Outcome of fetuses with prenatal diagnosis of isolated severe bilateral ventriculomegaly: A systematic review and meta-analysis

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Abstract

Objective

To quantify survival and neurodevelopmental outcome of fetuses with prenatally detected isolated severe bilateral ventriculomegaly form published literature.

Methods

Medline, Embase and the Cochrane Library were searched electronically. Only cases with prenatal diagnosis of apparently isolated severe ventriculomegaly and postnatal neurodevelopment assessment were selected and included. Severe ventriculomegaly was defined by the authors as enlargement of the ventricular atria, with a diameter greater than 15 mm on the transventricular plane while all cases where the investigators were unable to detect associated structural abnormality, chromosomal abnormality or fetal infections, and regarded the ventriculomegaly to be apparently isolated were included. Those where an etiology was identified prenatally were excluded, whereas those with post-natal identification of underlying cause were not excluded since this information was not available prenatally.

The quality of the included studies was assessed using the Newcastle-Ottawa Scale (NOS) for cohort studies. Pregnancy outcomes, such as pregnancy termination, stillbirth, neonatal survival and developmental outcome of the baby were recorded. The degree of handicap was classified as no handicap, mild or severe handicap. Statistical assessment was performed by meta-analyses of proportions to combine data, weighing the studies by the inverse variance method and using a random-effects model. Proportions and confidence intervals were reported.

Results

Eleven studies with 137 fetuses were found. Twenty-seven pregnancies underwent termination and were excluded. The remaining 110 fetuses with apparently isolated severe ventriculomegaly, where continuation of pregnancy was intended, forms the population included in the study. The overall quality assessed using the Newcastle-Ottawa Scale (NOS) for cohort studies was good.

Survival was reported in 95/110 (pooled proportion 87.90%, 95% CI = 75.6% to 96.2%) cases. In 15/110 (pooled proportion 12.1%, 95% CI = 3.8% to 24.4%) either stillbirth or neonatal demise was reported. No handicap was reported in 41/95 of survivors (pooled proportion 42.2%, 95% CI = 27.5% to 57.6%). However, 17/95 showed mild-moderate handicap (pooled proportion 18.6%, 95% CI = 7.2% to 33.8%) and 37/95 were reported to have had severe handicap (pooled proportion 39.6%, 95% CI = 30.0% to 50.0%).

Conclusion

Four fifths of fetuses with severe ventriculomegaly survive and of these, just over two fifths show normal neurodevelopment. The overall survivors without handicap account for more than one third of the total. Given that many cases undergo termination of pregnancy and the need for longer follow-up in order to detect subtle abnormalities, mortality and prevalence of developmental delay may be even higher than that reported in this paper.

Introduction

Ventriculomegaly is one of the most frequently diagnosed fetal abnormalities of the fetal central nervous system [1]. It is defined as enlargement of the ventricular atria greater than 10 mm, measured on the trans-ventricular plane, at the level of the glomus of the choroid plexus, perpendicularly to the ventricular cavity, positioning the calipers inside the echoes generated by the lateral walls[2]. Severe VM is usually defined as enlargement of the ventricular atria, with a diameter greater than 15 mm on the transventricular plane, compared to mild to moderate ventriculomegaly when the atrium measures 10 to 15 mm [3]. The prevalence of severe ventriculomegaly at birth is 0.3-1.5 per 1000 pregnancies[4,5]. Prognosis is strongly dependent on the etiology, frequently challenging to identify antenatally, and is worse in cases with associated abnormalities[6].

There are many publications on isolated mild or moderate ventriculomegaly[7]. However, data on isolated severe ventriculomegaly is scarce. Most frequently the literature describe cases of severe ventriculomegaly associated to extra-cranial abnormalities, leading to poor outcome (livebirth rate 30-40%[4,8,9]). The high mortality rate is partly due to the inclusion of terminations of pregnancy, cephalocentesis and cases that were not actively treated post-natally [10]. Conversely, pediatric surgical literature reports high survival rates and low rates of neurodevelopmental handicap, with a 10-year survival rate after surgery of 60% or more, and normal intelligence in half of the surviving patients [11]. In the study of Lumenta et al, normal development is reported in 62.8% of children, while 29.8% had mild developmental delay, and only 7.4%

reported severe developmental delay[12]. After surgery, the proportion of children with normal intelligence, measured by IQ, was reported between 50 and 63% with integration into normal school for 60% of the children[13].

In the series showing mainly poor prognosis[14,15,4], additional abnormalities were seen in the majority of cases. The literature on the neurodevelopmental outcomes of isolated cases remains still quite sparse [16,] negatively impacting parents' counselling and remaining for them a source of considerable anxiety [17,18].

The aim of this study was to collate published data on survival and neurodevelopmental outcome of prenatally detected cases of apparently isolated severe ventriculomegaly.

Methods

Protocol, Eligibility Criteria, Information Sources and Search

We performed a systematic review following the recommendations for systematic reviews and meta-analyses[19,20]. The search strategy was set up using a combination of relevant medical subject heading (MeSH) terms, keywords and word variants for "prenatal", "diagnosis", "ultrasound", "severe ventriculomegaly" "neurodevelopment". We searched Medline, Embase and the Cochrane Library including the Cochrane Database of Systematic Reviews (CDSR), Database of Abstracts of Reviews of Effects (DARE) and The Cochrane Central Register of Controlled Trials (CENTRAL) on the 11th of July and 24th of August 2017. No language restrictions were applied. We limited the search to the year 1990 or later, because the diagnostic techniques (high

resolution ultrasound, fetal Magnet Resonance Imaging (MRI), chromosomal micro-Array) were not widely available before then. No restrictions were applied in terms of study designs and size except for case series, observational studies or case reports of less than three cases, which were excluded to minimize publication bias. Additional relevant articles were identified by manual search in the reference lists of the included publications. The study was registered with PROSPERO database, http://www.crd.york.ac.uk/PROSPERO/display_record.asp?ID=CRD42017048712, (registration number CRD42017048712).

