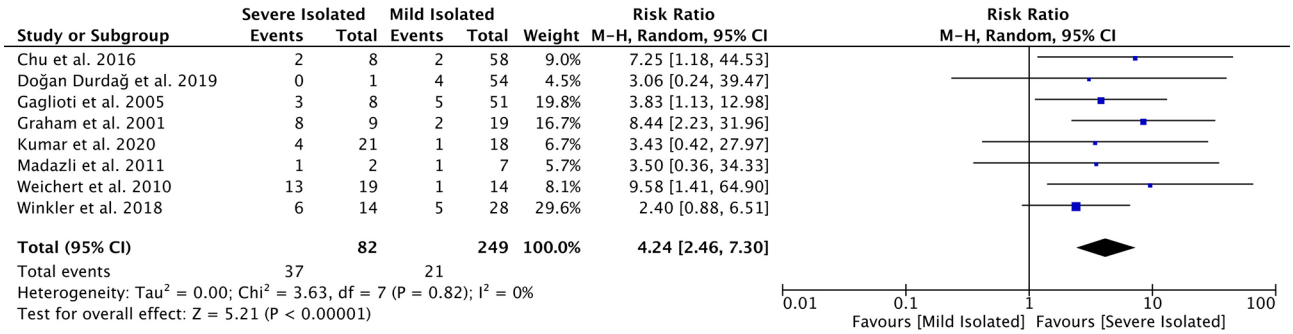

Figure 2 Forest plot of the proportion of subjects with neurodevelopmental delay in mild *vs.* severe isolated fetal ventriculomegaly, individually for each of the eight included studies and pooled for all studies. The relative risk of neurodevelopmental delay in severe cases was 4.24 (95% CI: 2.46–7.30) times the risk in mild cases of isolated fetal ventriculomegaly. The size of the boxes is proportional to the study sample size. M-H, Mantel-Haenszel; CI, confidence interval.

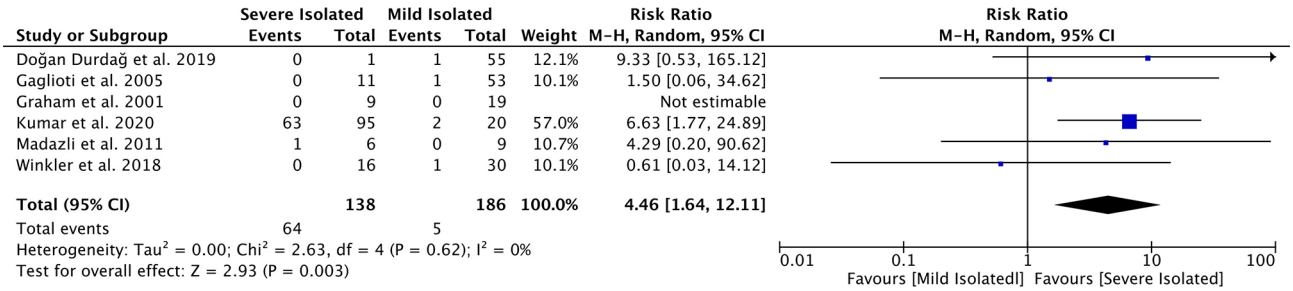

Figure 3 Forest plot of the proportion of cases of intrauterine fetal demise in mild *vs.* severe isolated fetal ventriculomegaly, individually for each of the six included studies and pooled for all studies. The relative risk of intrauterine fetal demise in severe cases was 4.46 (95% CI: 1.64–12.11) times the risk in mild cases of isolated fetal ventriculomegaly. The size of the boxes is proportional to the study sample size. M-H, Mantel-Haenszel; CI, confidence interval.

