Systematic review and meta-analysis on the role of prenatal magnetic resonance imaging in the era of fetal neurosonography: mild and moderate ventriculomegaly

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ABSTRACT

Objectives: To report the rate of additional anomalies detected exclusively on prenatal MRI in fetuses affected by isolated mild or moderate ventriculomegaly (VM) according to the type of ultrasound protocol adopted (dedicated neurosonography vs standard assessment of fetal brain) and to explore whether the diagnostic performance of fetal MRI in detecting such anomalies is affected by gestational age at scan and laterality of ventricular dilatation.

Methods: The primary aim was to report the rate of additional anomalies detected exclusively on prenatal MRI in fetuses affected by isolated mild and moderate VM (ventricular dilatation between 10-15 mm) undergoing compared to those not undergoing dedicated neurosonography, defined as a detail assessment of fetal brain according to the International Society of Ultrasound in Obstetrics and Gynecology guidelines. Medline, Embase, Cinahl and Clinicaltrials.gov databases were searched. Additional anomalies were classified in: callosal, septal, posterior fossa, white matter, intra-ventricular hemorrhage, cortical, peri-ventricular heterotopia, peri-ventricular cysts and complex malformations. Furthermore, we calculated the rate of additional CNS anomalies missed at prenatal MRI and detected only at birth in fetuses who had early (≤24 weeks) compared to late (>24 weeks of gestation) MRI. A sub-analysis was performed according to the laterality (uni- vs bi-lateral VM) and the degree (mild vs moderate, defined as ventricular dilatation between 10-12 and 13-15 mm respectively) of ventricular dilatation. Finally, we explore whether MRI assessment led to a significant change in the prenatal management. Random-effect meta-analyses of proportions were used to analyze the data.

Results: 16 studies (1159 fetuses) were included in the systematic review. Overall, fetal MRI detected 10.0% (95% CI 6.2-14.5; 92/1159) of fetal anomalies not detected on ultrasound. However, when stratifying the analysis according to the type of ultrasound assessment performed, the rate of associated anomalies detected only on MRI was 5.0% (95% CI 3.0-7.0; 28/596) when dedicated neurosonography was undertaken compared to 16.8% (95% CI 8.3-27.6; 64/563) of anomalies detected in cases undergoing a standard assessment of fetal brain though the axial plane. The overall rate of additional anomalies detected only at birth and missed at prenatal MRI was 0.9% (95% CI 0.04-1.5, I^2: 0%; 8/1159). There was no difference in the rate of associated anomalies detected only after birth when fetal MRI was carried out before compared to after 24 weeks of gestation (p=0.265). The risk of detecting associated CNS abnormalities on MRI was higher for fetuses with moderate compared to mild VM (OR: 8.1, 95% CI 2.3-29.0, p= 0.001), while there was no difference for those presenting with bilateral compared to unilateral (p= 0.333) dilatation. Finally, a significant change in perinatal management, mainly TOP for parental request, following MRI detection of associated anomalies was observed in 2.9% (95% CI 0.01-1.0) of fetuses

undergoing neurosonography compared to 5.1% (95% CI 3.2-7.5) of those having standard assessment.

Conclusions: In fetuses undergoing dedicated neurosonography, the rate of CNS anomalies detected exclusively on MRI is lower compared to what has been previously reported. Early MRI has an excellent diagnostic performance in identifying additional CNS anomalies, although the findings from this review suggest that MRI performed in the third trimester may be associated with a better detection rate for some types of anomalies, such as cortical, white matter and intracranial hemorrhage.

INTRODUCTION

Ventriculomegaly (VM) encompasses a spectrum of conditions characterized by a dilatation of the lateral ventricles of the brain, typically defined as greater than 10 mm at the level of the atria, with or without dilatation of the third or fourth ventricles[1-4]. VM is the most common brain anomaly diagnosed during fetal life, with a reported prevalence ranging from 1:50 to 1:1600 newborns.[1-4]

VM is commonly categorized according to the degree of ventricular dilatation as mild (10-12 mm), moderate (13-15 mm), or severe (>15 mm); the rationale for such classification relies on the fact that the risk of associated anomalies and abnormal neurodevelopmental outcome is higher with increasing degree of dilation.[5] VM is not a unique condition, but rather a sonographic sign that represents a common endpoint of various pathologic processes with different outcomes and prognosis; it may also be a physiologic finding representing an extreme normal variation.[6-8]

The main determinants of post-natal outcome in fetuses presenting with VM are the etiology, presence of associated anomalies and severity of ventricular dilation. Thus, the main issues to be resolved during the diagnostic work-up of a fetus with VM are to rule out infection, chromosomal, central nervous system (CNS) and extra-CNS anomalies.[7]

Fetal magnetic resonance imaging (MRI) has been shown to add additional information compared to ultrasound in fetuses affected by CNS anomalies.[10] The overall prevalence of MRI-detected additional brain abnormalities prenatally has been reported to be as high as 19% in fetuses with VM, irrespective of the degree of ventricular dilatation.[11] However, the majority of these studies do not report the type of ultrasound assessment performed and the MRI is performed at varying gestational ages. The International Society of Ultrasound in Obstetrics and Gynecology recommends that fetuses presenting with CNS anomalies should undergo a multiplanar assessment of the brain through axial, coronal and sagittal views of the fetal head.[9] Therefore, it is plausible that the rate of associated anomalies detected exclusively on MRI reported in the published literature may be affected by the type of ultrasound assessment performed.

The primary aim of this systematic review was to report the rate of additional anomalies detected exclusively on prenatal MRI in fetuses affected by isolated VM according to the type of ultrasound protocol adopted. The secondary aim was to explore whether the diagnostic performance of fetal MRI in detecting such anomalies is affected by gestational age at scan.

