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Systematic review and meta-analysis of isolated posterior fossa malformations on prenatal ultrasound imaging (part 1): nomenclature, diagnostic accuracy and associated anomalies

F. D'ANTONIO*, A. KHALIL*, C. GAREL†, G. PILU‡, G. RIZZO§, T. LERMAN-SAGIE¶, A. BHIDE*, B. THILAGANATHAN*, L. MANZOLI** and A. T. PAPAGEORGHIOU*

**Fetal Medicine Unit, Division of Developmental Sciences, St George's University of London, London, UK; †Hôpital d'Enfants Armand-Trousseau – Service de Radiologie, Cedex 12, Paris, France; ‡Department of Obstetrics and Gynecology, Sant'Orsola-Malpighi Hospital, University of Bologna, Bologna, Italy; §Department of Obstetrics and Gynecology, Università di Roma, Tor Vergata, Rome, Italy; ¶Fetal Neurology Clinic and Paediatric Neurology Unit, Wolfson Medical Center, Holon, Sackler School of Medicine, Tel Aviv University, Tel Aviv, Israel; **Department of Medicine and Aging Sciences, University of Chieti-Pescara, and EMISAC, CeSI Biotech, Chieti, Italy*

KEYWORDS: Blake's pouch cyst; Dandy–Walker malformation; mega cisterna magna; posterior fossa; vermian hypoplasia

ABSTRACT

Objective *To explore the outcome in fetuses with prenatal diagnosis of posterior fossa anomalies apparently isolated on ultrasound imaging.*

Methods *MEDLINE and EMBASE were searched electronically utilizing combinations of relevant medical subject headings for 'posterior fossa' and 'outcome'. The posterior fossa anomalies analyzed were Dandy–Walker malformation (DWM), mega cisterna magna (MCM), Blake's pouch cyst (BPC) and vermian hypoplasia (VH). The outcomes observed were rate of chromosomal abnormalities, additional anomalies detected at prenatal magnetic resonance imaging (MRI), additional anomalies detected at postnatal imaging and concordance between prenatal and postnatal diagnoses. Only isolated cases of posterior fossa anomalies – defined as having no cerebral or extracerebral additional anomalies detected on ultrasound examination – were included in the analysis. Quality assessment of the included studies was performed using the Newcastle–Ottawa Scale for cohort studies. We used meta-analyses of proportions to combine data and fixed- or random-effects models according to the heterogeneity of the results.*

Results *Twenty-two studies including 531 fetuses with posterior fossa anomalies were included in this systematic review. The prevalence of chromosomal abnormalities in fetuses with isolated DWM was 16.3% (95% CI, 8.7–25.7%). The prevalence of additional central nervous system (CNS) abnormalities that were missed at ultrasound examination and detected only at prenatal MRI was 13.7% (95% CI, 0.2–42.6%), and the prevalence of additional CNS anomalies that were missed at prenatal imaging and detected only after birth was 18.2% (95% CI, 6.2–34.6%). Prenatal diagnosis was not confirmed after birth in 28.2% (95% CI, 8.5–53.9%) of cases. MCM was not significantly associated with additional anomalies detected at prenatal MRI or detected after birth. Prenatal diagnosis was not confirmed postnatally in 7.1% (95% CI, 2.3–14.5%) of cases. The rate of chromosomal anomalies in fetuses with isolated BPC was 5.2% (95% CI, 0.9–12.7%) and there was no associated CNS anomaly detected at prenatal MRI or only after birth. Prenatal diagnosis of BPC was not confirmed after birth in 9.8% (95% CI, 2.9–20.1%) of cases. The rate of chromosomal anomalies in fetuses with isolated VH was 6.5% (95% CI, 0.8–17.1%) and there were no additional anomalies detected at prenatal MRI (0% (95% CI, 0.0–45.9%)). The proportions of cerebral anomalies detected only after birth was 14.2% (95% CI, 2.9–31.9%). Prenatal diagnosis was not confirmed after birth in 32.4% (95% CI, 18.3–48.4%) of cases.*

Conclusions *DWM apparently isolated on ultrasound imaging is a condition with a high risk for chromosomal and associated structural anomalies. Isolated MCM and BPC have a low risk for aneuploidy or associated structural anomalies. The small number of cases with isolated VH prevents robust conclusions regarding their management from being drawn. Copyright © 2015 ISUOG. Published by John Wiley & Sons Ltd.*

Correspondence to: Dr A. T. Papageorghiou, Fetal Medicine Unit, Division of Developmental Sciences, St George's University of London, London, SW17 0RE, UK (e-mail: apapageo@sgul.ac.uk)

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INTRODUCTION

The cerebellum and cerebellar vermis undergo protracted development during fetal and neonatal life such that the imaging appearance of the structures of the posterior fossa varies considerably with age at assessment[1]. In pregnancy, routine ultrasound examination of the fetal head includes assessment of the shape and structure of the posterior fossa in the axial cerebellar plane[2].