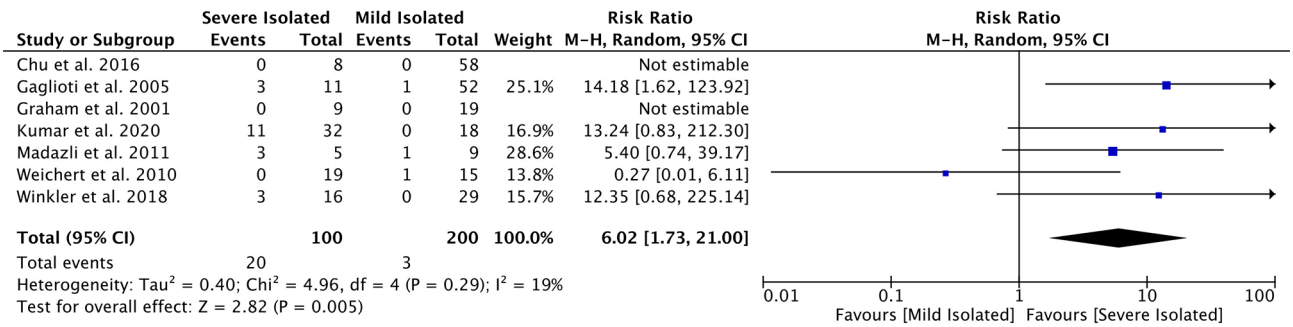

Figure 4 Forest plot of the proportion of cases of infant mortality in mild *vs.* severe isolated fetal ventriculomegaly, individually for each of the seven included studies and pooled for all studies. The relative risk of neonatal and postnatal death in severe cases was 6.02 (95% CI: 1.73–21.00) times the risk in mild cases of isolated fetal ventriculomegaly. The size of the boxes is proportional to the study sample size. M-H, Mantel-Haenszel; CI, confidence interval.

on neurodevelopmental delay and perinatal outcomes. Qualitative synthesis was conducted across all studies with mild or severe cases of fetal ventriculomegaly; the rates at which the outcomes of interest occurred were consistently lower in infants with mild ventriculomegaly compared to severe ventriculomegaly. In fact, the rates of adverse outcomes in mild cases of IVM were somewhat comparable to that of the general population (36). In addition, meta-analysis was also performed. This revealed a relative risk of 4.24 for adverse neurodevelopmental outcomes in severe cases of ventriculomegaly, compared to mild. Similarly, for severe cases there is a relative risk of 4.46 and 6.02 for the risk of intrauterine fetal demise and infant mortality, respectively, compared to mild ventriculomegaly. The relative effects estimated from this meta-analysis were all significant. Thus, these findings show that the degree of ventriculomegaly is significantly associated with prognosis and infants with mild isolated fetal ventriculomegaly have better outcomes compared to those with severe isolated fetal ventriculomegaly.

Strengths and limitations

A strength of this systematic review is the use of an extensive search strategy, including numerous large-scale medical research databases. This reduces likelihood of neglecting any relevant studies, thus ensuring the evidence from this review is strong and up-to-date. Another asset of this review is the inclusion of several outcomes including adverse neurodevelopmental outcomes, intrauterine fetal demise as well as infant mortality. Thus, these results not only support the existing literature on the association between isolated fetal ventriculomegaly and adverse neurodevelopmental outcome, but also add to the scarce research on the association with perinatal outcomes.

Something that should be considered is the inclusion of prenatally diagnosed cases of IVM with associated abnormalities discovered postnatally or 'apparently isolated' cases. These cases were included to maintain enough studies for qualitative synthesis and meta-analysis. However, their inclusion may have influenced the findings, as the presence of associated abnormalities is more frequently associated with severe cases of ventriculomegaly, and associated abnormalities are linked to a poorer prognosis. Thus, the findings of this review may overestimate the risk of neurodevelopmental delay and adverse perinatal outcomes in mild versus severe cases of ventriculomegaly.

Moreover, whilst our aim was to focus on studies published after the year 2000 to account for technological advancements, we understand that certain studies included populations dating back to the 1990s. Thus, the technology employed at the time may not be comparable to the modern neurosonography methods and fetal MRI. This may have introduced variability in the data and the potential inclusion of non-isolated cases, which could impact the generalizability of our findings.

In addition, we would have benefitted from the inclusion of individual patient data within the meta-analysis, to generate a summary estimate of the impact of the degree of ventriculomegaly on the prognosis. The use of individual patient data, rather than aggregate data, is valuable for the purpose of data manipulation, including subgroup analysis. Furthermore, this would aid in reducing between-study heterogeneity further (37).

