# SYSTEMATIC REVIEW AND META-ANALYSIS OF ISOLATED POSTERIOR FOSSA MALFORMATIONS ON PRENATAL ULTRASOUND:

# NOMENCLATURE, DIAGNOSTIC ACCURACY AND ASSOCIATED ANOMALIES

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**ABSTRACT**

**Objective:** The aim of this systematic review and meta-analysis was to explore the pregnancy outcome in fetuses with prenatal diagnosis of isolated posterior fossa anomalies.

**Methods:** Medline and Embase were searched electronically utilizing combinations of the relevant medical subject heading for "posterior fossa", and "outcome. The posterior fossa anomalies analysed were: Dandy Walker malformation (DWM), mega cisterna magna (MCM), Blake's pouch cyst (BPC) and vermian hypoplasia (VH). The outcomes observed were: the rate of chromosomal abnormalities, additional anomalies detected only at pre-natal magnetic resonance imaging (MRI), additional anomalies detected only at post-natal imaging and concordance between pre-natal and post- diagnosis. Only isolated cases of posterior fossa anomalies were included in the analysis, defined as having no cerebral or extra-cerebral additional anomalies detected at the scan. Quality assessment of the included studies was performed using the Newcastle-Ottawa Scale (NOS) 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:** A total of 22 studies including 531 fetuses with posterior fossa anomalies were included in the 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 CNS abnormalities detected only at prenatal MRI but missed at ultrasound was 13.7 (95% CI 0.2-42,6), while those of additional CNS and extra-CNS anomalies missed at prenatal imaging and detected only after birth were 18.2% (95% CI 6.2-34.6) and 18,9 (6,3-36,2) respectively. Prenatal diagnosis was not confirmed in 28.2% (95% CI 8.5-53.9) of the cases (Table 4).

None of the fetuses with isolated MCM tested prenatally were found to have a chromosomal abnormality (0%, 95% CI 0-4,7). There were no significant associations with associated anomalies detected at pre-natal MRI, nor with associated CNS and extra-CNS anomalies detected after birth and missed pre-natally. Prenatal diagnosis was not confirmed in 7.1% (95% CI 2.3-14.5) of the 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 only at prenatal MRI and missed at the scan (0%, 95% CI 0-6,4). Likewise, no associated CNS or extra-CNS anomalies were detected only after birth. Prenatal diagnosis of BPC was not confirmed after birth in 9.8% (95% CI 2.9-20.1) of the cases.

The rate of chromosomal anomalies in fetuses with isolated VH was 6.5% (95% CI 0.8-17.1) and no additional anomalies were detected at prenatal MRI and missed at the scan (PP: 0%, 95% CI 0-45,9). Finally, the proportions of cerebral and extra-cerebral anomalies detected only after birth were 14.2% (95% CI 2.9-31.9) and 0% (95% CI 0-18,5), respectively. Prenatal diagnosis was not confirmed in 32.4% (95% CI 18.3-48.4) of the cases.

**Conclusions:** Isolated DWM is a condition at high risk of chromosomal and associated structural anomalies. Isolated MCM and BPC have a low risk of aneuploidy or associated structural anomalies. The small number of cases with isolated VH precludes drawing any robust evidence regarding their management.

## Introduction

The cerebellum and cerebellar vermis undergoe protracted development during fetal and neonatal life so that the imaging appearance of the structures of the posterior fossa varies considerably with the age at assessment[1]. In pregnancy, routine ultrasound examination of fetal head included assessment of the shape and structure of the posterior fossa on the axial, transverse 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 properly counsel 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 to make a definite diagnosis when dealing with posterior fossa malformations. In addition to careful multiplanar sonography, magnetic resonance imaging (MRI) is usually performed prenatally to confirm the diagnosis and assess 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 negative rates[4,5]. Likewise, pathological confirmation of posterior fossa anomalies has been reported to have a low level of concordance with prenatal imaging[5,6].

The adoption of different nomenclatures, diagnostic criteria and outcome measures has made parental counselling of 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 did 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 pregnancy outcome in fetuses with prenatal diagnosis of isolated posterior fossa anomalies. We herein will discuss the accuracy in the association with other misdiagnosed anomalies and the accuracy of prenatal imaging in correctly labelling these anomalies.

## METHODS

### *Protocol, eligibility criteria, information sources and search*

This review was performed according to an a-priori designed protocol and recommended for systematic reviews and meta-analysis[9-11]and following the PRISMA guidelines were followed[10]. Medline and Embase were searched electronically on the 15th February 2014 utilizing combinations of the relevant medical subject heading (MeSH) terms, key words, and word variants for "posterior fossa", "Dandy Walker," "Blake's pouch cyst", "vermian hypoplasia" and "outcome" (Supplementary Table 1). The search was then updated on the14th July 2014. The search and selection criteria were restricted to 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 posterior fossa.

Two authors (FD, AK) reviewed all abstracts independently. Agreement regarding potential relevance was reached by consensus; full text copies of those papers were obtained and the same two 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 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 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[13]. 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 on the basis of 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[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 the results*

The posterior fossa anomalies considered in this systematic were defined on the basis of the morphological approach proposed by Tortori-Donati and were[14]:

1) Dandy Walker malformation (DWM) defined by the classic triad of complete or partial agenesis of the cerebellar vermis, cystic dilatation of the 4th ventricle and

enlarged posterior fossa with the upward displacement of the tentorium, torcula and transverse sinuses.
2) Mega-cisterna magna (MCM) defined as a large cisterna magna measuring >10 mm and a normal vermis.
3) Blake's pouch cyst (BPC) defined as the presence of an upward displaced normal cerebellar vermis, normal appearing fastigium, tentorium and size of the cisterna magna.
4) Isolated vermian hypoplasia (VA) defined as a normally formed vermis but of smaller size, with an otherwise normal size and anatomy of the posterior fossa.

The incidence of the following outcomes were analysed:

1) Chromosomal abnormalities
2) Rate of additional major central nervous system (CNS) anomalies detected only at prenatal magnetic resonance imaging (MRI) but missed at the initial scan
3) Additional CNS and extra-CNS major anomalies detected only at post-natal imaging or clinical evaluation but missed at prenatal imaging.
4) Concordance between pre- and post- natal diagnosis.

For the 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 who had their full karyotype tested either pre-or post-natally were included. The presence of additional anomalies detected only at pre- and post- natal MRI and the rate of concordance between pre and post-natal diagnosis were assessed only in fetuses with no additional anomalies and normal karyotype. In case of DWM, ventriculomegaly was not included as an associated cerebral malformation because its development is related to cerebrospinal fluid dynamic changes, secondary to the mass effect of the cystic malformation.