METHODS

Protocol, eligibility criteria, information sources and search

This review was performed according to a priori designed protocol recommended for systematic reviews and meta-analysis.[12-14] Medline, Embase, Cinahl and Clinicaltrials.gov databases were searched electronically in June 2018, utilizing combinations of the relevant medical subject heading (MeSH) terms, key words, and word variants for "magnetic resonance imaging" and "ventriculomegaly" (Supplementary Table 1). The search and selection criteria were restricted to English language. Reference lists of relevant articles and reviews were hand searched for additional reports. PRISMA and MOOSE guidelines were followed.[15-17] The study was registered with the PROSPERO database (Registration number: CRD42018104173).

Study selection, data collection and data items

The primary aim was to report the rate of additional anomalies detected exclusively on prenatal MRI in fetuses affected by isolated mild and moderate VM, defined as ventricular dilatation between 10-15 mm, undergoing compared to those not undergoing dedicated neurosonography, defined as a detail assessment of fetal brain through axial, sagittal and coronal views according to ISUOG guidelines.

Additional anomalies were classified into:

- Callosal anomalies, including complete and partial agenesis (ACC), hypoplasia and dysgenesis of the corpus callosum
- Septal anomalies, including all the anomalies characterized by a primary involving the septum pellucidum with a normally present corpus callosum
- Posterior fossa anomalies, including all defects involving the cerebellar vermis and/or hemispheres
- Intra-ventricular hemorrhage
- Cortical anomalies, including all abnormalities associated with a primary defect in neuronal migration towards the cortical surface of the brain
- Peri-ventricular heterotopia
- Other white matter anomalies
- Peri-ventricular cysts
- Complex brain anomalies including all defects characterized by the presence of multiple intra-cranial anomalies
- Other cerebral anomalies

For the purpose of the analysis, we did not consider as associated anomalies biometric variation in brain structures, such as mega cisterna magna, increased or reduced degree of ventricular dilation or of cranial size.

Furthermore, we aimed to perform a sub-group analysis according to the laterality (unilateral-vs bilateral VM) and degree (10-12 mm vs 13-15 mm) of ventricular dilatation.

The secondary aim was to elucidate whether the diagnostic performance of fetal MRI for detected additional CNS anomalies was affected by gestational age at scan. For the purpose of the analysis, we calculated the rate of additional CNS anomalies missed at prenatal MRI and detected only at birth in fetuses who had early (≤24 weeks) compared to late (>24 weeks of gestation) MRI. Finally, we explored whether MRI detection of associated anomalies led to a change in the prenatal management of the pregnancy, mainly defined as termination of pregnancy (TOP) for parental request due to the higher risk of abnormal neurodevelopmental outcome followed by the MRI detection of associated anomalies.

Only studies reporting the prevalence of brain anomalies diagnosed on MRI in fetuses affected by isolated VM and confirmed at post-natal imaging or post-mortem examination, in case of termination of pregnancy or fetal demise, were considered eligible for the inclusion in the present systematic review. VM was defined as isolated when no other CNS and extra-CNS anomalies, were detected on ultrasound.

Studies including cases with fetal anomalies, those including exclusively cases of severe VM (defined as ventricular dilation >15 mm) and those not reporting the degree of ventricular dilation were excluded in view of the higher risk of associated brain anomalies in cases presenting with additional anomalies and/or severe VM. Case reports, conference abstracts and case series with fewer than 3 cases were excluded to avoid publication bias. Furthermore, studies published before ISUOG statement for a detailed assessment of fetal brain was released (2007) were also excluded as advances in prenatal imaging and difficulties in extrapolating the type of ultrasound protocol make them less relevant.

Two authors (DDM, FGS) reviewed all abstracts independently. Agreement regarding potential relevance was reached by consensus or resolved by discussion with a third reviewer (FDA). Full text copies of those papers were obtained, and the same reviewers independently extracted relevant data regarding study characteristics and pregnancy outcome. Inconsistencies were discussed by the reviewers and consensus reached or by discussion with a third author. If more than one study was published on the same cohort with identical endpoints, the report containing the most

comprehensive information on the population was included to avoid overlapping populations. For those articles in which information was not reported but the methodology was such that this information would have been recorded initially, the authors were contacted.

Quality assessment of the included studies was performed using the Newcastle-Ottawa Scale (NOS) for cohort studies. According to NOS, each study is judged on three broad perspectives: the selection of the study groups, the comparability of the groups, and the ascertainment outcome of interest.[18] Assessment of the selection of a study includes the evaluation of the representativeness of the exposed cohort, selection of the non-exposed cohort, ascertainment of exposure and the demonstration that outcome of interest was not present at start of study. Assessment of the comparability of the study includes the evaluation of the comparability of cohorts based on the design or analysis. Finally, the ascertainment of the outcome of interest includes the evaluation of the type of the assessment of the outcome of interest, length and adequacy of follow-up. According to NOS a study can be awarded a maximum of one star for each numbered item within the Selection and Outcome categories. A maximum of two stars can be given for Comparability.[18]

Statistical analysis

First, we performed random-effect meta-analyses of proportions to estimate the pooled rates of each brain anomaly in fetuses affected by isolated VM undergoing MRI assessment. Second, we used random-effect head-to-head meta-analyses to directly compare the risk for detecting an associated anomaly in fetuses undergoing early (≤24 weeks) compared to late (>24 weeks) fetal MRI, expressing the results as summary odds ratio (OR) and relative 95% Confidence Interval (CI), and evaluating the statistical heterogeneity through I^2 metric. Data from individual studies were also combined to estimate the weighted mean gestational age at diagnosis (of brain anomalies) among fetuses with VM detected through multiplanar approach. Only sparse data on gestational age were available for the standard US group, as well as on the time interval between US and MRI exams for both groups. In these cases, no meta-analyses were performed, and the results were reported only narratively for descriptive purposes. All included studies reported single-group analyses, and no outcome comparison between groups was available, thus no head-to-head meta-analysis could be performed.

