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Neurodevelopmental outcome in isolated mild fetal ventriculomegaly: systematic review and meta-analysis

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KEYWORDS: fetal; follow-up; isolated; mild; neurodevelopmental; outcome; review; ventriculomegaly

ABSTRACT

Objectives *The finding of fetal ventriculomegaly is variably associated with other fetal abnormalities and, even when isolated, is thought to be linked to abnormal neurodevelopmental outcome. The aim of this study was to undertake a systematic review and meta-analysis of the current literature to assess the prevalence of neurodevelopmental delay in cases of isolated mild fetal ventriculomegaly, as well as the false-negative rate of prenatal imaging for the diagnosis of associated abnormalities in patients referred for isolated mild ventriculomegaly.*

Methods *Studies that assessed neurodevelopmental outcome in isolated ventriculomegaly were identified from a search of scientific databases. Studies that did not check for karyotype or that excluded cases of bilateral ventriculomegaly were not included in the analysis. Ventriculomegaly was defined as mild when the width of the ventricular atrium was between 10 and 15 mm. Cases in which an associated abnormality (abnormal karyotype, structural abnormality or fetal infection) was observed either before or after birth were not considered as part of the isolated group. Neurodevelopmental delay was defined as an abnormal quotient score, according to the test used.*

Results *The search yielded 961 possible citations; of these, 904 were excluded by review of the title or abstract as they did not meet the selection criteria. Full manuscripts were retrieved for 57 studies, and 20 were included in the review with a total of 699 cases of isolated mild ventriculomegaly. The overall prevalence of neurodevelopmental delay was 7.9% (95% CI, 4.7–11.1%). Of the 20 studies included in the systematic review, nine reported data on postnatal imaging, showing a prevalence of previously undiagnosed findings of 7.4% (95% CI, 3.1–11.8%).*

Conclusions *The false-negative rate of prenatal imaging is 7.4% in apparently isolated fetal ventriculomegaly of ≤ 15 mm. The incidence of neurodevelopmental delay in truly isolated ventriculomegaly of ≤ 15 mm is 7.9%. As the latter rate is similar to that noted in the general population, large prospective cohort studies assessing the prevalence of childhood disability, rather than subtle neurodevelopmental delay, are required.*

INTRODUCTION

Fetal ventriculomegaly is defined as an enlargement of the atrium of the lateral ventricle. The diagnosis of ventriculomegaly is usually based on reference ranges established by Cardoza *et al.*, in 1988, in which the upper limit of the fetal ventricular measurement does not change during gestation[1]. According to these criteria, a width of less than 10.0 mm is considered normal. Measurements between 10.0 and 15.0 mm are often described as mild or moderate ventriculomegaly and a measurement of more than 15.0 mm is described as severe[2]. The prevalence of mild ventriculomegaly, based on current criteria, is estimated to be around 0.7%[3]. Clinically, ventriculomegaly is defined as isolated if no ultrasound evidence of associated structural malformations or markers of aneuploidy are observed at the time of presentation[3].

The finding of fetal ventriculomegaly is variably associated with chromosomal and structural abnormalities and fetal infections, and even when isolated, it is thought to be linked to abnormal neurodevelopmental outcome[3–5]. While the latter is well accepted for the severe form[5], the literature about this issue in isolated mild ventriculomegaly is conflicting, showing a prevalence of neurodevelopmental delay of between 0% and 40%[6]. The aim of this study was to undertake a systematic review and meta-analysis of the current literature to assess the prevalence of neurodevelopmental delay in cases of fetal isolated mild ventriculomegaly and the false-negative rate of prenatal imaging for the diagnosis of associated abnormalities in patients referred for isolated mild ventriculomegaly.

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METHODS

This review was performed according to a protocol designed *a priori* and recommended for systematic reviews and meta-analyses[7–9]. MEDLINE (1966 to March 2012), EMBASE (1974 to March 2012), Scopus (since inception) and the Cochrane Library (since inception), 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), were searched electronically on 9 April 2013 and on 31 August 2013 using combinations of the relevant medical subject heading (MeSH) terms, keywords and word variants for 'Fetal', 'Ventriculomegaly', 'Mild', 'Neurologic*', 'Neurodevelop*', 'Outcome' and 'Follow up'. Reference lists of relevant articles and reviews were hand searched for additional reports.