Only studies reporting a prenatal diagnosis of posterior fossa anomalies were considered suitable for the inclusion in the current systematic review; post-natal studies or studies from which cases diagnosed pre-natally 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 the 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 post-natal 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 2000, as we considered that advances in prenatal imaging techniques, 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 analysed were not considered suitable for the inclusion in the current review. The wide heterogeneity in nomenclature among published studies results in heterogeneity in risk stratification of these foetuses, 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 the inclusion; case reports, conference abstracts and case series with fewer than 3 cases of posterior fossa anomalies, irrespective of the fact that the anomalies were isolated or not, were also excluded in order to avoid publication bias.

We used meta-analyses of proportions to combine data[14,15]. Unfortunately, the scarce number of studies did not permit meaningful stratified meta-analyses to explore the test performance in subgroups of patients that may be less or more susceptible to bias. The assessment of the 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 scarce number of individual studies, which strongly limits the reliability of formal tests. Funnel plots displaying the outcome rate from individual studies versus their precision (1/standard error) were carried out with an exploratory aim. Tests for funnel plot asymmetry were not used when the total number of publications included for each outcome was less than ten. In this case, the power of the tests is too low to distinguish chance from real asymmetry[16,17].

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 $I^2$ values of $\geq$ 50% indicate a substantial level of heterogeneity. A fixed effects model was used if substantial statistical heterogeneity was not present. On the contrary, if there was evidence of significant heterogeneity between studies included, a random effect model was used.

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

## RESULTS

### *Study selection and characteristics*

A total of 2467 articles were identified, 97 were assessed with respect to their eligibility for inclusion (Supplementary Table 3). A total of 22 studies were included in the systematic review (Figure 1)[13,18-37]. These 22 studies included 531 fetuses with posterior fossa anomalies; of these, 42.6% (226/531) did not show any additional structural anomaly at the scan and represents the population of this systematic review.

The general characteristic of the studies included in the systematic review are reported in Table 1.

For most of the included studies, the posterior fossa anatomy was assessed by 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. Post-natal confirmation of the anomaly was performed in most of the cases by ultrasound, computer tomography (CT) and MRI; however, most of the studies lacks of a standardized protocol for the post-natal assessment of these patients.

Quality assessment of the included studies was performed using Newcastle-Ottawa Scale (NOS) for cohort studies. Almost all the included studies showed an overall good rate as regard for the 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 being series from high-risk populations and lack of a standardized post-natal confirmation. Furthermore, the relatively short period of follow-up after birth did not allow a precise estimation of the overall rate of additional anomalies detected only after birth and missed prenatally.

### *Synthesis of the results*

#### ***Dandy Walker Malformation (DWM)***

There were 217 fetuses (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 the cases. Ventriculomegaly was a common finding and detected prenatally in 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), with chromosomal deletions representing the most common anomaly (7.6%, 2.6-14.8%, Table 3). The occurrence of hydrocephalus requiring ventriculo-peritoneal shunt is common in cases of DWM after birth. Overall, ventriculomegaly before or after birth occurred in 68.0% (95% CI 32.3-94.5) of cases of DWM with no associated structural anomalies and normal karyotype. Ventriculomegaly requiring a ventriculo-peritoneal shunt to reduce raised intra-cranial pressure occurred in 62.7% (95% CI 27.9-91.3) of the cases.

The prevalence of additional CNS abnormalities detected only at prenatal MRI but missed at ultrasound was 13.72 (95% CI 0.2-42,6) (Table 3), while those of additional CNS and extra-CNS anomalies missed at prenatal imaging (either ultrasound or MRI) and detected only after birth were 18.2% (95% CI 6.2-34.6) and 18,9 (6,3-36,2). The prenatal diagnosis of DWM

was not confirmed in 28.2% (95% CI 8.5-53.9) of the cases (Table 4). Among those cases of isolated DWM not confirmed at birth (7 cases), 2 had a normal appearance of the posterior fossa at post-natal imaging, one a diagnosis of BPC, one of VH, one of Joubert syndrome, one of posterior fossa haemorrhage, while the last consisted in an association of DWM and abnormality of the cortex.

***Mega-cisterna magna (MCM)***

There were 144 fetuses (10 studies) with a prenatal diagnosis of MCM included. The prevalence 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).

None of the fetuses tested prenatally were found to have a chromosomal abnormality (0%, 95% CI 0,0-4,7) (Table 4).

In addition, there were no significant associations with additional anomalies detected only at pre-natal MRI, nor with associated CNS and extra-CNS anomalies detected after birth and missed pre-natally (Tables 4). The prenatal diagnosis of MCM was not confirmed in 7.1% (95% CI 2.3-14.5) of the cases. Among those cases not confirmed at birth, 3 were false positive diagnoses with a normal appearance of the posterior fossa described at post-natal imaging, while 1 was a posterior fossa arachnoid cyst.

***Blake's pouch cyst***

There were 77 fetuses (eight studies) with a prenatal diagnosis of BPC included. The prevalence 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 a single case of aneuploidy (Trisomy 21) detected among 45 fetuses tested (5.2% (95% CI 0.9- 12.7, Table 5).

There was no associated CNS anomaly detected only at prenatal MRI and missed at the scan in the cohort of fetuses included in this review (0%, 95% CI 0-6,4).

Likewise, no associated CNS (PP: 0%, 95% CI 0-8,6) or extra-CNS (PP: 0,00, 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 the cases (Table 5), consisting in one case of posterior fossa arachnoid cyst, one case of otherwise isolated MCM and one case with normal post-natal imaging.

***Vermian hypoplasia***

There were 63 fetuses (five studies) with a prenatal diagnosis of vermian hypoplasia included. The rate of associated CNS and extra-CNS anomalies was 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 (a chromosomal deletion) among the 30 fetuses tested (6.5%, 95% CI 0.8-17.1, Table 3). Although the number of fetuses including for this outcome was very small (Table 6), no additional anomalies were detected at prenatal MRI and missed at the scan (PP: 0%, 95% CI 0-45,9).

Finally, the proportions of cerebral and extra-cerebral anomalies detected only after birth were 14.2% (95% CI 2.9-31.9) and 0% (95% CI 0-18,5), respectively (Table 6). The prenatal diagnosis was not confirmed in 32.4% (95% CI 18.3-48.4) of the cases (10) (Table 6), all consisting in cases of false positive diagnoses with a normal appearance of the posterior fossa and cerebellar vermis at post-natal imaging and one in one case of VH and associated cortical abnormalities.