Study Selection, Data Collection and Data Items

Two independent reviewers (SC and A.K.) performed the literature search and identified the potentially relevant citations. The abstracts were screened independently, and relevant ones were selected for extraction of full text article. Relevant data were extracted, and potential inconsistencies were discussed by the authors and consensus was reached by weighing arguments. In instances where the data of interest were not explicitly reported by the authors of the papers, we contacted them for clarification or additional details.

The studies assessment and selection for inclusion was performed accordingly to the following criteria: population, outcomes and study design. The inception cohort was assembled at the time of prenatal detection of ventriculomegaly, where the intention was to continue the pregnancy. Severe ventriculomegaly was defined as an atrial measurement in the trans-ventricular plane of 15 mm or above for the purpose of this review. As mentioned previously, ventriculomegaly was considered apparently isolated if the

investigators were unable to detect other cranial/extracranial structural abnormality, chromosomal abnormality or fetal infection in the prenatal period. We excluded all non-isolated cases where an etiology was identified prenatally, such as chromosomal abnormalities, spina bifida, structural brain defect detected on ultrasound or MRI (encephalocele, neuronal migration defect etc.) and congenital infections. We also excluded ventriculomegaly complicating monochorionic twin due to the high likelihood that this was a consequence of placental sharing.

Studies where intrauterine treatments were systematically performed were excluded as it might have altered the natural history of the disease and being the techniques not standardized yet. Studies reporting only on unilateral ventriculomegaly were also excluded a priori. We included cases considered apparently isolated in the prenatal period. Cases with post-natal identification of underlying cause were not excluded since this information was not available prenatally. The pregnancy outcome (termination/stillbirth), neonatal survival and developmental outcome of the newborns were recorded. Cases were not eligible for inclusion if the ventriculomegaly was detected only post-natally.

For the assessment of presence and degree of handicap, no limitations or restrictions were planned on the diagnostic tools and/or duration of post-natal follow-up. The degree of handicap was classified as no handicap, mild or severe handicap. We reported the results obtained by the tools for the assessment of neurodevelopment used by the primary authors, and seeking clarification from them when necessary. Handicap was classified as severe motor when independent functioning of the individual was not deemed possible.

Sensorineural handicap was considered severe where the developmental assessment tool reported it as such, or when attendance of mainstream school was not deemed possible. Children who did not fit into either severe handicap or no handicap were classified as mild/moderate. If information on the specific clinical finding rather than specific degree of handicap at the postnatal follow-up was available, the handicap class was assigned based on the reported information.

Risk of Bias, Summary Measures and Synthesis of the Results

The quality of the included studies was assessed using the Newcastle-Ottawa Scale (NOS) for cohort studies[21]. The NOS judges each study according to the following categories: selection of the study groups, comparability of the groups and ascertainment of the outcome of interest. The selection of the study groups is performed by evaluating the representativeness of the exposed cohort, the selection of the non-exposed cohort, ascertainment of exposure and the demonstration that the outcome of interest was not present at the start of the study. Comparability of the groups was assessed by evaluating of the cohorts based on the design or analysis. The ascertainment of the outcome of interest included the evaluation of the assessment of the outcome parameters, and the length and adequacy of the follow-up. A study can be awarded a maximum of one star for each item within the selection and outcome categories. Additionally, a maximum of two stars can be given for comparability[21].

Statistical assessment was performed by meta-analyses of proportions to combine data. The studies were weighted by the inverse variance method for

pooling. Forest plots were used to explore graphically in between-study heterogeneity, while heterogeneity was statistically evaluated using I^2, which represents the percentage of between-study variation that is due to heterogeneity rather than to chance[22]. A I^2 of 0% indicates absence of heterogeneity, while values of or above 50% suggest considerable heterogeneity[23].

We used a random-effects model since it is more conservative, and the observed heterogeneity was >50%. Statistical analysis was carried out using StatsDirect 3.1.8 (StatsDirect Ltd, Altrincham UK, 2017). We did not use either Funnel Plots or formal statistical tests to explore publication bias. A total of 11 studies is not an adequate number for interpreting funnel plots. Moreover, funnel plots can be misleading for exploration of publication bias, particularly when the number of studies is relatively small[24].

Results

Study Selection and Characteristics

A total of 448 possible citations were identified with the initial databases electronic search. After review of titles and abstracts, 417 articles did meet the exclusion criteria and were excluded. For the 31 publications that potentially met the inclusion criteria, full text manuscripts were retrieved. Two additional studies were identified by manual search of the reference lists[8,15]. After the analysis of the full test manuscripts, 22 studies which did not fulfill the inclusion criteria were excluded. The remaining 11 articles were finally included in the systematic review[8,15–17,25–31] (Figure 1).

The quality assessment of the included studies using the NOS is shown in the supplementary material (Table S1). The included studies have an overall good quality for selection of group and the ascertainment of the outcome of interest. Common reasons for scoring low on quality assessment were cases derived from high-risk populations and lack of description of the outcome of individual cases. Follow-up varied widely in the different studies, ranging from one month up to 18 years. Several different assessment tools for the assessment of the neonatal neurodevelopmental outcome were used, ranging from self-rating questionnaires to standardized tests.

All the data from the included articles, published between 1999 and 2017, were collected in a time spanning from 1990 to 2013. Almost all the studies reported on ventriculomegaly in general, and included fetuses with severe (atrial diameter 15 mm or more) ventriculomegaly. We extracted information about apparently isolated severe ventriculomegaly from them. The gestational age at the ultrasound assessment varied from 15 weeks to term. General characteristics of the included studies are shown in table 1.