The study was registered with the PROSPERO database (registration number: CRD42013004804, http://www.crd.york.ac.uk/PROSPERO). All abstracts were reviewed independently by two authors (G.P. and F.P.). Agreement about potentially relevant articles was reached by consensus and full-text copies were obtained. Both authors independently extracted data on study characteristics, outcome and quality using the Strengthening the Reporting of Observational Studies in Epidemiology statement criteria[9]. Inconsistencies were discussed by the reviewers and consensus was reached. Authors were contacted for those articles in which information was not reported, but the methodology was such that this would have been recorded initially.

Studies were assessed and selected for inclusion according to the following criteria: population; outcome; and study design. Mild ventriculomegaly was defined as an atrial measurement of 10–15 mm, given previous data demonstrating that infant outcomes were similar for ventriculomegaly measurements of 10–12 and 12–15 mm[6]. Isolated (idiopathic) mild ventriculomegaly was defined as mild ventriculomegaly not associated with other structural abnormalities, abnormal karyotype or congenital infection. Neurodevelopmental delay was defined as abnormal neurodevelopmental score, according to the test used. Studies were excluded from the analysis for any of the following: fetal karyotype not available; bilateral ventriculomegaly reported as an exclusion criterion; and non-English language publication.

Cases in which an associated abnormality (abnormal karyotype, structural abnormality or fetal infection) was observed either before or after birth were excluded from the isolated group. For the purpose of this study, cases without a detected cause of ventriculomegaly (no infection, chromosomal defects or associated abnormalities) were defined as isolated (idiopathic) mild ventriculomegaly.

Studies that reported information on postnatal imaging, either ultrasound or magnetic resonance imaging (MRI), were included in the subanalysis. The false-negative rate of prenatal imaging was defined by the prevalence of new postnatal findings in the group of cases labeled as isolated prior to birth.

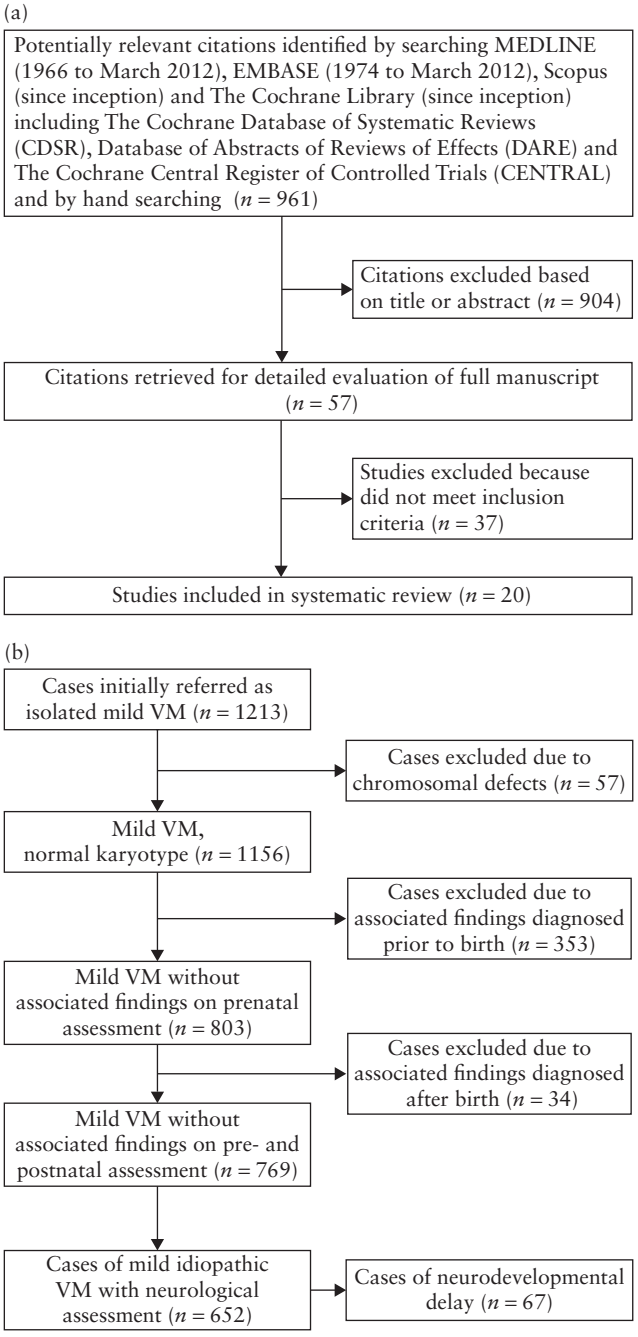

Figure 1 Flow charts of the studies (a) and truly isolated ventriculomegaly (VM) cases (b) included in the systematic review.