## DISCUSSION

### *Summary of evidence*

This systematic review demonstrates that 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 pre-natal MRI or after birth. Isolated VH is associated with low risk of aneuploidy and of additional anomalies detected only at prenatal MRI. A discrepancy between pre- and post-natal diagnosis of posterior fossa anomalies is common in cases of DWM and VH, but less frequent in cases of MCM and BPC.

### *Strengths and Limitations*

The strengths of this study are its robust methodology to identify all possible studies, assess data quality and synthesise all suitable data.

For several meta-analyses, the number of included studies was small and some included small numbers. 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 micro-deletions 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 underestimated the occurrence 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 in the last decade in order to minimize the effect of changing imaging protocols. Despite these limitations, however, our review represents the best published estimate of outcome for this group of conditions.

### *Implications for clinical practice*

Objective standardized assessment of the posterior fossa is needed to precisely differentiate 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. 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 range 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, but not for other anomalies. MCM was misdiagnosed in 7% of cases; in some a posterior fossa cyst was found after birth. Posterior fossa cyst 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 post-natally. Conversely, 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 pre-natal imaging and pathological examination in cases of pregnancy termination[5,6]. Challenges in 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 definitions of outcomes highlights the urgent need for prospective studies using standardised classification of these anomalies, correlating them with pregnancy and post-natal 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*

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

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**Table 1.** General characteristics of the included studies.

| Author | Year | Country | Study design | Pre-natal imaging | GA at scan | Anomalies analysed | US planes used for the diagnosis |
|---|---|---|---|---|---|---|---|
| Tarui[20] | 2014 | United States | Prospective | MRI | II-III trimester | VH | Multiplanar |
| Tonni[21] | 2014 | Italy/Chile | Prospective | US, MRI | II-III trimester | BPC, VH | Multiplanar |
| Zhao[22] | 2013 | China | Prospective | US, MRI | II-III trimester | BPC | Multiplanar |
| Ghali[23] | 2013 | Australia | Retrospective | US, MRI | II-III trimester | DWM, MCM, BPC | Multiplanar |
| Vatansaver[24] | 2013 | United Kingdom | Prospective | MRI | II-III trimester | MCM | Multiplanar |
| Guibaud[25] | 2012 | France | Retrospective | US, MRI | II-III trimester | DWM | Multiplanar |
| Gandolfi-Colleoni[26] | 2012 | Italy | Retrospective | US, MRI | II-III trimester | DWM, BPC, MCM, VH | Multiplanar |
| Paladini[27] | 2012 | Italy | Retrospective | US, MRI | II-III trimester | BPC | Multiplanar |
| Patek[28] | 2012 | USA | Retrospective | US, MRI | II-III trimester | DWM, MCM, VH | Multiplanar |
| Bertucci[29] | 2011 | Italy-Israel | Prospective | US, MRI | II-III trimester | DWM, BPC, MCM, VH | Multiplanar |
| Egle[30] | 2011 | Austria | Prospective | US | I-II-III trimester | BPC | Multiplanar |
| Ozkan[31] | 2011 | Turkey | Retrospective | US | II-III trimester | DWM | Multiplanar |
| Rizzo[32] | 2011 | Multicentre | Prospective | US | II-III trimester | DWM, MCM, BPC | Multiplanar |
| Dror[33] | 2009 | Israel | Prospective | US, MRI | II-III trimester | MCM | Multiplanar |
| Kontopoulos[34] | 2008 | United States | Retrospective | US | II-III trimester | DWM | Not stated |
| Forzano[35] | 2007 | United Kingdom | Retrospective | US, MRI | II trimester | MCM | Multiplanar |
| Long[36] | 2006 | United Kingdom | Retrospective | US | II-III trimester | MCM | Multiplanar |
| Zalel[37] | 2006 | Israel | Retrospective | US, MRI | II-III trimester | BPC | Multiplanar |
| Has[38] | 2004 | Turkey | Retrospective | US, MRI | II-III trimester | DW | Multiplanar |
| Leitner[39] | 2004 | Israel | Retrospective | US | II-III Trimester | MCM | Axial plane |
| Ecker[40] | 2000 | United States | Retrospective | US | II-III trimester | DWM | Axial plane |
| Kolble[41] | 2000 | Switzerland | Retrospective | US | I-II-III trimester | DWM | Axial plane |

DWM: Dandy Walker malformation, MCM: megacisterna magna, BPC: Blakes' pouch cyst, VH: vermian hypoplasia, US: ultrasound, MRI: magnetic resonance imaging

**Table 2.** Quality assessment of the included studies according to Newcastle-Ottawa Scale (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.

| Author | Year | Selection | Comparability | Outcome |
|---|---|---|---|---|
| Tarui | 2014 | ★★★★ | ★★ | ★★★ |
| Tonni | 2014 | ★★★ | ★ | ★★ |
| Zhao | 2013 | ★★ | ★ | ★★ |
| Ghali | 2013 | ★★★ | ★ | ★★★ |
| Vatansaver | 2013 | ★★★ | ★ | ★★ |
| Guibaud | 2012 | ★★★ | ★ | ★★★ |
| Gandolfi-Colleoni | 2012 | ★★★ | ★ | ★★ |
| Paladini | 2012 | ★★★ | ★ | ★★★ |
| Patek | 2012 | ★★★ | ★ | ★★★ |
| Bertucci | 2011 | ★★★ | ★ | ★★ |
| Rizzo | 2011 | ★★★ | ★ | ★★ |
| Egle | 2011 | ★★ | ★ | ★★ |
| Ozkan | 2011 | ★★ | ★ | ★ |
| Dror | 2009 | ★★★ | ★★ | ★★★ |
| Kontopoulos | 2008 | ★★ | ★ | ★★ |
| Forzano | 2007 | ★★ | ★ | ★★ |
| Long | 2006 | ★★★ | ★ | ★★ |
| Zalel | 2006 | ★★★ | ★ | ★★★ |
| Has | 2004 | ★★★ | ★ | ★★ |
| Leitner | 2003 | ★★ | ★ | ★★ |
| Ecker | 2000 | ★★★ | ★ | ★★ |
| Kolble | 2000 | ★★★ | ★ | ★★★ |

**Table 3.** Pooled proportions for the outcomes explored in this systematic review in fetuses with isolated Dandy Walker Malformation (DWM).

| Outcome | N. of Studies (n) | Fetuses (n/N) | $I^2$ (%) | Raw % (95% CI) | Pooled proportion (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 post-natally | | | | | |
| ➢ 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 post-natal diagnosis | 6 | 7/33 | 54,9 | 21,21 (9,0-38,9) | 28.18 (8.5-53.9) |