Different development assessment tools were used in each study and the age of developmental assessment ranged from less than one to 18 years (see table 2 for more details). The karyotype was assumed to be normal if it was not performed before or after birth, provided the phenotype after birth was normal. Data on infection screening, details of ventriculoperitoneal shunt placement and post-mortem investigation were collected when available.

Four studies[15,26–28] reported the outcomes in two degrees of delay (normal or significant abnormal, good or poor prognosis and normal or evident

psychomotor delay). We classified the 'significant abnormal', 'poor prognosis' and 'evident psychomotor delay' as severe handicap. In one report[17], the authors described the outcome with the actual clinical finding (hemiparesis, impaired visual attention) rather than with a classified degree of handicap. This was recorded as severe handicap after obtaining clarification from the authors. Pregnancy terminations were reported when available but excluded from the calculation of the survival rate.

Synthesis of the Results

Significant heterogeneity was found between included studies, being I^2 above 50% in almost all the outcomes analyzed, hence the decision for a random-effect model. Heterogeneity was low for severe handicap over survivors, but the 95% confidence interval was relatively wide (I^2 = 4.2%, 95% CI: 0% to 53.2%).

Meta-analysis of proportions was performed and Forest plots were used to describe the rates of death, survival and neurodevelopmental delay in severe isolate ventriculomegaly. Individual results for each one of the 11 studies included in the meta-analysis were provided in terms of proportions and 95% C.I., together with pooled results for all studies, where size of boxes was proportional to the study sample size.

110 fetuses with prenatal apparently isolated severe ventriculomegaly were available. Of these, 95 survived and 15 had a stillbirth or neonatal demise. In 41 of the survivors, the outcome was classified as normal, 17 were classified as mild/moderate handicap and 37 were reported as having severe handicap (Table 3).

The pooled proportion of deaths accounted for 12.1%, (15/100) (95% CI = 3.8% to 24.4%) while that of survival was 87.9% (95/110) (95% CI = 75.6% to 96.2%), (Figure 2, Forest plot of deaths).

No handicap was reported in 41/95 of survivors (pooled proportion 42.2%, 95% CI = 27.5% to 57.6%) (Figure 3, Forest plot of no handicap over survivors). However, 17/95 showed mild-moderate handicap (pooled proportion 18.6%, 95% CI = 7.2% to 33.8%) (Figure S1, supplementary material, Forest plot of mild handicap over survivors) and 37/95 were reported to have had severe handicap (pooled proportion 39.6%, 95% CI = 30.0% to 50.0) (Figure 4, Forest plot of severe handicap over survivors).

An overview of individual and pooled proportion of the different outcomes is available in tables 3 and 4.

Additional anomalies were detected in nine cases (9.5%) only post-natally. The details of the additional anomalies are shown in Table S2. None of the infants with post-natally detected anomalies were free of handicap.

Discussion

Summary of Evidence

We report on the outcome of children with prenatal detection of apparently isolated severe ventriculomegaly. Survival without handicap was seen in just over one third of cases. Although the initial diagnosis was isolated severe ventriculomegaly, additional structural abnormalities were detected post-natally in some. The degree of information available about the post-natal diagnosis of associated abnormalities was variable. Details on number of patients affected

and impact on outcomes as well as post-natal confirmation of the absence of associated abnormalities was available only from some reports (see table S2 of the supplementary material). Additional anomalies were detected in nine cases (9.5%) only post-natally, none of whom were without handicap.

In cases of mild ventriculomegaly, the outcome is favorable in the absence of identifiable cause[7]. However, once the ventriculomegaly becomes severe, the outlook is unfavorable in the majority. The duration of follow-up was variable (Table 2) and may impact on the reported degree of handicap. Subtle abnormalities may not be uncovered until the child begins schooling. Therefore, the prevalence of developmental delay may be higher than that reported here.

Pediatric surgical literature reports that developmental outcome following ventriculo-peritoneal shunt for obstructive hydrocephalus is normal in the large majority[12,13]. The presumed underlying cause in those patients is isolated obstruction to CSF flow in cases were the other investigations are normal. The results from prenatal literature do not match with those reported in post-natal series. The most likely reason for the disparity in the results is selection of children undergoing the surgical procedure. Obstruction to CSF flow (aqueductal stenosis) may be due to congenital or acquired reasons. The results of this study suggest that the implications of the two are vastly different, and that the outlook for acquired aqueductal stenosis may be much more favorable as compared to that for congenital lesions. It could also be argued that children with severe ventriculomegaly that are asymptomatic after birth (hence with good prognosis) might never present for postnatal surgery. However, it is highly unlikely that fetuses with prenatal detection of severe

ventriculomegaly would not be followed up. On the other hand, pediatric surgeons do not see cases too compromised to undergo surgery in their series, in which case the selection bias would work against antenatally detected cases.

Fetal MRI was not performed in every case. Many of the ones that did undergo MRI investigation were excluded from the analysis because of antenatal detection of associated abnormalities. We did not investigate those further, being this out of the scope of this paper. Postnatally, additional abnormalities were found on MRI in four of the 17 cases (23.5%) of the mild and five of the 37 cases (13.5%) of severe developmental delay. It is difficult to say if all the abnormal findings would have been detected prenatally, had a fetal MRI been performed. Very often, parental wish against intervention is a deterrent for prenatal investigation. The structural abnormalities detected after birth are potentially detectable on MRI. Therefore, we would recommend a prenatal fetal MRI in cases of severe ventriculomegaly to ascertain the truly isolated cases. Similarly, not all parents chose to undergo an invasive test. Chromosomal micro-array is capable of detecting known pathogenic alterations in an additional 5% of cases even when conventional karyotype is normal[32]. This investigation has only recently become available in clinical practice and may not have been available for the series included in this review. Also, fetal MRI is able to diagnose additional brain abnormalities in 5% of cases[33], but only in the last decade it has gradually been introduced as an additional fetal CNS investigation. Some of the 'apparently' isolated cases may no longer remain isolated, had they been subjected to chromosomal micro-array analysis, fetal MRI or appropriate neuro-sonography accordingly to the current standard

guidelines (ISUOG guidelines). However, these are the reports of leading centers throughout the world, and the results are a pragmatic representation of real-life situations.