Statistical analysis

Continuous variables were reported as median and interquartile range (IQR) or range, when compared with the literature, and categorical variables were described as number (%). Between-study heterogeneity was explored graphically using forest plots and statistically assessed using the I^2 statistic, which represents the percentage of between-study variation that is due to heterogeneity rather than to chance[10]. A value of 0% indicates no observed heterogeneity, whereas I^2 values of $\geq 50\%$ indicate a substantial level of heterogeneity[11]. We planned

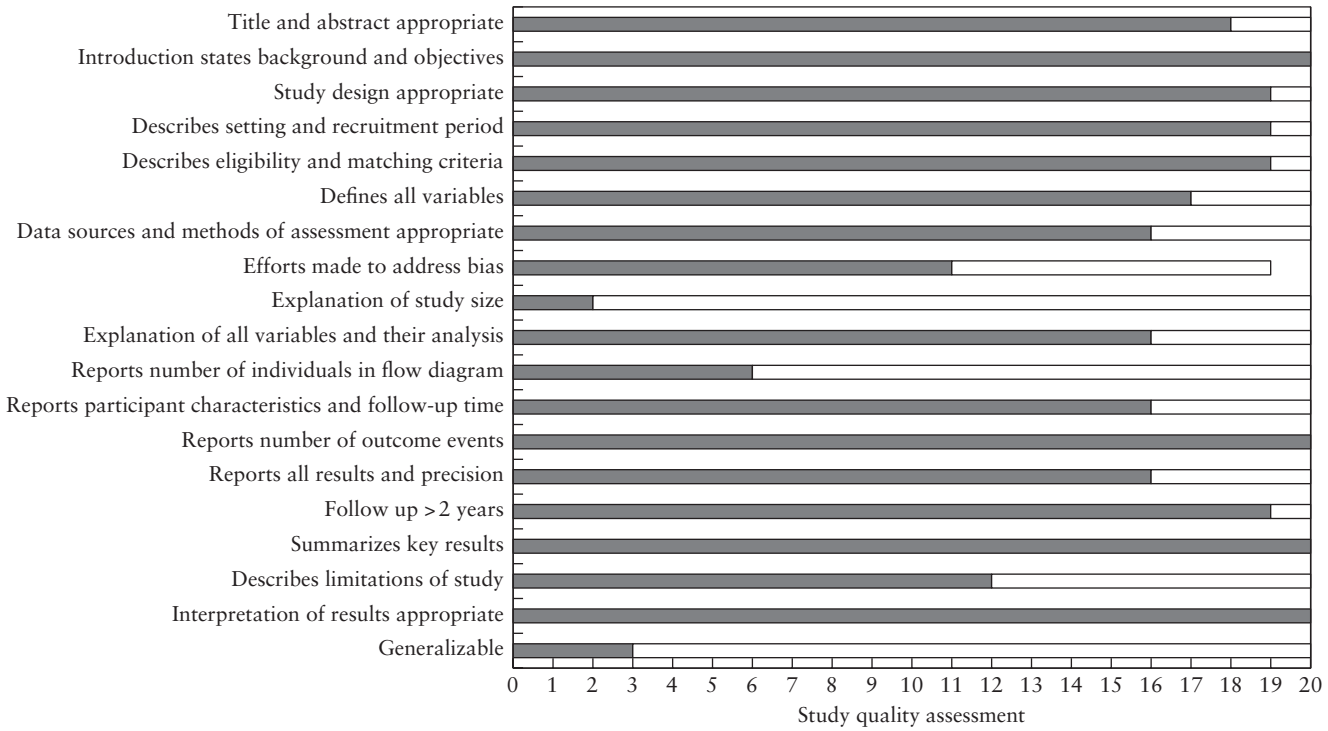

Figure 2 Quality criteria of the articles included in the systematic review, as assessed using the Strengthening the Reporting of Observational Studies in Epidemiology checklist. ■, Yes; □, no.