**Table 4.** Pooled proportions for the outcomes explored in this systematic review in fetuses with isolated Megacisterna Magna (MCM).

| Outcome | N. of Studies (n) | Fetuses (n/N) | $I^2$ (%) | Raw % (95% CI) | Pooled proportion (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 post-natally | | | | | |
| ➢ 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 | 2,5 (0,1-13,2) | 4,66 (0,5-12,7) |
| Discrepancy between pre and post-natal diagnosis | 8 | 4/59 | 43,2 | 6,78 (1,9-16,5) | 7.14 (2.3-14.5) |

*: Using Meta-Disc

**Table 5.** Pooled proportions for the outcomes explored in this systematic review in fetuses with isolated Blake's Pouch Cyst (BPC).

| Outcome | N. of Studies (n) | Fetuses (n/N) | $I^2$ (%) | Raw % (95% CI) | Pooled proportion (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 post-natally | | | | | |
| ➢ 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 post-natal diagnosis | 6 | 3/39 | 33,9 | 7,69 (1,6-20,9) | 9.79 (2.9-20.1) |

*: Using Meta-Disc

**Table 6.** Pooled proportions for the outcomes explored in this systematic review in fetuses with isolated Vermian Hypoplasia (VH).

| Outcome | N. of Studies (n) | Fetuses (n/N) | $I^2$ (%) | Raw % (95% CI) | Pooled proportion (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 post-natally | | | | | |
| ➢ 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 post-natal diagnosis | 4 | 10/32 | 0 | 31,25 (16,1-50,0) | 32.44 (18.3-48.4) |

*: Using Meta-Disc

**Figures legend:**

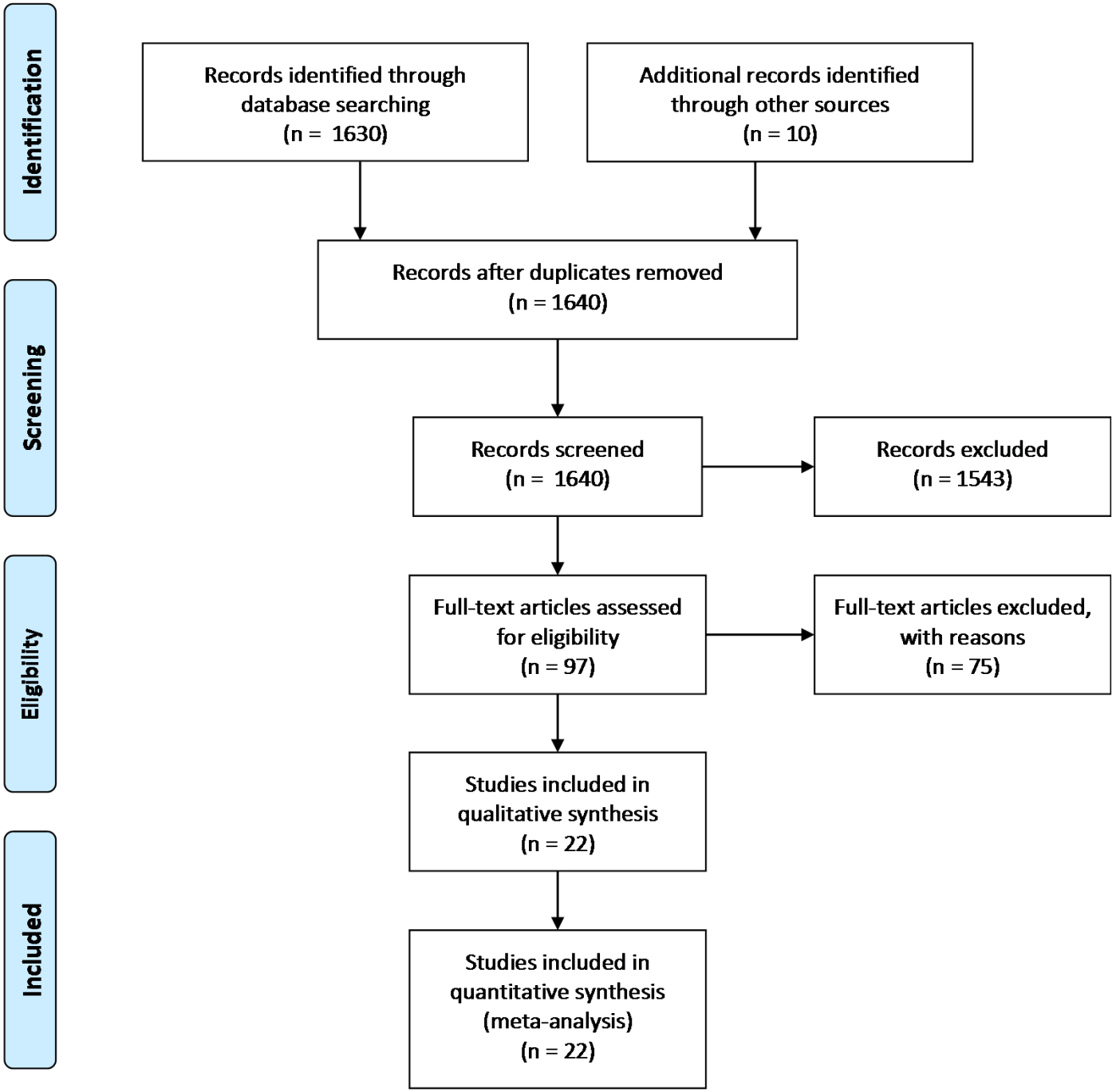
**Figure 1**. Systematic review flow chart.

**Figure 2.** Pooled proportions for the outcomes explored in this systematic review in fetuses with isolated Dandy Walker Malformation (DWM).