Posterior fossa malformations encompass a heterogeneous spectrum of conditions characterized by progressive abnormal development of the posterior and anterior membranous areas[3]. A precise definition of each of the posterior fossa anomalies is necessary in order to counsel properly parents about the outcome of the pregnancy; this is particularly important because the outcome of these conditions varies considerably in relation to the type of anomaly. Therefore, the standard axial plane is insufficient for definitive diagnosis when dealing with posterior fossa malformations. In addition to detailed multiplanar sonography, magnetic resonance imaging (MRI) is usually performed prenatally to confirm the diagnosis and assess for the presence of associated anomalies, which are important determinants of neurodevelopmental outcome. Nevertheless, although accurate, fetal MRI may be affected by a significant risk of both false-positive and false-negative cases[4,5]. Likewise, pathological confirmation of posterior fossa anomalies has been reported to have a low level of concordance with prenatal imaging[5–7].

The adoption of different nomenclature, diagnostic criteria and outcome measures has made parental counseling for posterior fossa anomalies extremely challenging. The presence of associated anomalies and the integrity of vermian structures are clearly important in determining the outcome of these conditions[8]. However, most of the published studies do not differentiate between cases with and without associated anomalies, and it is not certain whether these factors have an impact on outcome.

The aim of this systematic review and meta-analysis was to explore the outcome in fetuses with a prenatal ultrasound diagnosis of isolated posterior fossa anomalies. We discuss how accurate prenatal imaging is in reaching a correct diagnosis and establishing the presence of associated abnormalities.

METHODS

Protocol, eligibility criteria, information sources and search

This review was performed according to an *a-priori* designed protocol recommended for systematic reviews and meta-analyses[9–11]. MEDLINE and EMBASE were searched electronically on 15 February 2014, utilizing combinations of the relevant medical subject heading (MeSH) terms, keywords and word variants for 'posterior fossa', 'Dandy–Walker', 'Blake's pouch cyst', 'vermian hypoplasia' and 'outcome' (Appendix S1). The search was then updated on 14 July 2014. The search and selection criteria were restricted to the English language. Reference lists of relevant articles and reviews were hand-searched for additional reports. PRISMA guidelines were followed[12].

Study selection, data collection and data items

Studies were assessed according to the following criteria: population, outcome, gestational age at examination and type of imaging assessment of the posterior fossa.

Two authors (F.D., A.K.) reviewed all abstracts independently. Agreement regarding potential relevance was reached by consensus and full-text copies of relevant papers were obtained. The same two reviewers independently extracted relevant data regarding study characteristics and pregnancy outcome. Inconsistencies were discussed by the reviewers or with a third author and consensus reached. If more than one study was published for 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 of the articles were contacted.

Quality assessment of the included studies was performed using the Newcastle–Ottawa Scale (NOS) for cohort studies. According to the NOS, each study is judged on three broad perspectives: selection of the study groups, comparability of the groups and ascertainment of outcome of interest[13]. Assessment of the selection of a study includes evaluation of the representativeness of the exposed cohort, selection of the non-exposed cohort, ascertainment of exposure and demonstration that the outcome of interest was not present at the start of the study. Assessment of the comparability of the study groups includes evaluation of the comparability of cohorts on the basis of the design or analysis. Finally, ascertainment of the outcome of interest includes evaluation of the type of assessment of the outcome of interest and length and adequacy of follow-up[13]. 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.