Publication bias was assessed graphically, through funnel plots, and formally, through Egger's regression asymmetry test; formal tests for funnel plot asymmetry were not performed when the total number of publications included for each outcome is <10 because the power of the test is too low to distinguish chance from real asymmetry.

Both proportion meta-analyses and single-group meta-analyses of continuous data were performed using a random-effect model to account for inter-study heterogeneity, and all analyses were carried out using Stata, version 13.1 (Stata Corp., College Station, TX, 2013).

RESULTS

General characteristics

Six-hundred and twenty articles were identified, 66 were assessed with respect to their eligibility for inclusion (Supplementary Table 2) and 16 studies were included in the systematic review (Table 1, Figure 1, Supplementary Table 3)[19-34]. These sixteen studies included 1159 fetuses affected by isolated mild or moderate VM, defined as ventricular dilatation between 10 and 15 mm. The definition of isolated VM was based upon multiplanar neurosonography in eight studies (596 fetuses), while a standard axial assessment of fetal brain was undertaken in the remaining eight studies (563 fetuses). Mean gestational age at MRI was 27.2 (95% CI 26.8-27.6) weeks for fetuses undergoing neurosonography compared to 27.1 (95% CI 26.9-27.3) for those having standard assessment of the fetal brain.

Associated anomalies confirmed at birth or autopsy were found in 10.56% (95% CI 6.7-15.2, I^2: 78.7% 100/1159) of cases with a prenatal diagnosis of isolated VM on ultrasound.

The results of the quality assessment of the included studies using Newcastle-Ottawa Scale (NOS) are presented in Table 2. Most of the included studies showed an overall good score regarding the selection and comparability of the study groups, and for ascertainment of the outcome of interest. The main weaknesses of these studies were their retrospective design, small sample size, different gestational ages at scan and lack of stratification of the results according to laterality and degree of ventricular dilatation for most of the included studies. Furthermore, a comprehensive stratification of the analysis according to the gestational age at scan was possible only by adopting 24 weeks of gestation as cut-off, while we could not perform any meaningful sub-analysis considering different time intervals between US and MRI assessments.

Synthesis of the results

Sixteen studies[19-34] (1159 fetuses) explored the role of fetal MRI in detecting associated anomalies in fetuses with a prenatal diagnosis of isolated VM on ultrasound. Overall, fetal MRI detected 10.0% (95% CI 6.2-14.5) of fetal anomalies not detected on ultrasound (Table 3). However, when stratifying the analysis according to the type of ultrasound assessment performed, the rate of associated anomalies detected only on MRI was 5.0% (95% CI 3.0-7.0) when dedicated neurosonography was undertaken compared to 16.8% (95% CI 8.3-27.6) of anomalies detected in cases undergoing a standard assessment of fetal brain though the axial plane (Table 3, Figure 2).

When stratifying the analysis according to the type of anomaly, the incidence of undetected callosal anomalies on ultrasound was 0.7% (95% CI 0.2-1.5) in the group fetuses undergoing neurosonography and 2.9% (95% CI 1.1-5.7) for those having standard assessment of fetal brain,

while the corresponding figures for posterior fossa anomalies were 0.4% (95% CI 0.1-1.1) and 0.9% (95% CI 0.2-2.1).

Cortical anomalies missed at ultrasound were detected in 1.6% (95% CI 0.9-2.3) of fetuses with a prenatal diagnosis of isolated VM with no difference between cases undergoing neurosonography and standard assessment of fetal brain (PP: 1.6%, 95% CI 0.7-2.7 and 1.5%, 95% CI 0.7-2.7)). Hemorrhagic lesions were missed at ultrasound and detected exclusively on MRI in 1.1% (95% CI 0.3-2.4) of cases undergoing detailed neurosonography and 2.0% (95% CI 0.6-4.1) of those receiving standard assessment (Table 4). Finally, white matter anomalies were missed at ultrasound and detected on MRI in 1.4% (95% CI 0.6-2.5) of cases with an ultrasound diagnosis of isolated VM. When stratifying the analysis according to the type of ultrasound protocol adopted, the detection rate of fetal MRI in identifying white matter anomalies missed at the scan was 1.6% (95% CI 0.7-2.7) of cases undergoing neurosonography and 1.8% (95% CI 0.3-4.4) of cases receiving a standard ultrasound assessment.

The overall rate of additional anomalies detected only at birth and missed at prenatal MRI was 0.9% (95% CI 0.04-1.5, I^2:0%). The rate of associated CNS anomalies missed at prenatal MRI and diagnosed only at birth was 1.3% (95% CI 0.5-2.4) when the MRI was performed before and 0.8% (95% CI 0.3-1.7) when carried out after 24 weeks of gestation, with no significant difference between the two groups (OR: 2.3, 95% CI 0.5-9.9, I^2; 0%, p=0.265).

Sub-analyses according to laterality and degree of ventricular dilatation were carried out including exclusively fetuses undergoing multiplanar assessment and are shown in Supplementary Table 4 and 5.

The risk of detecting associated CNS on MRI was higher for fetuses with moderate (PP: 22.6%, 95% CI 11.1-36.7) compared to mild (PP: 3.5%, 95% CI 1.7-6.1) VM (OR: 8.1, 95% CI 2.3-29.0; I^2: 18.1%, p= 0.001), while there was no difference for those presenting with bilateral (PP: 7.2%, 95% CI 3.3-12.3, I^2: 6.7%) compared to unilateral (PP: 3.0%, 95% CI 0.8-6.3, I^2: 0%) (OR: 1.8, 95% CI 0.6-5.4; I^2: 8.1%, p= 0.333).