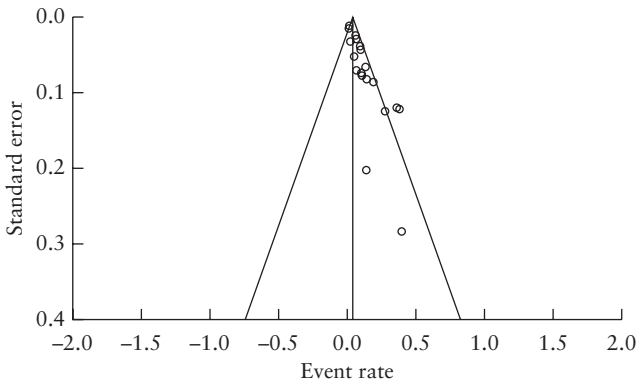

Figure 3 Funnel plot showing neurodevelopmental delay rates for cases of truly isolated mild ventriculomegaly.

to use a fixed-effects model if substantial statistical heterogeneity was not present. Random-effects models were used if heterogeneity was significant ($I^2 > 50\%$). Publication bias was explored using funnel plots and was assessed statistically using both Begg and Mazumdar's rank correlation test and the Egger test (which reports the rank correlation between the standardized effect size and the variances of these effects)[12]. Rosenthal's failsafe N test and cumulative meta-analysis were performed if publication bias was observed. Statistical analyses were performed using Stata 11 (release 11.2; StataCorp, College Station, TX, USA), Stats Direct (Version 2.7.8; Stats Direct Ltd, Altrincham, Cheshire, UK) and GraphPad Prism (GraphPad Software, San Diego, CA, USA) statistical software.

RESULTS

The electronic search yielded a total of 961 possible citations; of these, 904 were excluded by review of the title or abstract as they did not meet the selection criteria. Full manuscripts were retrieved for 57 citations, 37 of which were excluded because they did not meet the inclusion criteria. Therefore, in total, 20 studies (1213 pregnancies) were included in the meta-analysis[3,13–31] (Figure 1 and Table S1). Among these, two (10%) were designed as case–control studies[27,29] and four (20%) were prospective[3,22,26,29]. Mild ventriculomegaly was defined as a ventricular width of 10–12 mm or 10–15 mm in four (20%)[13,21,30,31] and 16 (80%)[14–21,23–30] studies, respectively. Nine (45%) studies[19,21,24–26,28–31] assessed both proximal and distal ventricles. Infection screening and fetal/neonatal MRI were undertaken systematically in 16 (80%)[2,16–22,24–31] and seven (35%)[18,20,25,26,29–31] studies, respectively. Quality assessment of the studies included in the meta-analysis is shown in Figure 2. The fixed-effects model showed significant heterogeneity ($I^2 > 50$) between included studies, and therefore a random-effects model was preferred.

The funnel plot for neurodevelopmental delay was observed to be asymmetric toward the right, indicating a lack of small studies with a low event rate (Figure 3). Both Begg and Mazumdar's rank correlation test and the Egger test showed significant publication bias ($P < 0.01$). Rosenthal's fail safe-N was 278, indicating that nearly 300 articles with a mean event rate of 1% would be needed in order to make the findings trivial. Cumulative meta-analysis was performed in order to assess the role