Risk of bias, summary measures and synthesis of results

The posterior fossa anomalies considered in this systematic review were defined on the basis of the morphological approach proposed by Tortori-Donati *et al.*[14], and were: (1) Dandy–Walker malformation (DWM), defined by the classic triad of complete or partial agenesis of the cerebellar vermis, cystic dilatation of the fourth ventricle and enlarged posterior fossa with upward displacement of the tentorium, torcula and transverse sinuses; (2) mega cisterna magna (MCM), defined as a cisterna magna measuring > 10 mm and a normal vermis; (3) Blake's

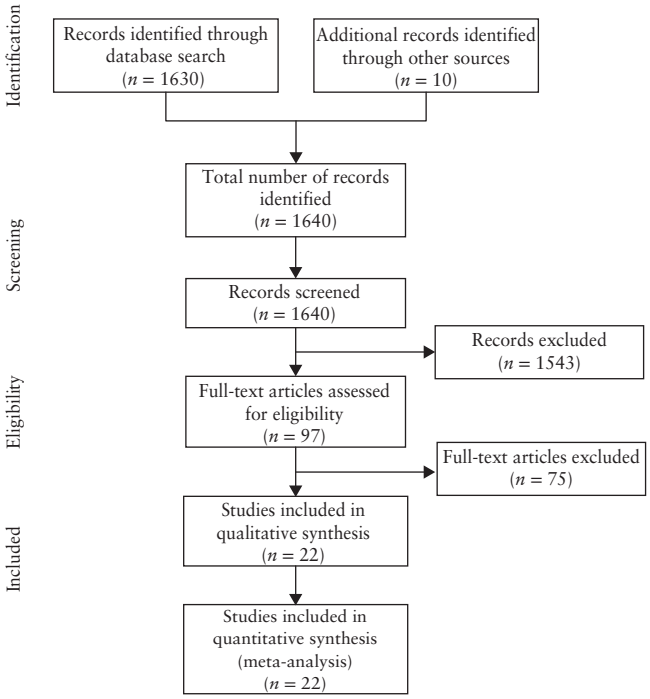

Figure 1 Flowchart summarizing selection of studies on isolated posterior fossa malformations diagnosed on prenatal ultrasound.

pouch cyst (BPC), defined as the presence of an upwardly displaced normal cerebellar vermis, normal appearance of the fastigium, tentorium and size of the cisterna magna; and (4) isolated vermian hypoplasia (VH), defined as a normally formed vermis but of smaller size, with an otherwise normal size and anatomy of the posterior fossa.

The rates of the following outcomes were analyzed: (1) chromosomal abnormalities; (2) additional major central nervous system (CNS) anomalies detected at prenatal MRI but missed at the initial ultrasound examination; (3) additional major CNS and extra-CNS anomalies detected at postnatal imaging or clinical evaluation but missed at prenatal imaging; and (4) concordance between prenatal and postnatal diagnoses.

For assessment of the incidence of abnormal karyotype, isolated posterior fossa anomalies were defined as having no additional CNS and extra-CNS anomalies detected at the ultrasound scan. Only cases that had their full karyotype tested pre- or postnatally were included. The presence of additional anomalies detected at pre- and postnatal MRI only and the rate of concordance between pre- and postnatal diagnoses were assessed only in fetuses with no additional anomalies and normal karyotype. In cases of DWM, ventriculomegaly was not included as an associated cerebral malformation because its development is related to dynamic changes in the cerebrospinal fluid, secondary to the mass effect of the cystic malformation.

Only studies reporting a prenatal diagnosis of posterior fossa anomalies were considered suitable for inclusion in the current systematic review; postnatal studies or studies from which cases diagnosed prenatally could not be extracted were excluded. Cases of Dandy–Walker variant and those with a lack of a clear definition of the anomaly were not considered suitable for inclusion. Autopsy-based studies were excluded on the basis that fetuses undergoing termination of pregnancy are more likely to show associated major structural and chromosomal anomalies. Studies reporting the concordance between pre- and postnatal diagnosis of posterior fossa anomalies were excluded unless they provided information about whether the anomaly was isolated or not. Studies of non-isolated cases of posterior fossa anomalies were excluded, as were studies published before the year 2000, as we considered that advances in prenatal imaging techniques and improvements in the diagnosis and definition of CNS anomalies make these less relevant. Finally, studies not providing a clear classification of the posterior fossa anomalies analyzed were not considered suitable for inclusion in the current review[15]. The wide heterogeneity in nomenclature among published studies results in heterogeneity in risk stratification of these fetuses, therefore we included only studies providing a definition of the anomaly in accordance with that reported above.