Finally, we explore the rate of the change in perinatal management after prenatal MRI. Overall 4.6% (95% CI 2.1-8.0; I^2: 61%) of fetuses with a prenatal diagnosis of isolated VM on ultrasound had a significant change in perinatal management, mainly TOP for parental request, following MRI detection of associated anomalies. When stratifying the analysis according to the type of ultrasound assessment performed, a significant change in perinatal management involved 2.9% (95% CI 0.01-

1.0, I^2: 65.3%) of fetuses undergoing neurosonography compared to 5.1% (95% CI 3.2-7.5; I^2: 7.8%) of those having standard assessment.

DISCUSSION

Main findings

The findings from this systematic review show that, in fetuses affected by VM undergoing dedicated neurosonography, the rate of CNS anomalies detected exclusively on MRI is lower compared to what has been previously reported. Fetal MRI has a high diagnostic accuracy in identifying associated anomalies regardless of gestational age at MRI. Finally, the risk of detecting associated anomalies is higher in fetuses with moderate compared to mild while there was no difference between cases with unilateral compared to bilateral VM.

Limitations

Retrospective design, small sample size, different gestational ages at scan and lack of stratification of the results according to laterality and degree of ventricular dilatation for most of the included studies represents the main limitations of the represent systematic review. Furthermore, not all cases presenting additional anomalies on MRI were screened for aneuploidies or infection. In this scenario, it might be entirely possible that some cases affected by aneuploidies of infection diagnosed only later on after birth were included in the analysis thus affecting the robustness of the results. Finally, it was not possible to completely rule-out inclusion of cases complicated by maternal medical conditions potentially leading to an increased risk of associated CNS in the setting of VM, which may explain the relatively high rate of acquired brain anomalies such as hemorrhage reported in this review.

Implications for clinical practice and research

Ruling out associated anomalies in fetuses with a prenatal diagnosis of VM is fundamental as neurodevelopmental outcome of these children is largely affected by the presence of associated malformations.

The International Society of Ultrasound in Obstetrics and Gynecology recommends that fetuses presenting with CNS anomalies should undergo a multiplanar assessment of fetal head, in order to rule associated anomalies which can be potentially missed on a standard assessment. Likewise, the Society for Maternal-Fetal Medicine suggests that MRI should be considered in cases of mild or moderate fetal VM although it may be of less value if the women has had a detailed ultrasound performed by an individual with specific experience and expertise in sonographic imaging of the fetal brain. These statements from the two major bodies society of maternal-fetal medicine highlight the need for a detailed assessment of fetal brain when VM is detected on the scan. Despite this, it is common clinical practice to refer fetuses presenting with VM to MRI without a detailed assessment

of the brain. This has led to a high reported incidence of associated anomalies detected only on MRI in fetuses presenting with isolated VM on ultrasound.

In the present review, the large majority of associated malformations undetected on ultrasound in cases undergoing standard assessment were callosal anomalies. This underlines the need for detailed neurosonography in fetuses presenting with ventricular dilatation in axial views in order to reduce the number of cases incorrectly labelled as isolated VM. This is also fundamental as fetal MRI may not be immediately available and a late diagnosis of associated anomalies may lead to increased parental stress and lack of legal options for the prenatal management of the pregnancy. This is also highlighted by the different rates in the change of prenatal management after MRI in fetuses undergoing compared to those not undergoing neurosonography.

Fetal MRI has been suggested to have a high diagnostic accuracy in detecting cortical malformations, such as polymicrogyria and schizencephaly.[10,35] The true prevalence of congenital cortical anomalies in the general population is largely unknown and some of these cases are suspected on fetal ultrasound during the third trimester of pregnancy based on the subjective findings of immature sulcation, thin and smooth cortex or wide and thick gyri. In the present systematic review, the rate of cortical anomalies detected exclusively on MRI was about 1.6%, highlighting the need for a detailed MRI assessment of fetal brain in order to rule out such anomalies.

The severity of ventricular dilatation is associated with an increasing risk of adverse neurodevelopmental outcome in fetuses presenting with isolated VM. In the present systematic review, the rate of associated anomalies detected only on MRI was 3.5% and 22.6% with mild and moderate VM, suggesting that increasing ventricular dilatation is associated with a higher risk of associated anomalies. Conversely, there was no difference in the rate of associated anomalies detected only on MRI in fetuses with unilateral compared to bilateral VM, although the very small number of cases included in this sub-analysis may have led to a lack of statistical power.

Gestational age at MRI is another important clinical information when assessing fetuses with an ultrasound diagnosis of isolated VM. Early (second trimester) MRI assessment is useful to confirm the diagnosis and rule out associated anomalies especially in those countries where termination of pregnancy beyond the second trimester is not allowed but may potentially overlook anomalies such as cortical malformations or hemorrhage which can become evident only later on in gestation. In the present systematic review, the overall rate of additional anomalies detected only at birth and

missed at prenatal MRI was 1.3% (95% CI 0.5-2.4) when MRI was performed before and 0.8% (95% CI 0.3-1.7) when carried out after 24 weeks of gestation. Although there was no statistical difference in the rate of undetected CNS anomalies between early and late MRI, it would be reasonable to perform an MRI scan in the third trimester of pregnancy as most of the anomalies co-existing with VM, such as cortical, white matter or hemorrhage can become more evident after 24 weeks' gestation. However, parents should be reassured that, in cases with VM apparently isolated on fetal MRI, the probability of undetected anomalies at birth is low.