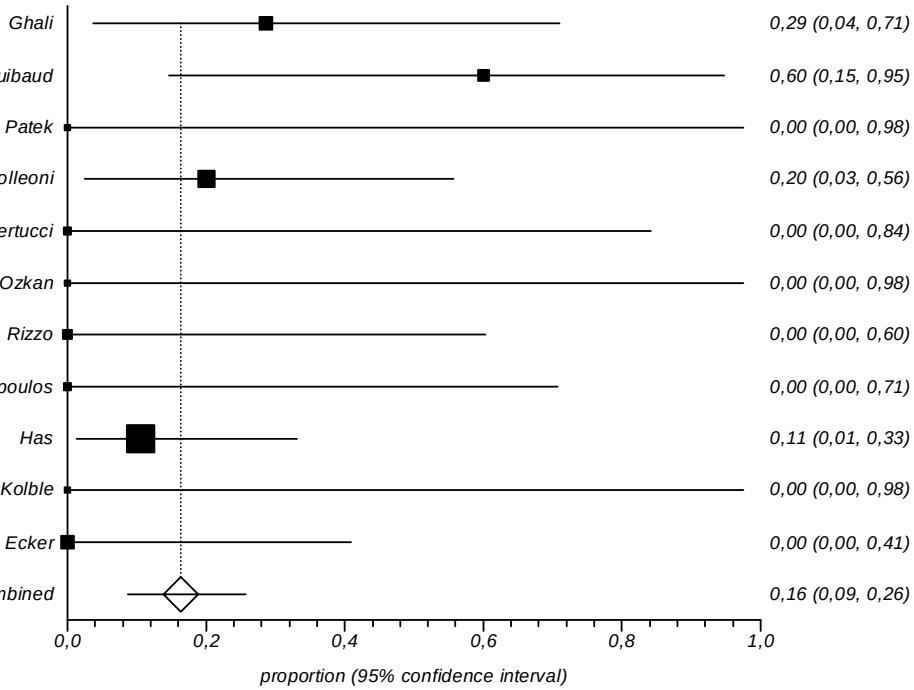
**Figure 3**. Pooled proportions for the outcomes explored in this systematic review in fetuses with isolated Megacisterna Magna (MCM).

**Figure 4**. Pooled proportions for the outcomes explored in this systematic review in fetuses with isolated Blake's Pouch Cyst (BPC).

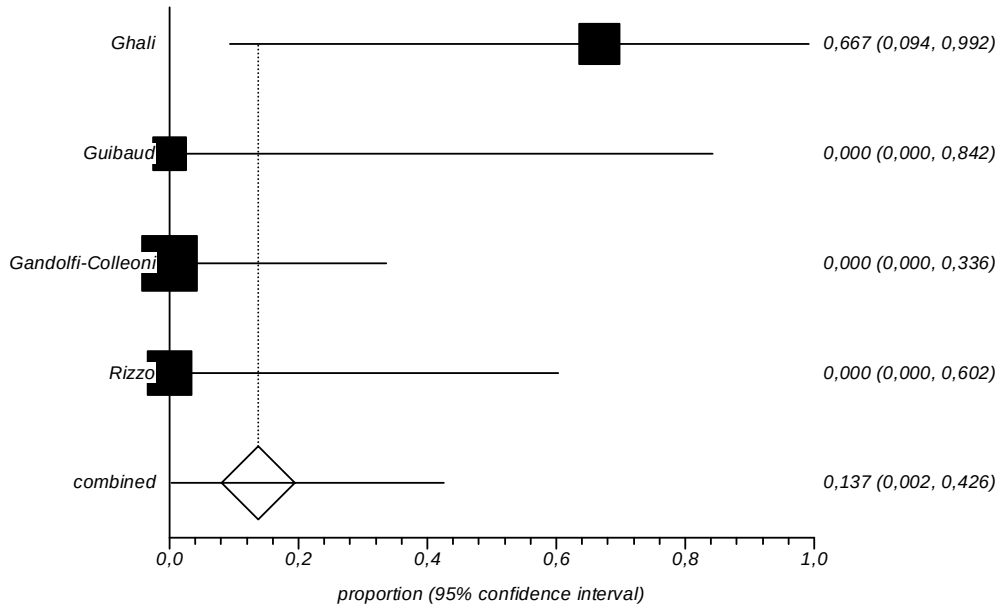
**Figure 5.** Pooled proportions for the outcomes explored in this systematic review in fetuses with isolated Vermian Hypoplasia (VH).