Limitations

We conducted a thorough search of the literature in duplicate, according to a pre-specified inclusion and exclusion criteria. We excluded case report with fewer than three cases in order to avoid publication bias. Therefore, the results of the review are robust. Apparently isolated severe ventriculomegaly is not a common condition. A considerable proportion of pregnancies are terminated, thus modifying the natural history. Both these are responsible for the limited number of cases this report is based on. It is possible that cases undergoing termination might have been the ones with most severe ventriculomegaly.

Table 2 displays the method used for assessment of neurodevelopment in the included studies. Some authors refers to Neuropediatric or Pediatricians' assessment without additional details [15,26]. Regardless of the method used to define degrees of neurodevelopmental delay, the focus of this systematic review was to identify cases with "normal" outcomes. The state of normality should be comparable between several studies, regardless of the method of neuro-developmental assessment.

Implications for Clinical Practice and Future Perspectives

The prevalence of developmental delay reported in this review may overestimate the real risk, given that not all the apparently isolated ventriculomegaly were truly isolated after birth, and some of them had

associated abnormalities. Due to parental choice, retrospective nature and availability of particular investigations, not all cases underwent a fetal MRI or tests to assess chromosomal imbalance.

The association between additional abnormalities and worse outcomes is well known. It may be argued that developmental delay may be related to the presence of associated abnormalities rather than the ventriculomegaly itself. However, the prevalence of developmental delay remains high even if cases of associated abnormalities are excluded. There are no data to support the assertion that developmental delay may be less frequent in 'truly isolated' severe ventriculomegaly. The figures contained in this systematic review is the current best evidence on which to base parental counselling.

Conclusion

After excluding cases of pregnancy termination, approximately four out of five of all fetuses with antenatal diagnosis of apparently isolated ventriculomegaly survive. There is a high (Three out of five) chance of neurodevelopmental delay in this group. The overall probability of survival without handicap is 41/110 (36.66% (CI = 0.23 to 0.52)).

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Legends for illustrations

Table 1- General characteristics of the 11 studies included in the systematic review.

Table 2- Developmental assessment tools adopted in the 11 studies included in the systematic review.

Table 3- Overview of meta-analysis of proportions for Deaths, Survivors, Total handicap and Normal outcome out of the total number of included cases.

Table 4- Overview of meta-analysis of proportions for Normal outcome, mild, severe and total handicap the total number of survivors.

Figure 1- Flow-chart of studies selection.

**Reasons for exclusion: In 2 studies all cases had associated abnormalities: in 1 study all cases had mild to moderate VM, but none had severe VM; in 5 studies the data collection started before 1990; in 1 study there were no antenatal information available; in 3 studies there was no postnatal follow information; in 7 studies, mild/moderate and severe VM were pooled together and was not possible to connect each one of the severe cases with the corresponding outcome; in 3 studies intrauterine treatments were systematically performed.