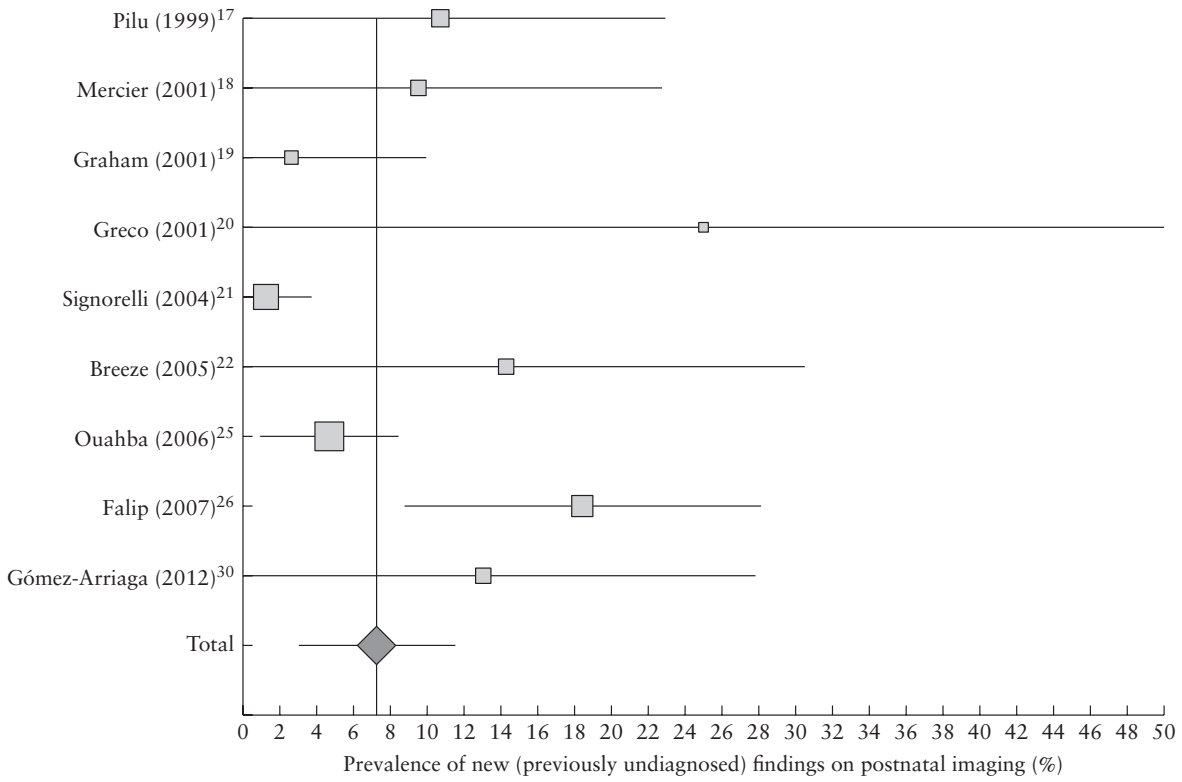

Figure 4 Forest plot (random-effects model) showing the prevalence of new/previously undiagnosed findings on neonatal imaging (either magnetic resonance imaging or ultrasound) for each of nine studies and pooled for all studies. The total prevalence was 7.4% (95% CI, 3.1–11.8%). Size of boxes is proportional to study sample size.