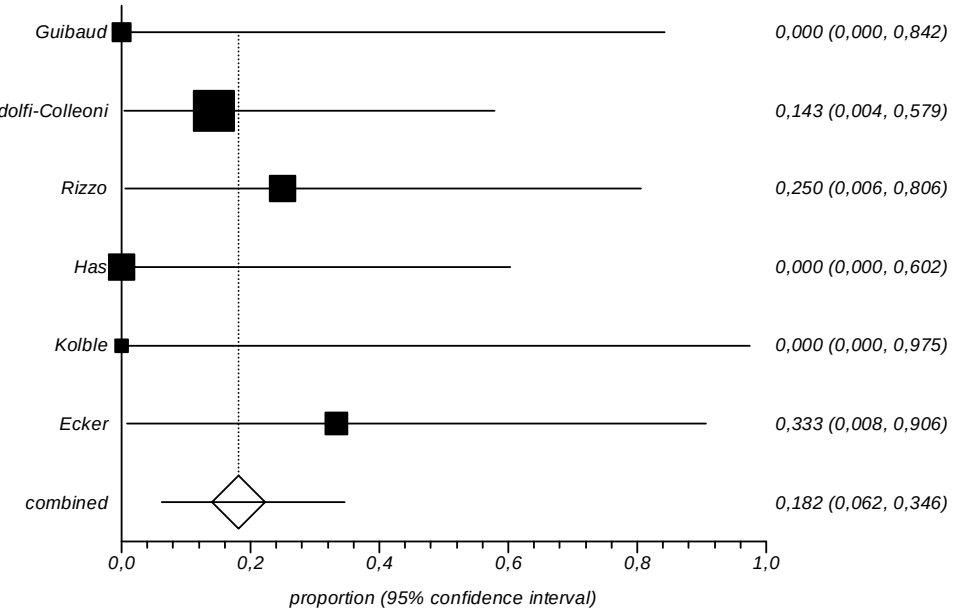
## Chromosomal anomalies



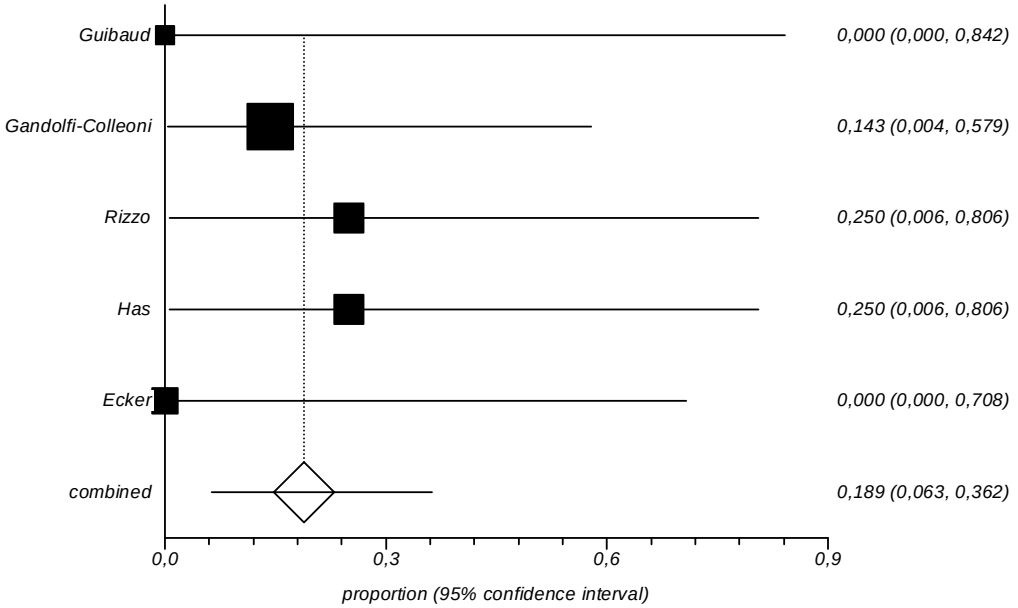

## Additional anomalies detected only at prenatal MRI

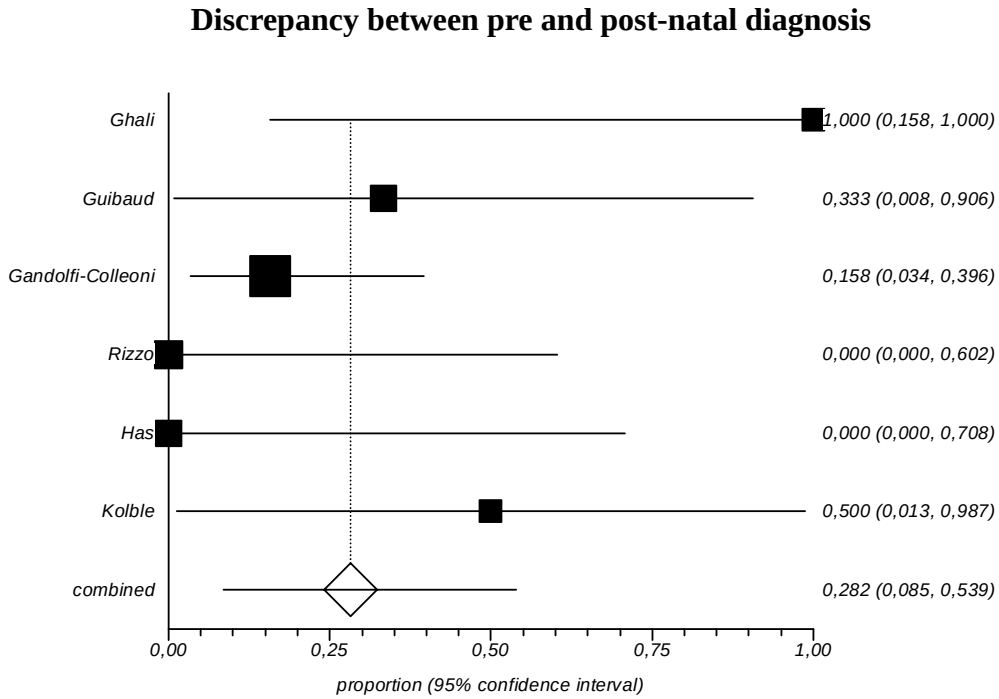


## Additional CNS anomalies detected only post-natally

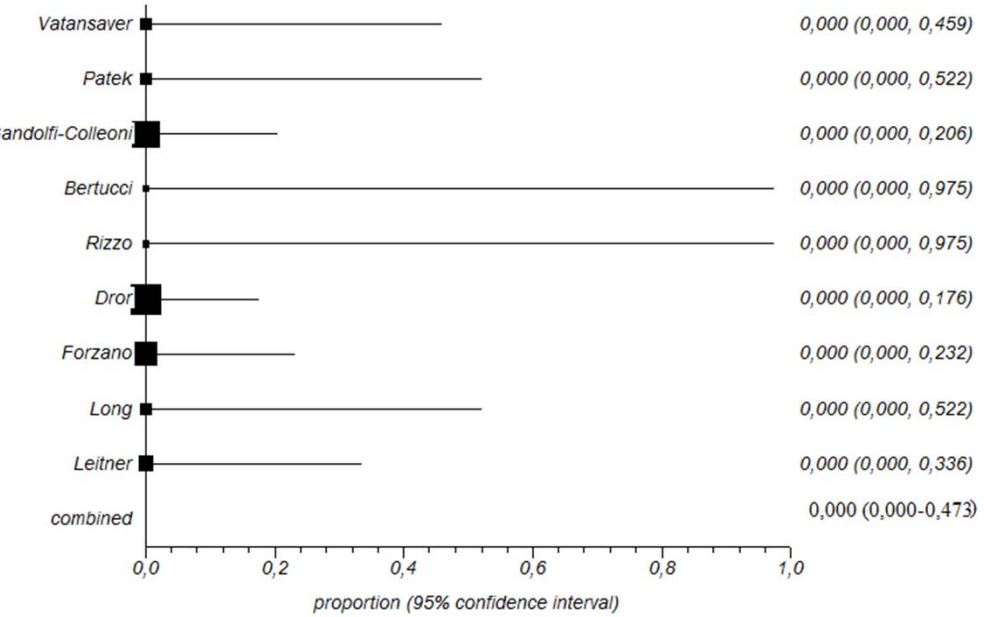