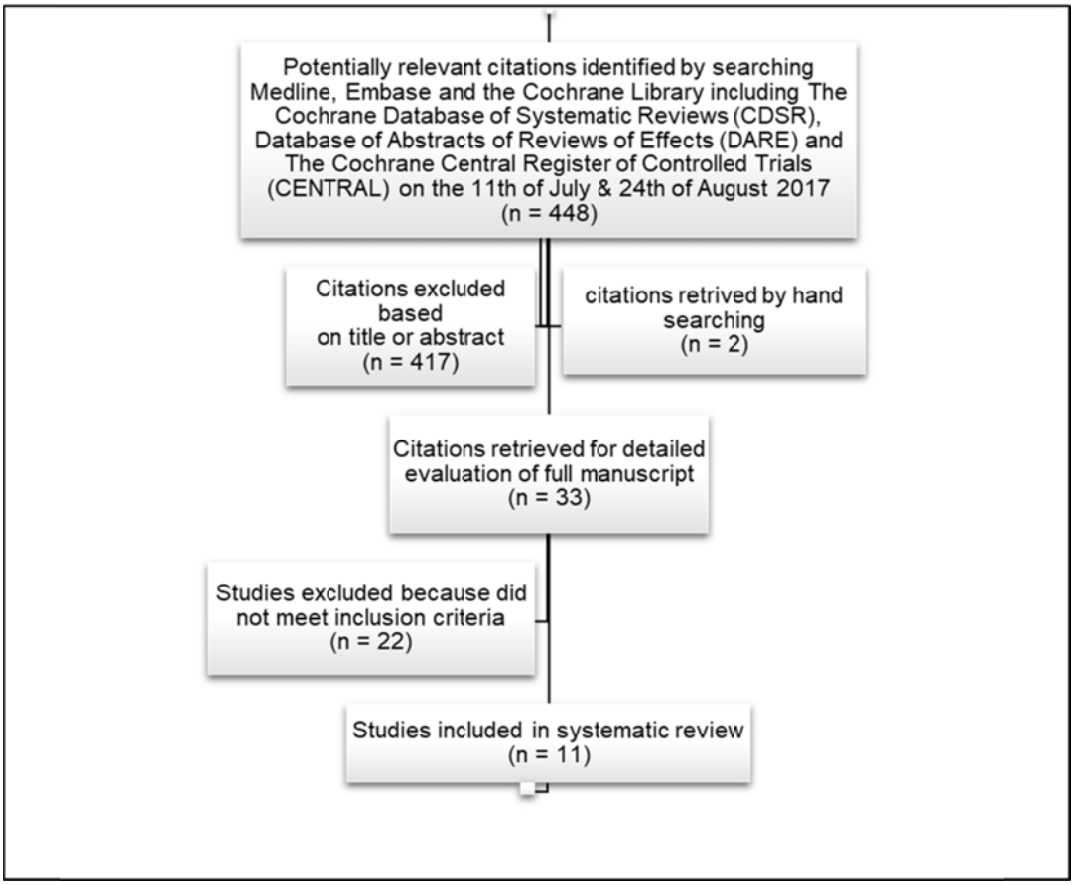

Figure 2- Forest plot (random-effect model) showing incidence of deaths in fetuses with isolated severe ventriculomegaly antenatally detected, individually for each of the 11 studies, and pooled for all studies. The pooled incidence was 12.10% (95% CI = 3.7 to 24.4; I^2 = 63.7%). The size of the boxes is proportional to the study sample size.

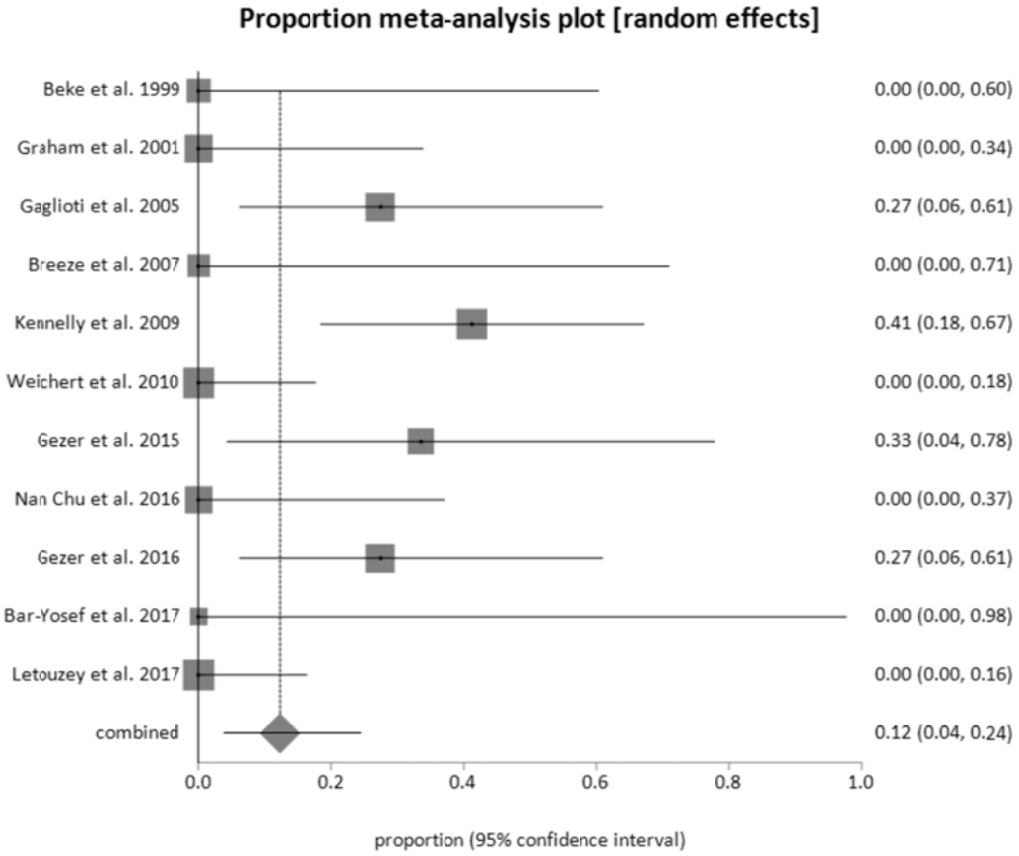

Figure 3- Forest plot (random-effect model) showing prevalence of normal neurodevelopment over survivors in fetuses with isolated severe ventriculomegaly antenatally detected, individually for each of the 11 studies (number of cases per study showed in square brackets), and pooled for all studies. The pooled prevalence was 42.2% (95% CI = 27.5% to 57.6%; I^2 = 54.7%). The size of the boxes is proportional to the study sample size.