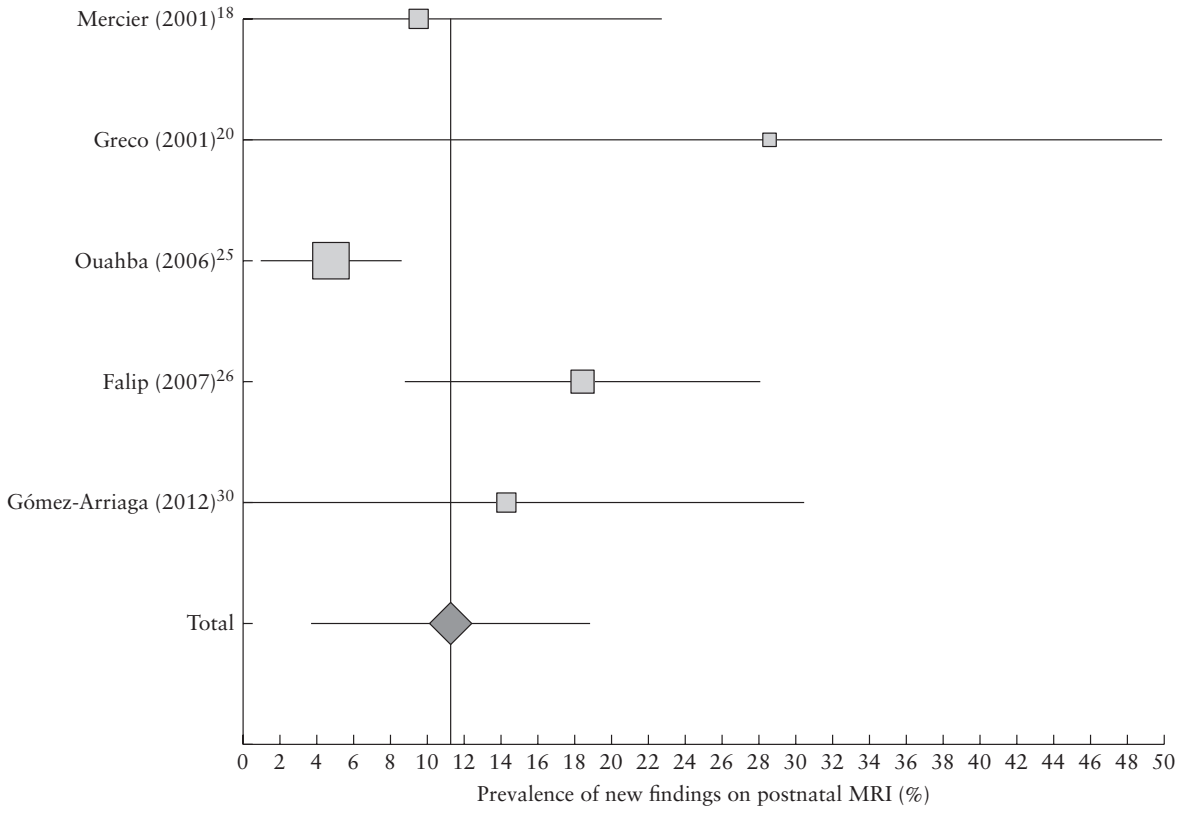

Figure 5 Forest plot (random-effects model) showing the prevalence of new/previously undiagnosed findings on neonatal magnetic resonance imaging, individually for each of five studies and pooled for all studies. The total prevalence was 11.2% (95% CI, 3.7–18.8%). Size of boxes is proportional to study sample size.