Conclusion

Fetuses affected by isolated VM on ultrasound screening examination should be referred to dedicated neurosonography in order to rule out associated anomalies which can potentially affect the short and long-term neurodevelopmental outcome of these children. Fetal MRI assessment of these fetuses is recommended to detect associated anomalies that can be missed on neurosonography in about 5% of the cases. Although early MRI is reliable, a third trimester scan is technically more feasible and may detect conditions potentially missed at second trimester scan, such as hemorrhage. Future, large, prospective studies sharing objective protocols for ultrasound imagining of fetal brain are needed to better elucidate the actual role of fetal MRI when fetal neurosonography is performed.

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REFERENCES

1. Achiron R, Schimmel M, Achiron A, Mashiach S. Fetal mild idiopathic lateral ventriculomegaly: is there a correlation with fetal trisomy? *Ultrasound Obstet Gynecol* 1993; **3**:89-92.
2. Alagappan R, Browing PD, Laorr A, McGahan JP. Distal lateral ventricular atrium: reevaluation of normal range. *Radiology* 1994; **193**:405-408.
3. Nomura ML, Barini R, De Andrade C, Milanez H, Simoni RZ, Peralta CF, Machado IN, Zambelli H, Maio KT. Congenital hydrocephalus: gestational age and neonatal outcomes. *Arch Gynecol Obstet* 2010; **282**:607-611.
4. Garel C, Luton D, Oury JF, Gressens P. Ventricular dilatations. Childs Nerv Syst 2003; **19**:517-523.
5. Society for Maternal-Fetal Medicine (SMFM); Fox NS, Monteagudo A, Kuller JA, Craigo S, Norton ME. Mild fetal ventriculomegaly: diagnosis, evaluation, and management. *Am J Obstet Gynecol* 2018; **219** :B2-B9.
6. Signorelli M, Tiberti A, Valsariati D, Molin E, Cerri V, Groli C, Bianchi UA. Width of fetal lateral ventricular atrium between 10 and 12 mm: a simple variation of the norm? *Ultrasound Obstet Gynecol* 2004; **23**:14-18.
7. Melchiorre K, Bhide A, Gika AD, Pilu G, Papageorghiou AT. Counseling in isolated mild fetal ventriculomegaly. *Ultrasound Obstet Gynecol* 2009; **34**:212-224.
8. Shizuo OI. Controversies in definition and classification of hydrocephalus. *Neurol Med Chir* 2010; **50**:859-869.
9. ISUOG Guidelines. Sonographic examination of the fetal central nervous system: guidelines for performing the 'basic examination' and the 'fetal neurosonogram' *Ultrasound Obstet Gynecol* 2007; **29**:109–116.
10. Rossi AC, Prefumo F. Additional value of fetal magnetic resonance imaging in the prenatal diagnosis of central nervous system anomalies: a systematic review of the literature. *Ultrasound Obstet Gynecol* 2014; **44**:388–393.
11. Scala C, Familiari A, Pinas A, Papageorghiou AT, Bhide A, Thilaganathan B, Khalil A. Perinatal and long-term outcome in fetuses diagnosed with isolated unilateral ventriculomegaly: systematic review and meta-analysis. *Ultrasound Obstet Gynecol* 2017; **49**:450-459.
12. Henderson LK, Craig JC, Willis NS, Tovey D, Webster AC. How to write a Cochrane systematic review. *Nephrology (Carlton)* 2010; 15: 617-624.

13. NHS Centre for Reviews and Dissemination. Systematic reviews: CRD's guidance for undertaking reviews in health care. University of York: York (UK), 2009. Available at: https://www.york.ac.uk/media/crd/Systematic_Reviews.pdf.
14. Welch V, Petticrew M, Petkovic J, Moher D, Waters E, White H, Tuqwell P. Extending the PRISMA statement to equity-focused systematic reviews (PRISMA-E 2012): explanation and elaboration. *J Clin Epidemiol* 2016; **70**:68-89.
15. Moher D, Liberati A, Tetzlaff J, Altman DG, and the PRISMA Group. Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. *Ann Intern Med* 2009; **151**:264–269.
16. Zorzela L, Loke YK, Ioannidis JP, Golder S, Santaguida P, Altman DG, Moher D, Vohra S; PRISMA harms group. PRISMA harms checklist: improving harms reporting in systematic reviews. *BMJ* 2016; **352**:i157.
17. Stroup DF, Berlin JA, Morton SC, Olkin I, Williamson GD, Rennie D, Moher D, Becker BJ, Sipe TA, Thacker SB. Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis of Observational Studies in Epidemiology (MOOSE) group. *JAMA* 2000; **283**:2008–2012.
18. Newcastle-Ottawa Scale for assessing the quality of nonrandomised studies in meta-analyses. Available at: http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp
19. Griffiths PD, Brackley K, Bradburn M, Connolly DJ, Gawne- Cain ML, Griffiths DI, Kilby MD, Mandefield L, Mooney C, Robson SC, Vollmer B, Mason G. Anatomical subgroup analysis of the MERIDIAN cohort: ventriculomegaly. *Ultrasound Obstet Gynecol* 2017; **50**:736-744.
20. Lavongtheung A, Jedraszak G, Naepels P, Tourneux P, Gondry-Jouet C, Le Moing AG, Gondry J, Chevreau J. Should isolated fetal ventriculomegaly measured below 12 mm be viewed as a variant of the norm? Results of a 5-year experience in prenatal referral center. *J Matern Fetal Neonatal Med* 2017; **11**:1-7.
21. Mehlhorn, AJ, Morin CE, Wong- You- Cheong JJ, Contag SA. Mild fetal cerebral ventriculomegaly: prevalence, characteristics, and utility of ancillary testing in cases presenting to a tertiary referral center. *Prenat Diagn* 2017; **37**:647–657.
22. Gezer NS, Gezer C, Ekin A, Yesilirmak DC, Solmaz U, Dogan A, Guleryuz H. Obstetric and neurodevelopmental outcome in fetal cerebral ventriculomegaly. *Clin Exp Obstet Gynecol* 2016; **43**:490-494.