There were significant disparities in outcome ascertainment, both in assessment methods and follow-up duration. Variations in the assessment of neurodevelopmental delay could influence results, as some tools may be more sensitive than others. Some studies used structured interviews and questionnaires instead of validated clinical tools, potentially introducing bias. Follow-up times varied greatly, with some studies following infants for as little as three months postnatally. Shorter follow-up may miss later neurodevelopmental outcomes, while longer follow-up could be influenced by external factors like education and socioeconomic status.

A significant factor, which was beyond the scope of our review, was analysis of the severity of neurodevelopmental delay and how this differs according to the extent of ventriculomegaly. Given the huge variation in the methods used to assess neurodevelopmental delay across the included papers, it was not possible to include this analysis. Thus, it is important to emphasise that, although severe ventriculomegaly is more associated with neurodevelopmental delay according to our findings, the extent of neurodevelopmental abnormality cannot be commented on and may range from mild to severe. We recognise that this knowledge could further be utilised by clinicians to provide more detailed information regarding prognosis.

Another aspect which would contribute further to this field of knowledge is sub-analysis comparing the outcomes for mild (10–12 mm), moderate (13–15 mm) and severe (above 15 mm). Unfortunately, given that the studies within our inclusion criteria reported mild and moderate ventriculomegaly as a single entity, we did not have a

sufficient number of cases to conduct a meaningful sub-analysis; utilising such restricted data would have limited statistical power and could lead to unreliable conclusions. We recognise this as a significant limitation of our study, given the conventional use of three categories to define the severity of fetal ventriculomegaly.

Comparison with similar researches

The reported rates of adverse neurodevelopmental outcome in this review are similar with reports from previous systematic reviews.

For mild isolated fetal ventriculomegaly, the risk of adverse neurodevelopmental outcome has been reported to vary from 7.9% to 12% (19,36,38). In this review, we report the risk of neurodevelopmental delay to be 11.1%. The subtle differences observed between these percentages may be due to several factors. Pagani *et al.* reported a prevalence of 7.9% which is lower than our findings (38). This may be due to the exclusion of cases with associated findings during a postnatal assessment, whereas we included cases of apparently isolated fetal ventriculomegaly. The review by Devaseelan *et al.* reported a higher estimate of 12%, which may be due to methodological differences in study design between the studies included in their paper and those included in this review (36). Melchiorre *et al.* reported a prevalence of 11% for neurodevelopmental delay in mild IVM cases which agrees with this review (19).

Carta *et al.* reported on the survival and neurodevelopmental outcomes in severe cases of isolated fetal ventriculomegaly. They reported a pooled prevalence of 12.1% for stillbirth or infant mortality. In addition, the pooled prevalence for normal neurodevelopment accounted for 42.2% of the survivors (39). In our review, we report higher percentages of intrauterine fetal demise and infant mortality at 24.3% and 17.1%, respectively. It is suspected that the explanation for this difference may be due to methodological differences. For example, we chose to report intrauterine fetal demise and infant mortality separately, which was not the case for the above-mentioned study. In addition, this study used a pooled prevalence, which is affected by the number of participants per study, whilst we used percentages. Concerning adverse neurodevelopmental outcomes, we report a prevalence of 58.4%, implying that normal neurodevelopment was observed in 41.6% of severe cases of isolated fetal ventriculomegaly. This figure is marginally less than the rate reported by Carta and colleagues (39).

Conclusions

This systematic review and meta-analysis aimed to investigate the impact of the severity of isolated fetal ventriculomegaly on perinatal and neurodevelopmental outcomes following a prenatal diagnosis. The findings show that mild isolated fetal ventriculomegaly is consistently associated with a better prognosis compared to severe cases. Overall, compared to mild cases, severe ventricular dilatation is associated with relative risks of 4.24, 4.46 and 6.02 for neurodevelopmental delay, intrauterine fetal demise and infant mortality, respectively. We were unable to analyse the impact of the severity of atrial width on the rates of preterm birth and low birth weight babies or length of stay in NICU, due to a lack of data.