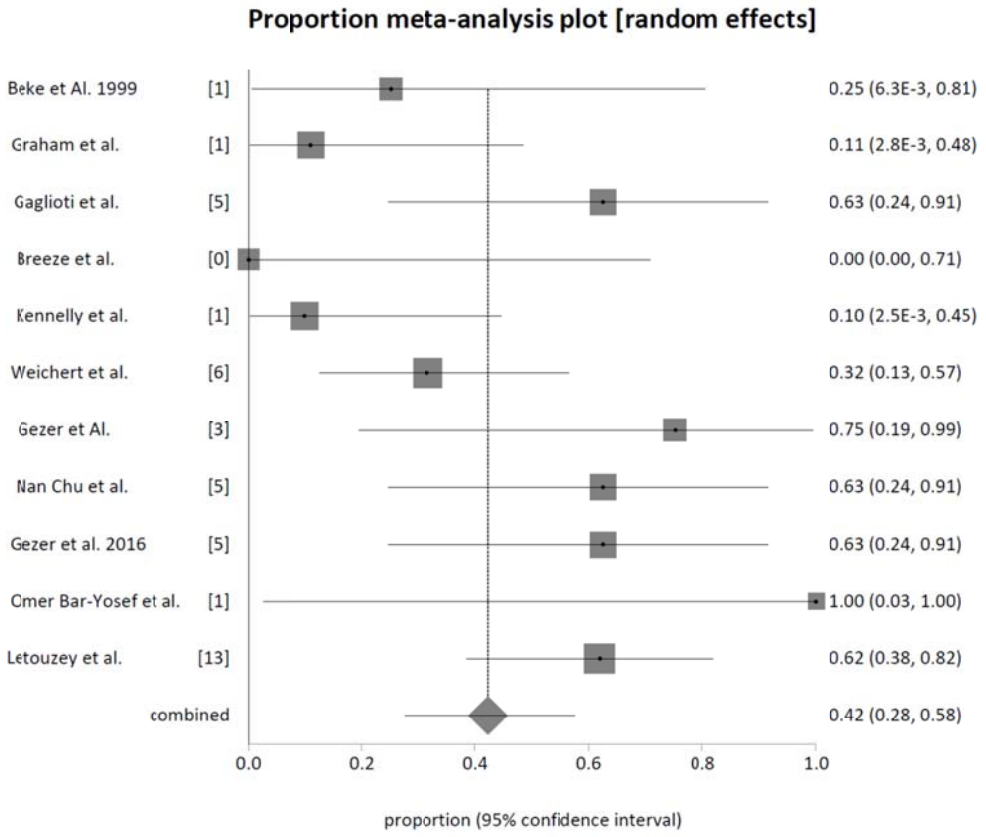

Figure 4- Forest plot (random-effect model) showing prevalence of severe handicap over survivors in fetuses with isolated severe ventriculomegaly antenatally detected, individually for each of the 11 studies (number of cases per study showed in square brackets), and pooled for all studies. The pooled prevalence was 39.6% (95% CI = 30.0% to 50.0%; I^2 = 4.2%). The size of the boxes is proportional to the study sample size.

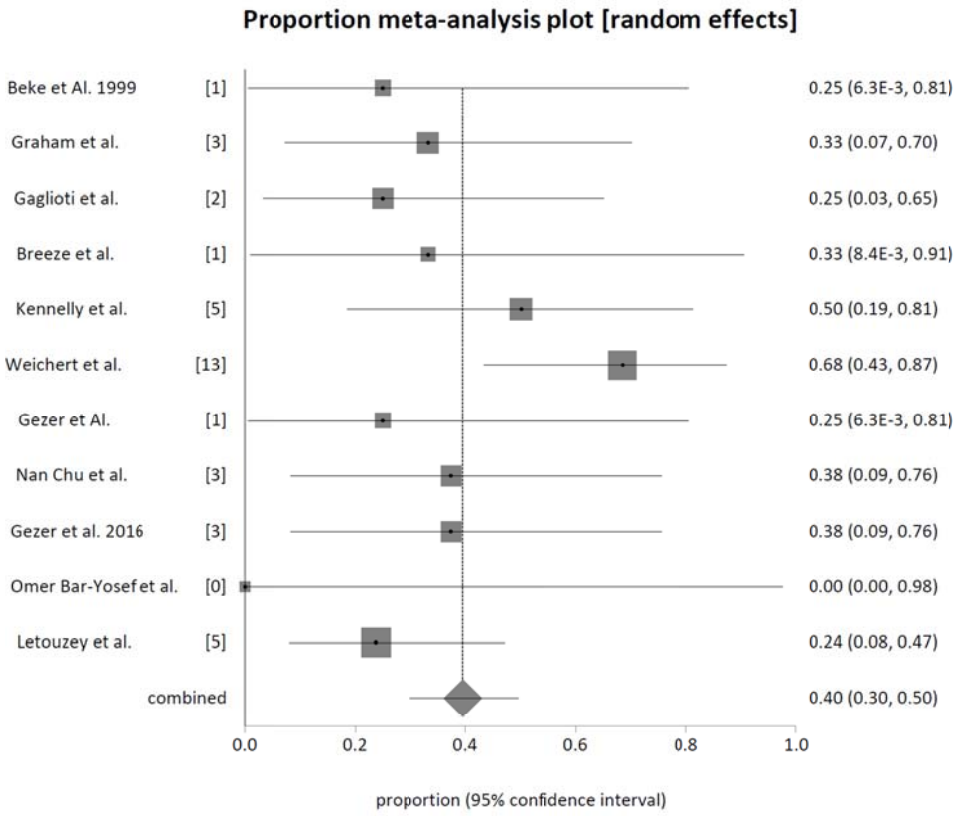

Table 1

Author	Data collection	Study Design	GA diagnosis (ws)	Definition of severe VM	Definition of Isolated VM	Time of follow-up
Beke et al. 1999	1993-1996	retrospective cohort study	27-36	ventricular atria width >15 mm on the transventricular USS plane	No evidence of associated anomalies, aneuploidy, chromosomal abnormalities, structural malformations, negative TORCH screening.	3 to 36 months
Breeze et al. 2007	2001-2005	retrospective cohort study	16-36	ventricular atria width >15 mm on the transventricular USS plane	Normal Karyotype, TORCH screening, FMAIT screening (offered to all patients), detailed fetal USS for anomalies by fetal medicine sub-specialist, MRI (offered if potentially influent on parents' decision-making process).	4 to 24 months
Gaglioti et al. 2005	1990-2000	retrospective cohort study	15-36	ventricular atria width >15 mm on the transventricular USS plane	Normal detailed USS evaluation of fetal anatomy, ECHO, Karyotype, TORCH (offered to all patients).	2 to 144 months
Gezer et al. 2015	2007-2009	retrospective cohort study	17-34	ventricular atria width >15 mm on the transventricular USS and MRI plane	No associated abnormalities on USS and MRI investigations, no evidence of chromosomal anomalies, confirmed after birth.	up to 24 months