23. Tonni G, Vito I, Palmisano M, Martins WP, Araujo Júnior E. Neurological Outcome in Fetuses with Mild and Moderate Ventriculomegaly. *Rev Bras Ginecol Obstet* 2016; **38**:436-442.
24. Baffero GM, Crovetto F, Fabietti I, Boito S, Fogliani R, Fumagalli M, Triulzi F, Mosca F, Fedele L, Persico N. Prenatal ultrasound predictors of postnatal major cerebral abnormalities in fetuses with apparently isolated mild ventriculomegaly. *Prenat Diagn* 2015; **35**:783–788.
25. Kandula T, Fahey M, Chalmers R, Edwards A, Shekleton P, Teoh M, Clark J, Goergen SK. Isolated ventriculomegaly on prenatal ultrasound: what does fetal MRI add? J Med Imaging *Radiat Oncol* 2015; **59**:154–162.
26. Paladini D, Quarantelli M, Sglavo G, Pastore G, Cavallaro A, D'Armiento MR, Salvatore M, Nappi C. Accuracy of neurosonography and MRI in clinical management of fetuses referred with central nervous system abnormalities. *Ultrasound Obstet Gynecol* 2014; **44**:188–196.
27. Pasquini L, Masini G, Gaini C, Franchi C, Trotta M, Dani C, Di Tommaso M. The utility of infection screening in isolated mild ventriculomegaly: an observational retrospective study on 141 fetuses. *Prenat Diagn* 2014; **34**:1295-1300.
28. Parazzini C, Righini A, Doneda C, Arrigoni F, Rustico M, Lanna M, Triulzi F. Is fetal magnetic resonance imaging indicated when ultrasound isolated mild ventriculomegaly is present in pregnancies with no risk factors? *Prenat Diag* 2012; **32**:752–757.
29. Miguelote RF, Vides B, Santos RF, Palha JA, Matias A, Sousa N. Cortical maturation in fetuses referred for 'isolated' mild ventriculomegaly: a longitudinal ultrasound assessment. *Prenat Diagn* 2012; **32**:1273-81.
30. Han Huang Y, Hang Ng S, Hong Toh C, Ming Wu Y, Fai Wong H, Ching Wong AM. Fetal Ventriculomegaly: Investigating Additional Brain Abnormalities by using MR Imaging. *J Radiol Sci* 2013; **38**:35-41.
31. Griffiths P, Reeves M, Morris J, Mason G, Russell S, Paley M, Whitby E. A prospective study of fetuses with isolated ventriculomegaly investigated by antenatal sonography and in utero MR imaging. *Am J Neuroradiol* 2010; **31**:106–111.
32. Yin S, Na Q, Chen J, Li-Ling J, Liu C. Contribution of MRI to detect further anomalies in fetal ventriculomegaly. *Fetal Diagn Ther* 2010; **27**:20–24.
33. Benacerraf BR, Shipp TD, Bromley B, Levine D. What does magnetic resonance imaging add to the prenatal sonographic diagnosis of ventriculomegaly? *J Ultrasound Med* 2007; **26**:1513–1522.

34. Morris JE, Rickard S, Paley MNJ, Griffiths PD, Rigby A, Whitby EH. The value of in-utero magnetic resonance imaging in ultrasound diagnosed foetal isolated cerebral ventriculomegaly. *Clin Radiol* 2007; **62**:140–144.
35. Glenn OA, Cuneo AA, Barkovich AJ, Hashemi Z, Bartha AI, Xu D. Malformations of cortical development: diagnostic accuracy of fetal MR imaging. *Radiology* 2012; **263**:843–855.

Figure legend

Figure 1. Systematic review flowchart.

Figure 2. Pooled rates of additional brain anomalies detected through MRI in fetuses with isolated ventriculomegaly diagnosed through multiplanar and standard ultrasound assessment of fetal brain respectively.

Table 1. General characteristics of the included studies.

Author	Year	Country	Study design	Study period	GA at MRI	US to MRI interval	Ultrasound assessment	Multiplanar US assessment	Field strength	Definition of VM	Post-natal imaging	Fetuses (n)
Griffiths[19]	2017	United Kingdom	Prospective	2011-2014	NS	14 days	NS	Not performed	1.5 T	10-15 mm	US, MRI, CT	280
Levaillant[20]	2017	France	Retrospective	2011-2015	31	Max 9 weeks	NS	Not performed	1.5 T	10-12 mm	US, MRI	14
Mehlhorn[21]	2017	United States	Retrospective	2009-2015	29.7	Max 5 weeks	TA	Not performed	1.5 T	10-15 mm	NS	24
Sozer[22]	2016	Turkey	Retrospective	2007-2009	NS	NS	NS	Not performed	1,5 T	10-15 mm	US, MRI, CT	14
Tonni[23]	2016	Italy	Prospective	2007-2010	26.6	1 week (mean)	NS	Performed	1.5 T	10-15 mm	US, MRI	54
Barrero[24]	2015	Italy	Retrospective	2001-2012	26.4 (20-36)	1.0 week (0.0-12.6)	TA	Performed	1.5 T	10-15 mm	US, MRI	118
Kandula[25]	2015	Australia	Prospective	2006-2013	28 (25.3-32)	2 weeks	NS	Not performed	1.5 T	10-15 mm	NS	52
Paladini[26]	2014	Italy	Retrospective	2005-2012	27 (21-36)	1 week	TA and TV	Performed	1.5 T	10-15 mm	US, MRI, CT	30
Pasquini[27]	2014	Italy	Retrospective	2007-2012	30.16	3.7 weeks	TA and TV	Performed	1.5 T	10-15 mm	US, MRI	132
Parazzini[28]	2012	Italy	Retrospective	2003-2010	26±4.2	7.6 days	TA and TV	Performed	1.5 T	<12 mm	US, MRI, CT	179
Miguelote[29]	2012	Portugal	Prospective	2010-2011	NS	NS	NS	Performed	1.5 T	10-15 mm	US, MRI	18
Huang[30]	2013	Taiwan	Retrospective	2003-2010	NS	NS	NS	Not reported	1.5 T	10-15 mm	NS	42
Griffiths[31]	2010	United Kingdom	Prospective	2005-2009	NS	4 days	NS	Not reported	1.5 T	10-12 mm	NS	119
Yin[32]	2010	China	Prospective	2006-2008	31-38	NR	TA	Performed	1.5 T	10-12 mm	NS	51
Benacerraf[33]	2007	United States	Prospective	NR	24.14±5.02	NR	TA and TV	Performed	1.5 T	10-12 mm	NS	14
Morris[34]	2007	UK	Retrospective	1999-2003	22.8	4 days	NS	Not performed	1.5 T	10-15 mm	NS	18