## Additional extra-CNS anomalies detected only post-natally

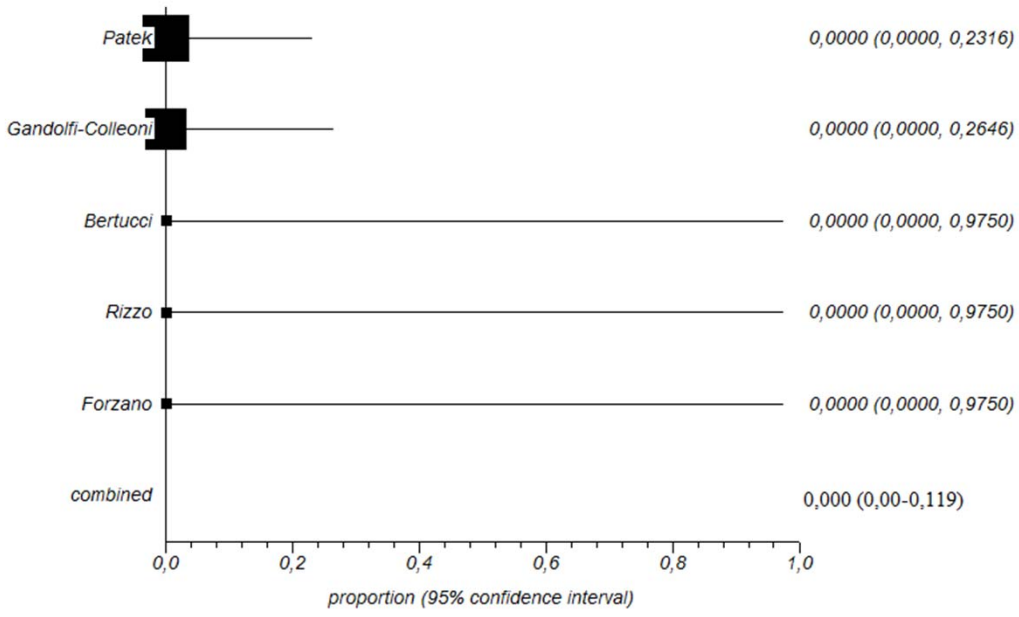




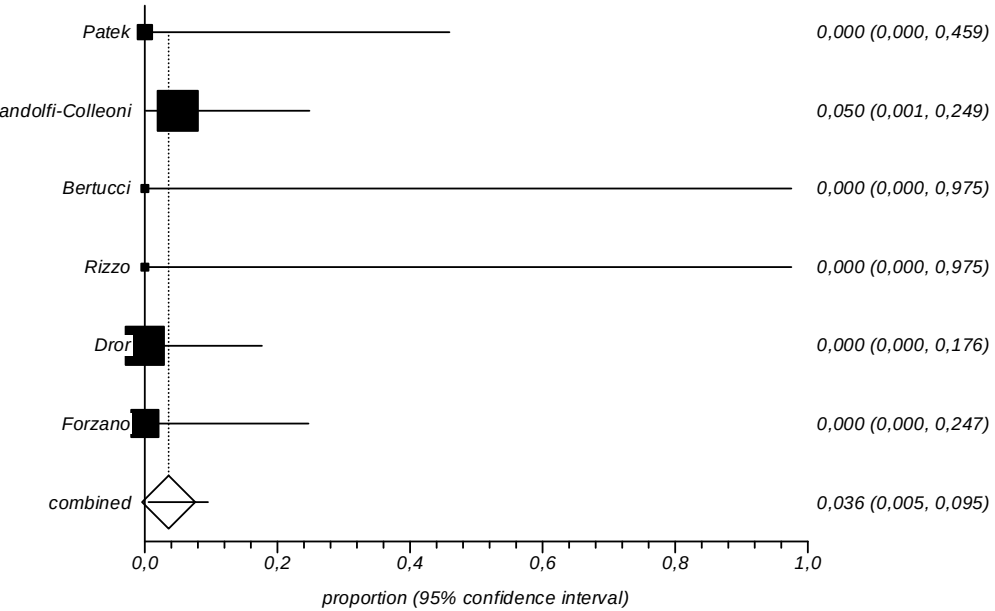
**Chromosomal anomalies**



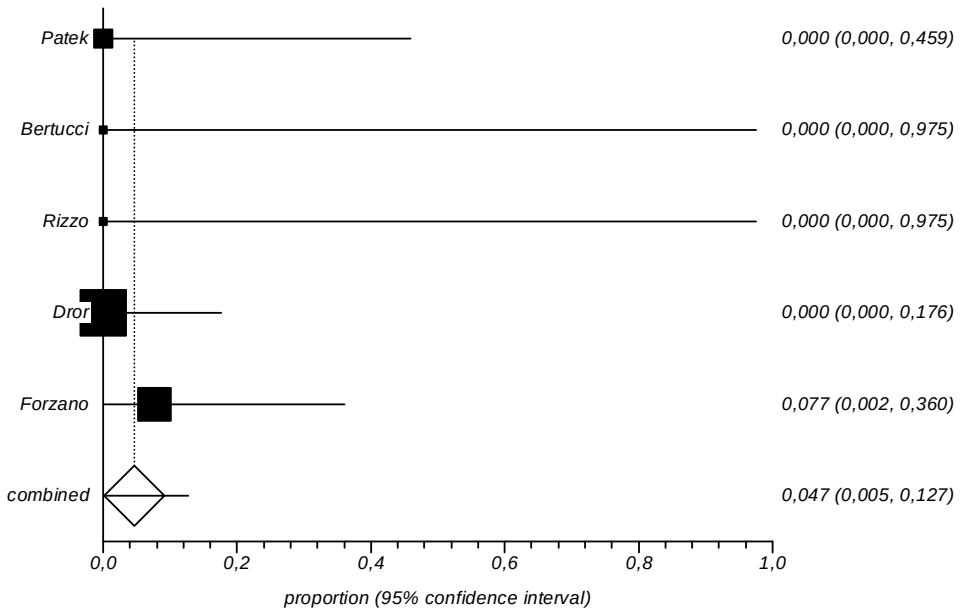

**Additional anomalies detected only at prenatal MRI**



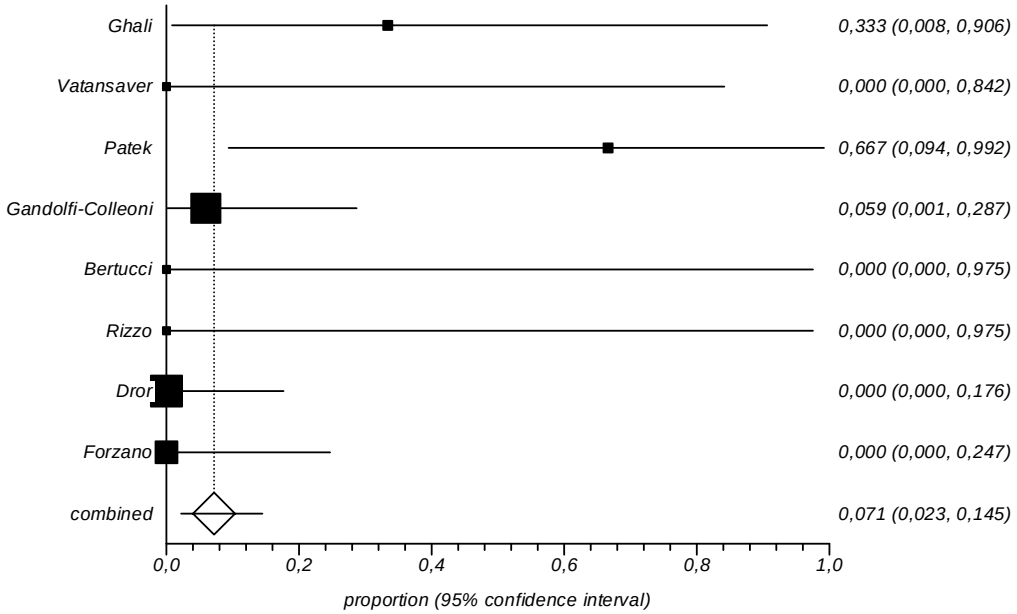
## Additional CNS anomalies detected only post-natally