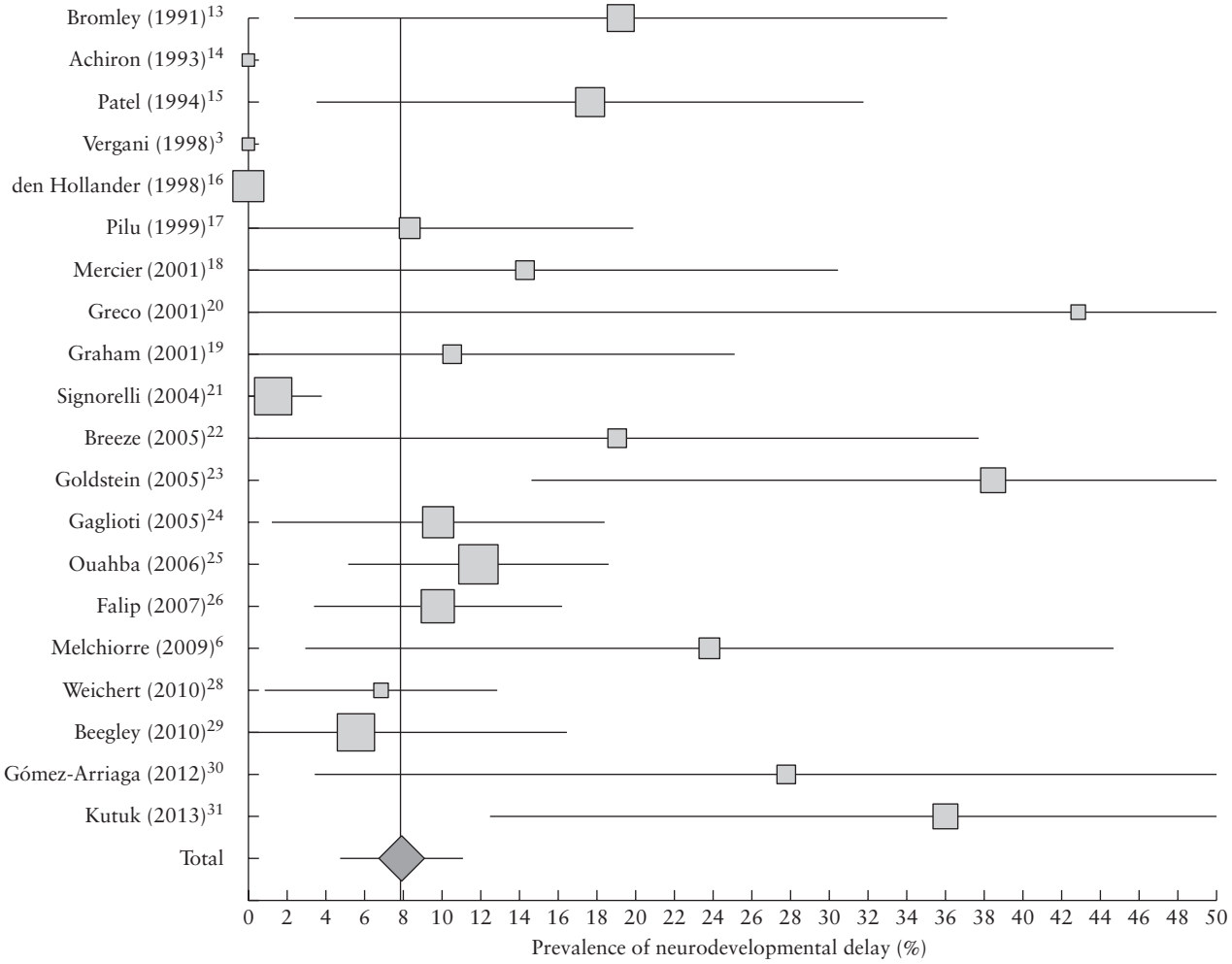

Figure 6 Forest plot (random-effects model) of the reported rates of neurodevelopmental delay in cases of truly isolated ventriculomegaly, individually for each of the 20 studies included in this review and pooled for all studies. The total prevalence was 7.9% (95% CI, 4.7–11.1%). Size of boxes is porportional to study sample size.

of size and time; however, even when either older or smaller studies were excluded, publication bias persisted and there was no significant difference in the overall neurodevelopmental delay rate.

Among the 1213 fetuses with a diagnosis of isolated mild ventriculomegaly at the time of the initial presentation, 57 (4.7%) showed an abnormal karyotype. Among those with a normal karyotype, associated abnormalities were observed in 387 (33.5%), 355 (91.7%) of which were diagnosed before birth.

Additional neonatal imaging, either ultrasound or MRI, was performed systematically in nine of 20 (45%) studies including 531 (43.8%) pregnancies[17–22,25,26,30]. Associated abnormalities were diagnosed on postnatal imaging in 34 cases (Table S2). Among the studies included in the subanalysis, prenatal imaging showed a false-negative rate of 7.4% (95% CI, 3.1–11.8%; $I^2 = 60.1\%$). Postnatal MRI was undertaken in five studies (25.0%) for a total of 354 (29.2%) pregnancies[18,20,25,26,30], providing additional information in 27 cases out of 256 previously considered as isolated (11.2%; 95% CI, 3.7–18.8%; $I^2 = 54.2\%$). The contribution of cumulative postnatal imaging (ultrasound and MRI) and MRI alone are shown in Figures 4 and 5, respectively.

There were 769 (63.4%) cases with isolated mild ventriculomegaly; postnatal follow-up was available for 652 (84.8%). Neurological assessment was undertaken at a mean age of 27.7 (median, 30; range, 3–151) months. A diagnosis of neurodevelopmental delay was made in 67 (7.9%; 95% CI, 4.7–11.1%; $I^2 = 55.9\%$) cases (Figure 6).

DISCUSSION

The results of this systematic review show that one-third of mild ventriculomegaly cases referred with isolated findings did, in fact, have associated anomalies. The overall prevalence of abnormal karyotype in the whole cohort was 1 in 20 (5%) and the false-negative rate after prenatal imaging was 1 in 14 (7.4%). However, when fetuses with and without associated prenatal ultrasound findings were considered separately, the prevalence of abnormal karyotype was 1 in 12 and 1 in 33 for associated and isolated cases, respectively. When the mild ventriculomegaly was confirmed to be isolated, the prevalence of neurodevelopmental delay was 1 in 12 (7.9%). Although the quality

assessment of the studies was generally high, the heterogeneity was significant for all the outcomes analyzed.