Only full-text articles were considered eligible for inclusion; case reports, conference abstracts and case series with fewer than three cases of posterior fossa anomaly, irrespective of the fact that the anomalies were isolated or not, were excluded in order to avoid publication bias.

We used meta-analyses of proportions to combine data[16,17]. Unfortunately, the low number of studies did not permit meaningful stratified meta-analysis to explore the test performance in subgroups of patients that may be less or more susceptible to bias. Assessment of potential publication bias was also problematic, both because of the outcome nature (rates with the left side limited to the value zero), which limits the reliability of funnel plots, and because of the low number of individual studies, which strongly limits the reliability of formal tests. Funnel plots displaying the outcome rate from individual studies *vs* their precision (1/standard error) were constructed with an exploratory aim. Tests for funnel plot asymmetry were not used when the total number of publications included for each outcome was < 10. In this case, the power of the tests was too low to distinguish chance from real asymmetry[18,19].

Between-study heterogeneity was explored using the I^2 statistic, which represents the percentage of between-study variation that is due to heterogeneity rather than chance. A value of 0% indicates no observed heterogeneity, whereas $I^2 \geq 50\%$ indicates a substantial level of heterogeneity. A fixed-effects model was used if substantial statistical heterogeneity was not present. On the other hand, if there was evidence of significant heterogeneity between included studies, a random-effects model was used.

All proportion meta-analyses were carried out using StatsDirect 2.7.9 (StatsDirect Ltd, Altrincham, UK) and MetaDisc (Meta-DiSc Statistical Methods, 2006, ftp://ftp.hrc.es/pub/programas/metadisc/MetaDisc_StatisticalMethods.pdf).

Table 1 General characteristics of 22 studies reporting on isolated posterior fossa malformations included in systematic review

Study	*Country*	*Study design*	*Prenatal imaging*	*GA at US*	*Anomalies analyzed*	*US plane used for diagnosis*
Tarui (2014)[20]	USA	Prospective	MRI	II–III trimester	VH	Multiplanar
Tonni (2014)[21]	Italy/Chile	Prospective	US, MRI	II–III trimester	BPC, VH	Multiplanar
Ghali (2014)[22]	Australia	Retrospective	US, MRI	II–III trimester	DWM, MCM, BPC	Multiplanar
Zhao (2013)[23]	China	Prospective	US, MRI	II–III trimester	BPC	Multiplanar
Vatansever (2013)[24]	UK	Prospective	MRI	II–III trimester	MCM	Multiplanar
Guibaud (2012)[25]	France	Retrospective	US, MRI	II–III trimester	DWM	Multiplanar
Gandolfi Colleoni (2012)[26]	Italy	Retrospective	US, MRI	II–III trimester	DWM, BPC, MCM, VH	Multiplanar
Paladini (2012)[27]	Italy	Retrospective	US, MRI	II–III trimester	BPC	Multiplanar
Patek (2012)[28]	USA	Retrospective	US, MRI	II–III trimester	DWM, MCM, VH	Multiplanar
Bertucci (2011)[29]	Italy/Israel	Prospective	US, MRI	II–III trimester	DWM, BPC, MCM, VH	Multiplanar
Egle (2011)[30]	Austria	Prospective	US	I–III trimester	BPC	Multiplanar
Ozkan (2011)[31]	Turkey	Retrospective	US	II–III trimester	DWM	Multiplanar
Rizzo (2011)[32]	Multicenter	Prospective	US, MRI	II–III trimester	DWM, MCM, BPC	Multiplanar
Dror (2009)[33]	Israel	Prospective	US, MRI	II–III trimester	MCM	Multiplanar
Kontopoulos (2008)[34]	USA	Retrospective	US	II–III trimester	DWM	Not stated
Forzano (2007)[35]	UK	Retrospective	US, MRI	II trimester	MCM	Multiplanar
Long (2006)[36]	UK	Retrospective	US	II–III trimester	MCM	Multiplanar
Zalel (2006)[37]	Israel	Retrospective	US, MRI	II–III trimester	BPC	Multiplanar
Has (2004)[38]	Turkey	Retrospective	US, MRI	II–III trimester	DWM	Multiplanar
Leitner (2004)[39]	Israel	Retrospective	US	II–III Trimester	MCM	Axial plane
Ecker (2000)[40]	USA	Retrospective	US	II–III trimester	DWM	Axial plane
Kölble (2000)[41]	Switzerland	Retrospective	US	I–III trimester	DWM	Axial plane

Only first author of each study is given. BPC, Blake's pouch cyst; DWM, Dandy–Walker malformation; GA, gestational age; MCM, mega cisterna magna, MRI, magnetic resonance imaging; US, ultrasound; VH, vermian hypoplasia.