Counselling parents on the prognosis of isolated fetal ventriculomegaly can be difficult, due to there often being no clear causal factor; for these infants the main indicator of prognosis is the extent of dilatation. The findings of this meta-analysis provide statistical evidence on the extent to which ventricular dilatation may impact prognosis, by providing information on relative risk of neurodevelopmental delay and adverse perinatal outcomes. Thus, these findings may be useful in clinical practice for the purpose of counselling parents faced with a diagnosis of isolated fetal ventriculomegaly on the risk of adverse outcomes. Such communication is crucial as it can aid parents on key decisions regarding their pregnancy and the health of the fetus.

These findings may also be useful in terms of risk stratification, where clinicians can use the severity of ventriculomegaly as a prognostic indicator to stratify patients into low and high-risk categories. Those with severe ventriculomegaly may require closer monitoring and more intensive interventions to those with mild ventriculomegaly.

Larger scale prospective cohort studies investigating the impact of the degree of truly isolated cases of ventriculomegaly on perinatal outcomes (intrauterine fetal demise, infant mortality) and neurodevelopmental outcomes is recommended. Ideally, neurodevelopmental delay and neurological disorders should be differentiated in the measurement of adverse neurodevelopmental outcomes in future research; for example, data on the number of neonates with severe isolated fetal ventriculomegaly who were later diagnosed with hydrocephalus could be particularly useful. In addition, the extent of neurodevelopmental delay and how this differs according

to the severity of ventriculomegaly, should be analysed to further aid clinicians in the assessment of prognosis. Information on perinatal outcomes should be extracted from national databases for increased consistency. These studies should include whether they used MRI scans, in addition to ultrasound (US), to define IVM and longer follow-up periods into childhood and adolescence would also be beneficial. For future systematic reviews and meta-analyses on the outcomes associated with severe versus mild fetal ventriculomegaly, it would be beneficial to include meta-regression analysis based on the year of study, as recent studies will use more advanced technology for diagnosis and measurement. This is for the purpose of enhancing the existing literature on fetal ventriculomegaly as well as improving clinicians' understanding of the prognosis of IVM.

Acknowledgments

Funding: This work was supported by the National Institute for Health Research (NIHR) Biomedical Research Centre based at Guy's and St Thomas' NHS Foundation Trust and King's College London. P.S. is funded by an NIHR Clinical Lectureship (No. CL-2018-17-002). K.H.N. is funded by the Fetal Medicine Foundation (registered charity: 1037116). T.A. was supported by a Medical Research Council (MRC) UK Clinician Scientist Fellowship (No. MR/P008712/1) and a Transition Support Award (No. MR/V036874/1). The views expressed are those of the authors and not necessarily those of the NHS, the NIHR or the Department of Health.

Footnote

Reporting Checklist: The authors have completed the PRISMA reporting checklist. Available at https://tp.amegroups.com/article/view/10.21037/tp-23-548/rc

Peer Review File: Available at https://tp.amegroups.com/article/view/10.21037/tp-23-548/prf

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://tp.amegroups.com/article/view/10.21037/tp-23-548/coif). T.A. was supported by a Medical Research Council (MRC) UK Clinician Scientist Fellowship (No. MR/P008712/1) and a Transition Support Award (No. MR/V036874/1). K.H.N. is funded by the Fetal Medicine Foundation (Registered charity: 1037116). P.S. is funded by an NIHR Clinical Lectureship (No. CL-2018-17-002). The other authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