Gezer et al. 2016	2007-2009	prospective cohort study	NR	ventricular atria width >15 mm on the transventricular USS and MRI plane	No evidence of chromosomal anomalies or congenital infections, normal first and second trimester screening.	6 to 24 months
Graham et al. 2001	1994-1999	retrospective cohort study	18-22	ventricular atria width >15 mm on the transventricular USS plane	Normal karyotype and detailed anomaly scan, negative infective screening (offered to all patients).	1 to 36 Months
Kennelly et al. 2009	2000-2008	retrospective cohort study	18-36	ventricular atria width >15 mm on the transventricular USS plane	Normal fetal anomaly USS performed by fetal medicine sub-specialist, ECHO, karyotype, TORCH screening, screening for alloimmune thrombocytopenia, fetal MRI (offered to all patients)	10 to 72 months
Letouzey et al. 2017	1994-2011	prospective cohort study	22-37	ventricular atria width >15 mm on the transventricular USS plane	Normal detailed USS, MRI, karyotype, infection screening (offered to all patients).	3 to 216 months
Nan Chu et al. 2016	2004-2013	retrospective cohort study	18-36	ventricular atria width >15 mm on the transventricular USS plane	Normal detailed USS, karyotype, TORCH screening (offered to all patients).	16 to 108 months
Omer Bar-Yosef et al. 2017	2010-2013	prospective cohort study	NR	ventricular atria width >15 mm on the transventricular USS plane	Normal detailed USS, karyotype, TORCH screening (offered to all patients).	18 to 36 months
Weichert et al. 2010	1993-2007	prospective cohort study	12-38	ventricular atria width >15 mm on the transventricular USS plane	Normal detailed USS, MRI, CGH-Array, genetic counselling, infection screening (offered to all patients).	1 to 151 months

Table 2

Author/ year	Assessment tool	Definition of normal	Definition of mild/moderate handicap	Definition of severe handicap	Time of follow-up
Beke, 1999	Brunet-Lezine (Hungarian adaptation) test in infants, from 3 months to 36 months of age; Hungarian adaptation of Stanford-Binet test (Budapest-Binet test).	None of the following	delayed somatic and psychomotor development, mild motor and sensory disorders, without mental retardation	neurological, mental or sensory disturbances, which permanently impair their social integration and limit educational goals. Children with cerebral palsy, microcephaly, sensory-neuronal hearing loss, poor vision or mental retardation DQ < 70	3 to 36 months
Breeze, 2007	Amiel-Tison Assessment	Complex scoring system, see reference	Complex scoring system, see reference	Complex scoring system, see reference	4 months to 2 years
Gaglioti, 2005	Structured questionnaire administered to the parents, investigating locomotor activities and co-ordination of movements; hearing and visual capacity; development and quality of speech and socialization skills; learning performance; evolution of diagnosed a		Mild anomaly: moderate motor skill problems (with or without tone and reflex anomalies), squint, nystagmus, mild speech difficulty, moderate learning problems and ventricular-peritoneal shunt with normal motor development	severe neurodevelopmental outcome: cerebral palsy (with or without the need for orthopaedic help, urinary incontinence, daily enemas, etc.), epilepsy, bradyacusia with prothesis, mono/bilateral blindness and mental retardation.	2 to 12 years

Gezer, 2015	neurophysiologic examinations by neonatologist (Denver Developmental Screening Test, audiometric test, weight, length and head circumference measurements, parents' questionnaires)	Infants with normal physical and neurologic development and no health issues associated with VM	N/A	Infants who died in the antenatal or postnatal period due to VM; underwent caesarean section upon the decision of the hospital's perinatology council on the basis of known poor prognostic factors such as progressive VM, intrauterine growth retardation, chromosomal abnormalities	up to 24 months
Gezer, 2016	Denver Developmental Screening test, audiometric test, mental status, strength, deep tendon reflexes, posture, tone, parental questionnaire	Normal neurodevelopment	N/A		6 to 24 months
Graham , 2001	CAT/CLAMS (for problem-solving abilities and visual–motor skills/language deficits)	score > 80	minor neurological morbidity: score of 70–80	Major neurological morbidity: score < 70, evidence of cerebral palsy, or seizure disorder	1 to 36 Months
Kennelly, 2009	Parents interview using the International manual of classification of impairments, disabilities and handicaps questionnaire – WHO 1980 evaluating locomotor activity, coordination of hand and eye, hearing and sight, development and quality of speech, learn		Mild anomaly: moderate motor skill problems (with or without tone and reflex anomalies), squint, nystagmus, mild speech difficulty, moderate learning problems and ventricular–peritoneal shunt with normal motor development	Severe neurodevelopmental: cerebral palsy (with or without the need for orthopaedic help, urinary incontinence), epilepsy, mono/bilateral blindness and significant developmental delay.	10 months to 6 years
Letouzey, 2017	Amiel-Tison scores, Denver Scale, Plalisano score, Wechsler Preschool and Primary Scale of Intelligence, Terman–Merrill scale, Wechsler Intelligence Scale for Children III or IV.	No motor or cognitive impairment was detected during follow-up	Minor motor disorders and/or cognitive disorders such as dyslexia, visuospatial attentional deficits or learning disabilities, and/or minor behavioural disorders requiring specific care.	Cerebral palsy grade 2 or greater on the Palisano scale, severe mental delay (IQ below 70)	3 months 18 years