RESULTS

Study selection and characteristics

A total of 1640 articles were identified, of which 97 full-text articles were assessed for their eligibility for inclusion (Appendix S2). A total of 22 studies were included in the systematic review (Figure 1)[20–41]. These 22 studies included 531 fetuses with posterior fossa anomalies; of these, 226 (42.6%) did not show any additional structural anomaly at the scan and represent the population of this systematic review. The general characteristics of the included studies are reported in Table 1. For most of the included studies, the posterior fossa anatomy was assessed using a multiplanar approach. Fetal MRI was performed to confirm the diagnosis and to look for associated anomalies in the majority of the included studies. Postnatal confirmation of the anomaly was performed in most cases by ultrasound, computed tomography or MRI, however the majority of the studies lacked a standardized protocol for the postnatal assessment of these patients.

Quality assessment of the included studies was performed using NOS for cohort studies (Table 2). Almost all included studies showed an overall good rate with regard to selection and comparability of the study groups and for the ascertainment of the outcome of interest. The main weaknesses of these studies were represented by their retrospective design, small sample size comprising series from high-risk populations and a lack of standardized postnatal confirmation. Furthermore, the relatively short period of follow-up after birth did not allow for a precise estimation of the overall rate of additional anomalies missed prenatally and detected only after birth.

Synthesis of results

Dandy–Walker malformation

There were 217 fetuses (in 11 studies) with DWM included in this review. Associated CNS and extra-CNS structural anomalies were present in 60.9% (95% CI, 45.3–75.3%) and 42.6% (95% CI, 22.7–64.0%) of cases, respectively. Ventriculomegaly was a common finding and was detected prenatally in 31.3% (95% CI, 14.0–51.8%) of cases with DWM.

The prevalence of chromosomal abnormalities in fetuses with DWM and no associated CNS or extra-CNS anomalies was 16.3% (95% CI, 8.7–25.7%; Table 3, Figure S1), with chromosomal deletions representing the most common anomaly (7.6% (95% CI, 2.6–14.8%)). The occurrence of hydrocephalus requiring ventriculoperitoneal shunt after birth is common in cases of DWM. Overall, ventriculomegaly occurred before or after birth in 68.0% (95% CI, 32.3–94.5%) of cases of DWM with no associated structural anomalies and normal karyotype. Ventriculomegaly requiring a ventriculoperitoneal shunt to reduce raised intracranial pressure occurred in 62.7% (95% CI, 27.9–91.3%) of cases.

The prevalence of additional CNS abnormalities missed at ultrasound and detected only on prenatal MRI was 13.7% (95% CI, 0.2–42.6%; Table 3), while the rates of additional CNS and extra-CNS anomalies

Table 2 Quality assessment of the 22 included studies according to Newcastle–Ottawa Scale

Study	*Selection*	*Comparability*	*Outcome*
Tarui (2014)[20]	★★★★	★★	★★★
Tonni (2014)[21]	★★★	★	★★
Ghali (2014)[22]	★★★	★	★★★
Zhao (2013)[23]	★★	★	★★
Vatansever (2013)[24]	★★★	★	★★
Guibaud (2012)[25]	★★★	★	★★★
Gandolfi Colleoni (2012)[26]	★★★	★	★★
Paladini (2012)[27]	★★★	★	★★★
Patek (2012)[28]	★★★	★	★★★
Bertucci (2011)[29]	★★★	★	★★
Egle (2011)[30]	★★	★	★★
Ozkan (2011)[31]	★★	★	★
Rizzo (2011)[32]	★★★	★	★★
Dror (2009)[33]	★★★	★★	★★★
Kontopoulos (2008)[34]	★★	★	★★
Forzano (2007)[35]	★★	★	★★
Long (2006)[36]	★★★	★	★★
Zalel (2006)[37]	★★★	★	★★★
Has (2004)[38]	★★★	★	★★
Leitner (2004)[39]	★★	★	★★
Ecker (2000)[40]	★★★	★	★★
Kölble (2000)[41]	★★★	★	★★★