References

1. Pisapia JM, Sinha S, Zarnow DM, et al. Fetal ventriculomegaly: Diagnosis, treatment, and future directions. Childs Nerv Syst 2017;33:1113-23.
2. Mirsky DM, Stence NV, Powers AM, et al. Imaging of fetal ventriculomegaly. Pediatr Radiol 2020;50:1948-58.
3. Almog B, Gamzu R, Achiron R, et al. Fetal lateral ventricular width: what should be its upper limit? A prospective cohort study and reanalysis of the current and previous data. J Ultrasound Med 2003;22:39-43.
4. Cardoza JD, Goldstein RB, Filly RA. Exclusion of fetal ventriculomegaly with a single measurement: the width of the lateral ventricular atrium. Radiology 1988;169:711-4.
5. Sethna F, Tennant PWG, Rankin J, et al. Prevalence, natural history, and clinical outcome of mild to moderate ventriculomegaly. Obstet Gynecol 2011;117:867-76.
6. Pilu G, Hobbins JC. Sonography of fetal cerebrospinal anomalies. Prenat Diagn 2002;22:321-30.
7. Mercier A, Eurin D, Mercier PY, et al. Isolated mild fetal cerebral ventriculomegaly: a retrospective analysis of 26 cases. Prenat Diagn 2001;21:589-95.
8. Signorelli M, Tiberti A, Valseriati D, et al. Width of the fetal lateral ventricular atrium between 10 and 12 mm: a simple variation of the norm? Ultrasound Obstet Gynecol 2004;23:14-8.
9. Myrianthopoulos NC. Epidemiology of central nervous system malformations. Handb Clin Neurol 1977;1977:139-71.
10. Gaglioti P, Danelon D, Bontempo S, et al. Fetal cerebral

ventriculomegaly: outcome in 176 cases. Ultrasound Obstet Gynecol 2005;25:372-7.
11. Society for Maternal-Fetal Medicine (SMFM); Norton ME, Fox NS, et al. Fetal Ventriculomegaly. Am J Obstet Gynecol 2020;223:B30-3.
12. Thorup E, Jensen LN, Bak GS, et al. Neurodevelopmental disorder in children believed to have isolated mild ventriculomegaly prenatally. Ultrasound Obstet Gynecol 2019;54:182-9.
13. Kelly EN, Allen VM, Seaward G, et al. Mild ventriculomegaly in the fetus, natural history, associated findings and outcome of isolated mild ventriculomegaly: a literature review. Prenat Diagn 2001;21:697-700.
14. Scala C, Familiari A, Pinas A, et al. Perinatal and long-term outcomes in fetuses diagnosed with isolated unilateral ventriculomegaly: systematic review and meta-analysis. Ultrasound Obstet Gynecol 2017;49:450-9.
15. Weichert J, Hartge D, Krapp M, et al. Prevalence, characteristics and perinatal outcome of fetal ventriculomegaly in 29,000 pregnancies followed at a single institution. Fetal Diagn Ther 2010;27:142-8.
16. Winkler A, Tölle S, Natalucci G, et al. Prognostic Features and Long-Term Outcome in Patients with Isolated Fetal Ventriculomegaly. Fetal Diagn Ther 2018;44:210-20.
17. Ge CJ, Polan RM, Baranano KW, et al. Acceleration and plateau: two patterns and outcomes of isolated severe fetal cerebral ventricular dilation. J Matern Fetal Neonatal Med 2021;34:3014-20.
18. Chu N, Zhang Y, Yan Y, et al. Fetal ventriculomegaly: Pregnancy outcomes and follow-ups in ten years. Biosci Trends 2016;10:125-32.
19. Melchiorre K, Bhide A, Gika AD, et al. Counseling in isolated mild fetal ventriculomegaly. Ultrasound Obstet Gynecol 2009;34:212-24.
20. Brown KA, Parikh S, Patel DR. Understanding basic concepts of developmental diagnosis in children. Transl Pediatr 2020;9:S9-S22.
21. Breeze AC, Dey PK, Lees CC, et al. Obstetric and neonatal outcomes in apparently isolated mild fetal ventriculomegaly. J Perinat Med 2005;33:236-40.
22. Doğan Durdağ G, Yılmaz Baran Ş, Kalaycı H, et al. Is fetal magnetic resonance imaging indicated in patients with isolated ventriculomegaly? Eur J Obstet Gynecol Reprod Biol 2019;240:52-6.
23. Gezer NS, Gezer C, Ekin A, et al. Obstetric and neurodevelopmental outcome in fetal cerebral ventriculomegaly. Clin Exp Obstet Gynecol 2016;43:490-4.
24. Gómez-Arriaga P, Herraiz I, Puente JM, et al. Mid-term neurodevelopmental outcome in isolated mild ventriculomegaly diagnosed in fetal life. Fetal Diagn Ther 2012;31:12-8.
25. Graham E, Duhl A, Ural S, et al. The degree of antenatal ventriculomegaly is related to pediatric neurological morbidity. J Matern Fetal Med 2001;10:258-63.
26. Hannon T, Tennant PW, Rankin J, et al. Epidemiology, natural history, progression, and postnatal outcome of severe fetal ventriculomegaly. Obstet Gynecol 2012;120:1345-53.
27. Kennelly MM, Cooley SM, McParland PJ. Natural history of apparently isolated severe fetal ventriculomegaly: perinatal survival and neurodevelopmental outcome. Prenat Diagn 2009;29:1135-40.
28. Kumar M, Garg N, Hasija A, et al. Two-year postnatal outcome of 263 cases of fetal ventriculomegaly. J Matern Fetal Neonatal Med 2020;33:1492-8.
29. Kutuk MS, Ozgun MT, Uludag S, et al. Postnatal outcome of isolated, nonprogressive, mild borderline fetal ventriculomegaly. Childs Nerv Syst 2013;29:803-8.
30. Leitner Y, Goez H, Gull I, et al. Antenatal diagnosis of central nervous system anomalies: can we predict prognosis? J Child Neurol 2004;19:435-8.
31. Leitner Y, Stolar O, Rotstein M, et al. The neurocognitive outcome of mild isolated fetal ventriculomegaly verified by prenatal magnetic resonance imaging. Am J Obstet Gynecol 2009;201:215.e1-6.
32. Litwinska M, Litwinska E, Czaj M, et al. Ventriculo-amniotic shunting for severe fetal ventriculomegaly. Acta Obstet Gynecol Scand 2019;98:1172-7.
33. Madazli R, Sal V, Erenel H, et al. Characteristics and outcome of 102 fetuses with fetal cerebral ventriculomegaly: experience of a university hospital in Turkey. J Obstet Gynaecol 2011;31:142-5.
34. Tugcu AU, Gulumser C, Ecevit A, et al. Prenatal evaluation and postnatal early outcomes of fetal ventriculomegaly. Eur J Paediatr Neurol 2014;18:736-40.
35. Dekkers OM, Egger M, Altman DG, et al. Distinguishing case series from cohort studies. Ann Intern Med 2012;156:37-40.
36. Devaseelan P, Cardwell C, Bell B, et al. Prognosis of isolated mild to moderate fetal cerebral ventriculomegaly: a systematic review. J Perinat Med 2010;38:401-9.
37. Stewart LA, Tierney JF. To IPD or not to IPD? Advantages and disadvantages of systematic reviews using individual patient data. Eval Health Prof 2002;25:76-97.
38. Pagani G, Thilaganathan B, Prefumo F.