NS: not stated; MRI; magnetic resonance imaging; US: ultrasound; CT: computerized tomography

Table 2. Quality assessment of the included studies according to Newcastle-Ottawa Scale (NOS) for cohort studies; a study can be awarded a maximum of one star for each numbered item within the Selection and Outcome categories. A maximum of two stars can be given for Comparability.

Author	Year	Selection	Comparability	Outcome
Griffiths[19]	2017	★★	★	★★
Lavongtheung[20]	2017	★★	★	★★
Mehlhorn[21]	2017	★★	★	★★
Gezer[22]	2016	★★	★	★★
Tonni[23]	2016	★★	★	★★
Baffero[24]	2015	★★	★	★★
Kandula[25]	2015	★★	★	★
Paladini[26]	2014	★★	★★	★★
Pasquini[27]	2014	★★	★	★★
Parazzini[28]	2012	★★	★	★★
Miguelote[29]	2012	★★	★	★
Huang[30]	2013	★★	★	★
Griffiths[31]	2010	★★	★	★★
Yin[32]	2010	★★	★	★★
Benacerraf[33]	2007	★★	★	★★
Morris[34]	2007	★★	★	★★

Table 3. Contribution (expresses as pooled proportion, PP) of fetal MRI in detecting associated anomalies in fetuses affected by isolated VM on ultrasound (95% CI between parentheses).

	Studies	**Fetuses (n/N)**	**Pooled proportions**	**I^2**
All cases	16	92/1159	9.95 (6.2-14.5)	78.7
Cases undergoing neurosonography	8	28/596	5.00 (3.0-7.0)	5.9
Cases undergoing standard assessment	8	64/563	16.83 (8.3-27.6)	86.1

Table 4: Pooled proportion (95%CI) for the rate of additional anomalies detected only on fetal MRI in fetuses with a prenatal diagnosis of isolated VM according to different ultrasound assessments of fetal brain.