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.

missed at prenatal imaging by either ultrasound or MRI and detected only after birth were 18.2% (95% CI, 6.2–34.6%) and 18.9% (95% CI, 6.3–36.2%), respectively. The prenatal diagnosis of DWM was not confirmed after birth in 28.2% (95% CI, 8.5–53.9%) of cases (Table 3). Among the cases of isolated DWM that were not confirmed at birth ($n = 7$), two had a normal appearance of the posterior fossa on postnatal imaging, one a diagnosis of BPC, one of VH, one of Joubert syndrome and one of posterior fossa hemorrhage, while the last case showed an association of DWM and abnormality of the cortex.

Mega cisterna magna

There were 144 fetuses (in 10 studies) with a prenatal diagnosis of MCM included. The rates of additional CNS and extra-CNS anomalies were 12.6% (95% CI, 2.9–27.6%) and 16.6% (95% CI, 6.2–30.8%), respectively, with ventriculomegaly being the most common associated anomaly (11.7% (95% CI, 2.8–25.6%)). No fetus tested prenatally was found to have a chromosomal abnormality (0% (95% CI, 0.0–4.7%); Table 4, Figure S2). In addition, there were no significant associations with additional anomalies detected only at prenatal MRI, or with associated CNS and extra-CNS anomalies missed prenatally and detected after birth (Table 4). The prenatal diagnosis of MCM was not confirmed in 7.1% (95% CI, 2.3–14.5%) of cases. Among the cases not confirmed at birth, three were false-positive diagnoses with a normal appearance of the posterior fossa described at postnatal imaging, and one was a posterior fossa arachnoid cyst.

Blake's pouch cyst

There were 86 fetuses (in nine studies) with a prenatal diagnosis of BPC included. The rates of associated CNS and extra-CNS structural anomalies were 11.5% (95% CI, 4.3–21.5%) and 25.3% (95% CI, 9.0–46.5%), respectively. There was only a single case of aneuploidy (trisomy 21) detected among 45 fetuses tested (Table 5, Figure S3). There was no case of associated CNS anomaly missed at the ultrasound scan and detected only at prenatal MRI in the cohort of fetuses included in this review (0% (95% CI, 0.0–6.4%)). Similarly, no associated CNS (0% (95% CI, 0.0–8.6%)) or extra-CNS (0% (95% CI, 0.0–16.1%)) anomalies were detected only after birth (Table 5). The prenatal diagnosis of BPC was not confirmed after birth in 9.8% (95% CI, 2.9–20.1%) of cases (Table 5), consisting of one case of posterior fossa arachnoid cyst, one of otherwise isolated MCM and one with normal postnatal imaging.

Vermian hypoplasia

There were 63 fetuses (in five studies) with a prenatal diagnosis of VH included. The rates of associated CNS and extra-CNS anomalies were 56.1% (95% CI, 25.0–84.7%) and 49.2% (95% CI, 31.5–67.1%), respectively. There was only one chromosomal anomaly detected (chromosomal deletion) among the 30 fetuses tested (Table 6, Figure S4). Although the number of fetuses with this outcome was very small, no additional anomalies were detected only at prenatal MRI (0% (95% CI, 0.0–45.9%)).

Finally, the proportions of cerebral and extra-CNS anomalies detected only after birth were 14.2% (95% CI, 2.9–31.9%) and 0% (95% CI, 0.0–18.5%), respectively (Table 6). The prenatal diagnosis was not confirmed in 32.4% (95% CI, 18.3–48.4%) of cases; all 10 cases consisted of false-positive diagnoses, with a normal appearance of the posterior fossa and cerebellar vermis at postnatal imaging in nine and one case of VH and associated cortical abnormalities.