Neurodevelopmental outcome in isolated mild fetal ventriculomegaly: systematic review and meta-analysis. Ultrasound Obstet Gynecol 2014;44:254-60.
39. Carta S, Kaelin Agten A, Belcaro C, et al. Outcome of fetuses with prenatal diagnosis of isolated severe bilateral ventriculomegaly: systematic review and meta-analysis. Ultrasound Obstet Gynecol 2018;52:165-73.

Cite this article as: Ali F, Gurung F, Nanda S, Bakalis S, Sankaran S, Arichi T, Nicolaides KH, Shangaris P. Perinatal and neurodevelopmental outcomes of fetal isolated ventriculomegaly: a systematic review and meta-analysis. Transl Pediatr 2024;13(4):555-574. doi: 10.21037/tp-23-548

Supplementary

Appendix 1

MeSH search terms used:

- Cerebral ventriculomegalies, fetal
- Cerebral ventriculomegaly, fetal
- Fetal cerebral ventriculomegalies
- Fetal cerebral ventriculomegaly
- Ventriculomegalies, fetal cerebral
- Ventriculomegaly, fetal cerebral
- Mortalities, perinatal
- Mortality, perinatal
- Perinatal mortalities
- Perinatal mortality
- Stillbirth
- Stillbirths

Key phrases/words used: Neurodevelopment, Isolated fetal ventriculomegaly, Perinatal outcome, Perinatal mortality, Mild ventriculomegaly, Severe ventriculomegaly, Fetal ventriculomegaly, Neurodevelopmental outcome.

https://dx.doi.org/10.21037/tp-23-548