The findings of this review regarding the prevalence of chromosomal defects in mild ventriculomegaly are consistent with the literature[6,32]. In contrast, the observed prevalence of neurodevelopmental delay was lower than the prevalences of 10.9% and 12% previously reported[6,32]. This discrepancy may be the result of improved recent knowledge about the associations of ventriculomegaly and better prenatal diagnosis of these abnormalities, such as callosal agenesis and posterior fossa abnormalities[33]. The lower rate of neurodevelopmental delay may also be a consequence of the exclusion of patients with associated findings on neonatal imaging. Nevertheless, the observed value was higher than the 2–3% estimated for childhood disability in the general population by epidemiological studies[34,35]. However, there are case–control studies showing a higher (10%) prevalence of neurodevelopmental delay in structurally normal appropriate-for-gestational-age term fetuses[36]. Moreover, we can argue that if postnatal imaging was undertaken systematically in all cases, the proportion of associated abnormalities would be increased, thereby further lowering the prevalence of neurodevelopmental delay in the isolated ventriculomegaly group.

The findings of this meta-analysis provide evidence to aid the counseling of patients referred for isolated ventriculomegaly regarding the rate of abnormal karyotype, the prevalence of associated abnormalities, the false-negative rate of prenatal imaging and the prevalence of neurodevelopmental delay in cases confirmed to be isolated after birth.

The main strengths of this review are the comprehensive research strategy, the identification of the false-negative rate of prenatal imaging and the exclusion of cases with associated abnormalities on neonatal imaging from the group of 'isolated' cases. With regard to the results of neonatal findings, previous reviews are likely to have been biased by underestimating the prevalence of associated abnormalities and consequently overestimating the prevalence of neurodevelopmental delay in isolated mild ventriculomegaly. The main limitations of this review are the publication bias and the heterogeneity of the studies. The former reflects the lack of small studies with a low rate of neurodevelopmental delay, which probably resulted in a subtle overestimation of the rate of neurodevelopmental delay. Study heterogeneity is mainly caused by the different accuracies of prenatal and postnatal imaging, the different tests undertaken to assess neurological outcome and the different lengths of postnatal follow-up. Although guidelines for the performance of fetal neurosonography are available[2], the diagnostic interpretation of ultrasound images is difficult to standardize and is influenced by examiner and center experience. Moreover, it may be argued that some of the additional abnormalities detected postnatally could have been identified by fetal MRI in the second or third trimesters. The role of fetal MRI in the assessment of mild fetal ventriculomegaly is a matter of debate[37,38], and investigating its value was beyond the scope of the present review. The optimal time to assess neurodevelopmental outcome is debatable, as it is apparent that some disabilities may not be apparent until school age. On the other hand, we can argue that increasing the length of follow-up increases the possibility for confounding variables (i.e. socioeconomic or environmental factors) to bias the results, making it impossible to ascertain whether a disability is caused by the mild ventriculomegaly *per se* or is a consequence of other factors. Another limitation of the studies included in the review is that the majority did not discriminate between mild, moderate and severe neurodevelopmental disability. We can argue that if the impact of mild delay on quality of life is debatable, the impact of severe delay is striking. In fact, while mild neurodevelopmental delay is rarely associated with a disability, the converse is true for severe delay. Furthermore, the identification of neurodevelopmental delay may trigger appropriate interventions when available, with the final result of reducing disability. Hence, it seems crucial to discriminate between 'neurodevelopmental delay' and 'neurological disability'. With that in mind, future studies to investigate the prevalence of disability, as opposed to neurodevelopmental delay, could be more useful for clinical counseling.

The false-negative rate of prenatal imaging is 7.4% in apparently isolated fetal ventriculomegaly of ≤ 15 mm. Confirmed mild isolated ventriculomegaly is related to a prevalence of neurodevelopmental delay of 7.9%. The latter rate is similar to that reported in the general population and the published studies on ventriculomegaly do not allow accurate assessment of the severity of the neurodevelopmental delay. In conclusion, large cohort studies investigating the prevalence of childhood disability, instead of subtle neurodevelopmental delay, are required in children with isolated ventriculomegaly.

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SUPPORTING INFORMATION ON THE INTERNET

The following supporting information may be found in the online version of this article:

Table S1 Characteristics of studies included in the meta-analysis

Table S2 Additional anomalies found on postnatal imaging (ultrasound or magnetic resonance imaging)

This article has been selected for Journal Club.

A slide presentation, prepared by Dr Katherine Goetzinger, one of UOG's Editors for Trainees, is available online.