DISCUSSION

Summary of evidence

This systematic review demonstrates that apparently isolated DWM carries a high risk of chromosomal abnormalities and associated malformations that can be misdiagnosed before birth. In contrast, isolated MCM and BPC are associated with a very low risk of aneuploidy and of associated structural anomalies discovered only at prenatal MRI or after birth. Isolated VH is associated with a low risk of aneuploidy and of additional anomalies detected only at prenatal MRI. A discrepancy between

Table 3 Pooled proportions (PP) for outcomes in fetuses with isolated Dandy–Walker malformation assessed prenatally for additional anomalies

Outcome	*Studies* (n)	*Fetuses* (n/N)	I^2 *(%)*	*Raw (95% CI) (%)*	*PP (95% CI) (%)*
Chromosomal anomalies	11	9/60	0	15.00 (7.1–26.6)	16.32 (8.7–25.7)
Additional anomalies detected only at prenatal MRI	4	2/18	56.1	11.11 (1.4–34.7)	13.72 (0.2–42.6)
Additional anomalies detected only postnatally					
CNS anomalies	6	3/21	0	14.29 (3.1–36.3)	18.19 (6.2–34.6)
Extra-CNS anomalies	5	3/20	0	15.00 (3.2–37.9)	18.93 (6.3–36.2)
Discrepancy between pre- and postnatal diagnosis	6	7/33	54.9	21.21 (9.0–38.9)	28.18 (8.5–53.9)

CNS, central nervous system; MRI, magnetic resonance imaging.

Table 4 Pooled proportions (PP) for outcomes in fetuses with isolated mega cisterna magna assessed prenatally for additional anomalies

Outcome	*Studies* (n)	*Fetuses* (n/N)	I^2 *(%)*	*Raw (95% CI) (%)*	*PP (95% CI) (%)*
Chromosomal anomalies	9	0/76	0	0.00 (0.0–4.7)	0.00 (0.0–4.7)*
Additional anomalies detected only at prenatal MRI	5	0/29	0	0.00 (0.0–11.9)	0.00 (0.0–11.9)*
Additional anomalies detected only postnatally					
CNS anomalies	6	1/60	0	1.67 (0.04–8.9)	3.65 (0.5–9.5)
Extra-CNS anomalies	5	1/40	0	2.50 (0.1–13.2)	4.66 (0.5–12.7)
Discrepancy between pre- and postnatal diagnosis	8	4/59	43.2	6.78 (1.9–16.5)	7.14 (2.3–14.5)

*Using Meta-Disc statistical analysis. CNS, central nervous system; MRI, magnetic resonance imaging.

pre- and postnatal diagnoses of posterior fossa anomalies is common in cases of DWM and VH, but less frequent in cases of MCM and BPC.

Strengths and limitations of the study

The strengths of this study are its robust methodology for identifying all possible studies for inclusion, assessing data quality and synthesizing all suitable data.

For several meta-analyses, the number of included studies was small, and some included small populations. Furthermore, many of the studies reviewed did not allow extraction of individual case data. Another limitation is the significant heterogeneity in the definitions used[42].

Subtle chromosomal abnormalities such as microdeletions may be overlooked by routine chromosome analysis, highlighting the need for molecular cytogenetic techniques, which were not used in some of the included studies. It is therefore possible that this systematic review underestimates the prevalence of chromosomal abnormalities[43].

Advances in prenatal imaging techniques have led to more comprehensive assessment of the fetal brain; in this review, we considered only studies published between 2000 and 2014 in order to minimize the effect of changing imaging protocols. Despite these limitations, however, our review represents the best published estimate of outcomes for this group of conditions.

Implications for clinical practice

Objective standardized assessment of the posterior fossa is needed to differentiate precisely the possible diagnoses. One such approach has been proposed[3,25]: our review suggests that this approach is quite effective in the identification of MCM and BPC, but less effective for DWM, and inadequate for VH. Indeed variable criteria for the diagnosis of VH were used in different studies.

Isolated DWM was frequently associated with chromosomal aberrations and we therefore believe that karyotyping should be offered for fetuses with this prenatal diagnosis. Microarray analysis can also be considered where available. On the other hand, the risk of chromosomal anomalies is very low in cases of isolated MCM. With isolated BPC, the rate of chromosomal anomalies was in the order of 5%, but this should be considered with caution given the small number of cases.

Antenatal MRI is certainly indicated with isolated DWM, as associated intracranial anomalies escaping sonographic diagnosis were frequent, which was not the case for other anomalies. MCM was misdiagnosed in 7% of cases; in some a posterior fossa cyst was found after birth. Posterior fossa cysts may expand and cause obstructive hydrocephalus. MRI may be more effective than ultrasound, not only in differentiating isolated MCM from posterior fossa cysts, but also in identifying periventricular nodular heterotopia, a neuronal migration disorder with significant clinical implications[44]. Isolated DWM is frequently found in association with anomalies that are only identified postnatally. However, parents of fetuses with isolated MCM or BPC can be reassured that this rarely occurs in such cases.