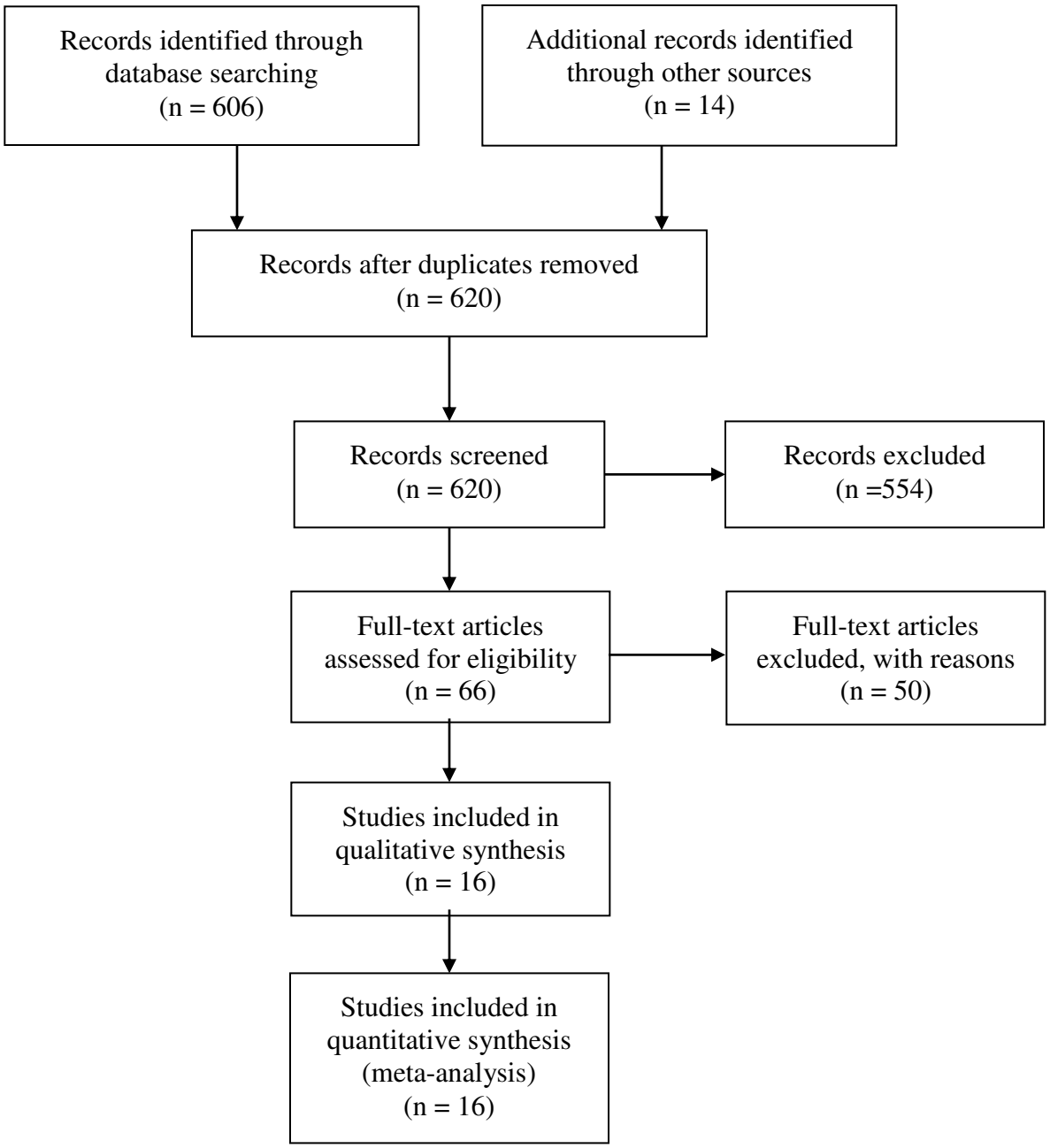
	All cases				*Cases undergoing neurosonography*				*Cases undergoing standard assessment*			
CNS anomalies	**Studies (n)**	**Fetuses (n/N)**	**Pooled proportions**	**I^2 (%)**	**Studies (n)**	**Fetuses (n/N)**	**Pooled proportions**	**I^2 (%)**	**Studies (n)**	**Fetuses (n/N)**	**Pooled proportions**	**I^2 (%)**
Callosal	16	15/1159	1.42 (0.7-2.4)	26.0	8	2/596	0.67 (0.2-1.5)	0	8	13/563	2.92 (1.1-5.7)	46.3
Septal	16	2/1159	0.45 (0. 1-0.9)	0	8	0/596	0 (0-0.9)	0	8	2/563	0.66 (0.2-1.5)	0
Posterior fossa	16	5/1159	0.56 (0.2-1.1)	5.8	8	2/596	0.44 (0.1-1.1)	0.8	8	3/563	0.85 (0.2-2.1)	19.7
Hemorrhage	16	14/1159	1.43 (0.6-2.5)	35.4	8	5/596	1.07 (0.3-2.4)	32.1	8	9/563	1.97 (0.6-4.1)	39.2
Cortical	16	15/1159	1.55 (0.9-2.3)	0	8	8/596	1.56 (0.7-2.7)	0	8	7/563	1.53 (0.7-2.7)	0
eriventricular heterotopia	16	0/1159	0 (0-0.7)	0	8	0/596	0 (0.0.9)	0	8	0/563	0 (0-0.9)	0
White matter	16	15/1159	1.39 (0.6-2.5)	32.8	8	8/596	1.57 (0.7-2.7)	0	8	7/563	1.75 (0.3-4.4)	57.9
Periventricular cyst	16	2/1159	0.41 (0.1-0.9)	0	8	1/596	0.45 (0.01-1.1)	0	8	1/563	0.36 (0.03-1.0)	0
Complex	16	8/1159	0.85 (0.4-1.5)	0	8	1/596	0.44 (0.01-1.1)	0	8	7/563	1.55 (0.7-2.7)	0
Other	16	16/1159	1.68 (0.5-3.5)	67.9	8	1/596	0.38 (0.001-1.0)	0	8	15/563	4.03 (0.7-9.9)	82.8

Identification

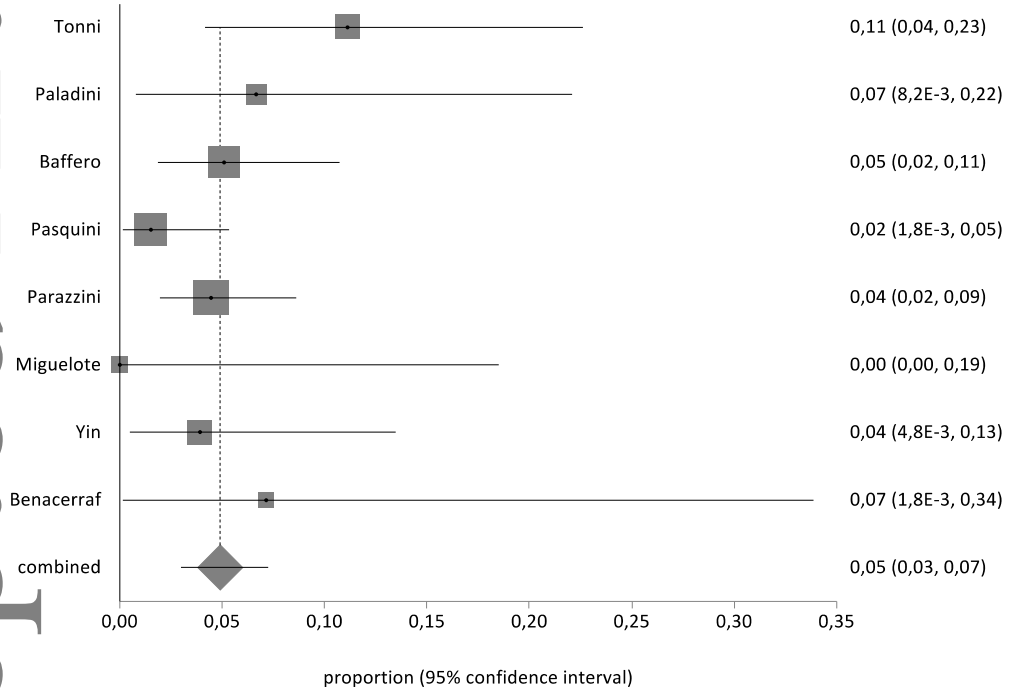
Screening

Eligibility

Included



Dedicated neurosonography



Standard assessment of fetal brain