Nan Chu, 2016	paediatricians' assessment (growth, locomotor activities, coordination, hearing and visual function, speech and socialization capacities, neurodevelopmental anomalies, other abnormalities and subsequent treatments), telephone interview, no reference to spec		N/A	Significant abnormity: structural malformations; poor locomotor, speech or socialization skills; abnormal hearing or visual function; and neurodevelopmental delay or other anomalies	16 months to 9 years
Bar-Yosef,	Vineland Adaptive Behaviour Scales (VABS)	Score above 85	N/A	Score below 85	18 to 36 months
Weichert, 2010	Neuropediatric assessment, no reference to specific tools.		N/A	Psychomotor delay if evidence of neuropsychological impairments (ranging from language delay to severe mental retardation) or motor disabilities (including cerebral palsy, hemi- and tetraparesis) on neuropediatric assessment.	1 to 151 months

Table 3

Authors	Deaths (IUD&NND)	Proportion	95% CI		Livebirths/ survivors	Proportion	95% CI		Tot Handicap	Proportion	95% CI		Normal	Proportion	95% CI		Tot N. of Woman	TOP
Beke et Al. 1999	0	0.0%	0.00	0.60	4	100.0%	0.40	1.00	3	75.0%	0.19	0.99	1	25.0%	0.01	0.81	4	0
Graham et al. 2001	0	0.0%	0.00	0.34	9	100.0%	0.66	1.00	8	88.9%	0.52	1.00	1	11.1%	0.00	0.48	9	0
Gaglioti et al. 2005	3	27.3%	0.06	0.61	8	72.7%	0.39	0.94	3	27.3%	0.06	0.61	5	45.5%	0.17	0.77	11	13
Breeze et al. 2007	0	0.0%	0.00	0.71	3	100.0%	0.29	1.00	3	100.0%	0.29	1.00	0	0.0%	0.00	0.71	3	0
Kennelly et al. 2009	7	41.2%	0.18	0.67	10	58.8%	0.33	0.82	9	52.9%	0.28	0.77	1	5.9%	0.00	0.29	17	1
Weichert et al. 2010	0	0.0%	0.00	0.18	19	100.0%	0.82	1.00	13	68.4%	0.43	0.87	6	31.6%	0.13	0.57	19	7
Gezer et Al. 2015	2	33.3%	0.04	0.78	4	66.7%	0.22	0.96	1	16.7%	0.00	0.64	3	50.0%	0.12	0.88	6	1
Nan Chu et al. 2016	0	0.0%	0.00	0.37	8	100.0%	0.63	1.00	3	37.5%	0.09	0.76	5	62.5%	0.24	0.91	8	5
Gezer et al. 2016	3	27.3%	0.06	0.61	8	72.7%	0.39	0.94	3	27.3%	0.06	0.61	5	45.5%	0.17	0.77	11	NK
Omer Bar-Yosef et al. 2017	0	0.0%	0.00	0.98	1	100.0%	0.03	1.00	0	0.0%	0.00	0.98	1	100.0%	0.03	1.00	1	0
Letouzey et al. 2017	0	0.0%	0.00	0.16	21	100.0%	0.84	1.00	8	38.1%	0.18	0.62	13	61.9%	0.38	0.82	21	NK
Total	**15**	**12.1%**	**0.04**	**0.24**	**95**	**87.9%**	**0.76**	**0.96**	**54**	49.9%	0.36	0.64	**41**	36.7%	0.23	0.52	**110**	**27**

Table 4

Authors	Normal	Proportion	95% CI		Mild handicap	Proportion	95% CI		Severe handicap	Proportion	95% CI		Total Handicap	Proportion	95% CI		Tot. Survivors
Beke et Al. 1999	1	25.0%	0.01	0.81	2	50.0%	0.07	0.93	1	25.0%	0.01	0.81	3	75.0%	0.19	0.99	4
Graham et al. 2001	1	11.1%	0.00	0.48	5	55.6%	0.21	0.86	3	33.3%	0.07	0.70	8	88.9%	0.52	1.00	9
Gaglioti et al. 2005	5	62.5%	0.24	0.91	1	12.5%	0.00	0.53	2	25.0%	0.03	0.65	3	37.5%	0.09	0.76	8
Breeze et al. 2007	0	0.0%	0.00	0.71	2	66.7%	0.09	0.99	1	33.3%	0.01	0.91	3	100.0%	0.29	1.00	3
Kennelly et al. 2009	1	10.0%	0.00	0.45	4	40.0%	0.12	0.74	5	50.0%	0.19	0.81	9	90.0%	0.55	1.00	10
Weichert et al. 2010	6	31.6%	0.13	0.57	0	0.0%	0.00	0.18	13	68.4%	0.43	0.87	13	68.4%	0.43	0.87	19
Gezer et Al. 2015	3	75.0%	0.19	0.99	0	0.0%	0.00	0.60	1	25.0%	0.01	0.81	1	25.0%	0.01	0.81	4
Nan Chu et al. 2016	5	62.5%	0.24	0.91	0	0.0%	0.00	0.37	3	37.5%	0.09	0.76	3	37.5%	0.09	0.76	8
Gezer et al. 2016	5	62.5%	0.24	0.91	0	0.0%	0.00	0.37	3	37.5%	0.09	0.76	3	37.5%	0.09	0.76	8
Omer Bar-	1	100.0%	0.03	1.00	0	0.0%	0.00	0.98	0	0.0%	0.00	0.98	0	0.0%	0.00	0.98	1

Yosef et al. 2017																	
Letouzey et al. 2017	13	61.9%	0.38	0.82	3	14.3%	0.03	0.36	5	23.8%	0.08	0.47	8	38.1%	0.18	0.62	21
Total	**41**	42.2%	0.28	0.58	**17**	**18.6%**	**0.07**	**0.34**	**37**	**39.6%**	**0.30**	**0.50**	**54**	**57.8%**	**0.42**	**0.72**	**95**