Our review highlights the need for an objective standard to confirm the diagnosis after birth. Recent studies have shown a low level of agreement between prenatal imaging

Table 5 Pooled proportions (PP) for outcomes in fetuses with isolated Blake's pouch cyst assessed prenatally for additional anomalies

Outcome	*Studies (n)*	*Fetuses (n/N)*	I^2 *(%)*	*Raw (95% CI) (%)*	*PP (95% CI) (%)*
Chromosomal anomalies	8	1/45	0	2.22 (0.1–11.8)	5.16 (0.9–12.7)
Additional anomalies detected only at prenatal MRI	8	0/56	0	0.00 (0.0–6.4)	0.00 (0.0–6.4)*
Additional anomalies detected only postnatally					
CNS anomalies	6	0/41	0	0.00 (0.0–8.6)	0.00 (0.0–8.6)*
Extra-CNS anomalies	5	0/21	0	0.00 (0.0–16.1)	0.00 (0.0–16.1)*
Discrepancy between pre- and postnatal diagnosis	6	3/39	33.9	7.69 (1.6–20.9)	9.79 (2.9–20.1)

*Using Meta-Disc statistical analysis. CNS, central nervous system; MRI, magnetic resonance imaging.

Table 6 Pooled proportions (PP) for outcomes in fetuses with isolated vermian hypoplasia assessed prenatally for additional anomalies

Outcome	*Studies (n)*	*Fetuses (n/N)*	I^2 *(%)*	*Raw (95% CI) (%)*	*PP (95% CI) (%)*
Chromosomal anomalies	4	1/30	0	3.33 (0.1–17.2)	6.54 (0.8–17.1)
Additional anomalies detected only at prenatal MRI	3	0/6	0	0.00 (0.0–45.9)	0.00 (0.0–45.9)*
Additional anomalies detected only postnatally					
CNS anomalies	3	2/18	0	11.11 (1.4–34.7)	14.20 (2.9–31.9)
Extra-CNS anomalies	3	0/18	0	0.00 (0.0–18.5)	0.00 (0.0–18.5)
Discrepancy between pre- and postnatal diagnosis	4	10/32	0	31.25 (16.1–50.0)	32.44 (18.3–48.4)

*Using Meta-Disc statistical analysis. CNS, central nervous system; MRI, magnetic resonance imaging.

and pathological examination in cases of termination of pregnancy[5,6]. Challenges in the pathological assessment of posterior fossa structures, inconsistencies in diagnostic criteria and the lack of multiplanar assessment in older studies, may account for this heterogeneity.

Implications for research

The wide heterogeneity in classification and the definition of outcomes highlights the urgent need for prospective studies using a standardized classification of these anomalies, correlating them with pregnancy and postnatal outcomes.

Although posterior fossa anomalies are usually diagnosed in the second trimester, early detection has been reported[30,44,45]. Large prospective studies on low-risk populations are needed to ascertain whether first-trimester assessment of the posterior fossa may lead to reliable early diagnosis.

Conclusions

DWM that is isolated on prenatal ultrasound imaging is frequently associated with chromosomal and structural anomalies. MCM and BPC are rarely associated with malformations that are undetected by ultrasound, and isolated MCM has a low risk for aneuploidy. The group of fetuses with an antenatal diagnosis of VH was heterogeneous, and the condition was often not confirmed at birth. We suggest that MRI is indicated in cases of DWM and MCM. Studies using a standardized classification are needed to define objectively the prognosis of these anomalies.

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SUPPORTING INFORMATION ON THE INTERNET

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

Appendix S1 Search strategy

Appendix S2 Excluded studies and reason for exclusion

Figures S1–S4 Pooled proportions of the incidence of chromosomal anomalies (a), additional anomalies detected only at prenatal magnetic resonance imaging (b), additional central nervous system (CNS) (c) and extra-CNS (d) anomalies detected only after birth, and discrepancy between pre- and postnatal findings (e) in fetuses with isolated Dandy–Walker malformation (Figure S1), mega cisterna magna (Figure S2), Blake's pouch cyst (Figure S3) and vermian hypoplasia (Figure S4).