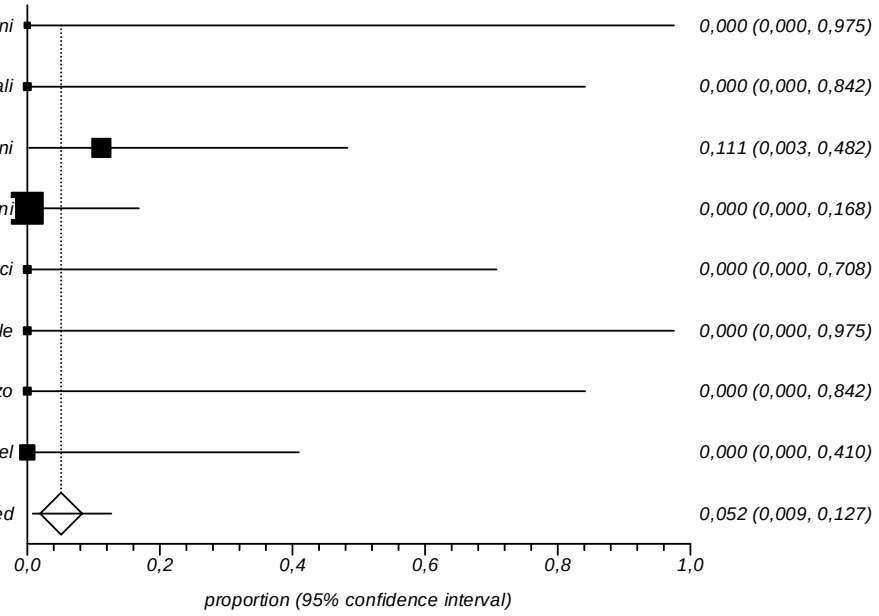

## Additional extra-CNS anomalies detected only post-natally



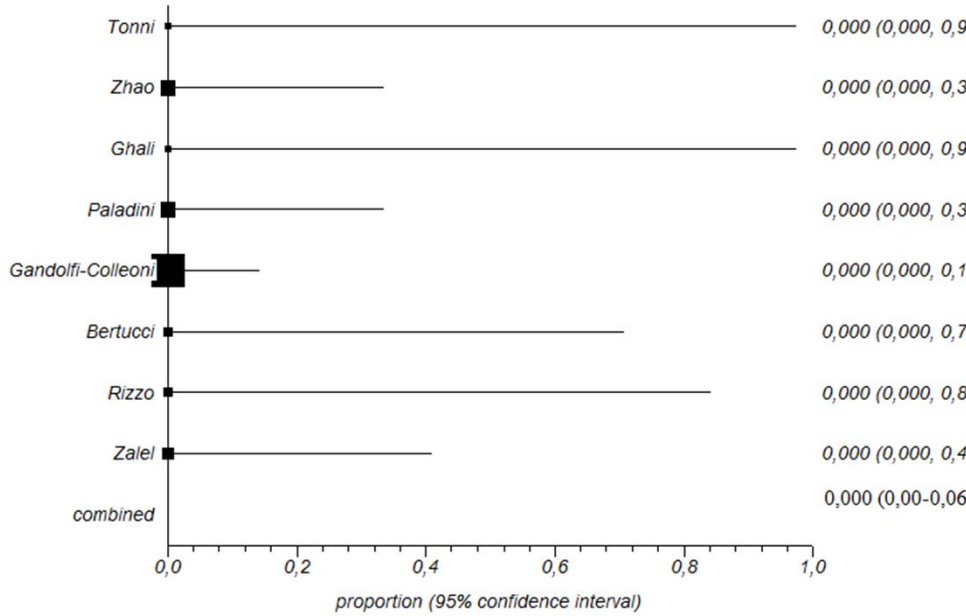
## Discrepancy between pre and post-natal diagnosis



**Chromosomal anomalies**




**Additional anomalies detected only at prenatal MRI**



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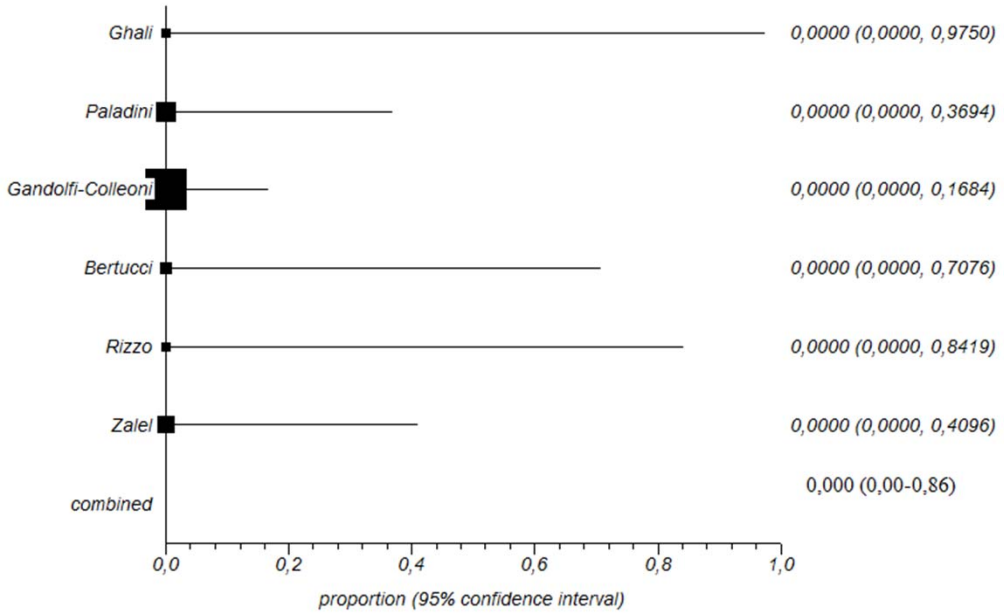
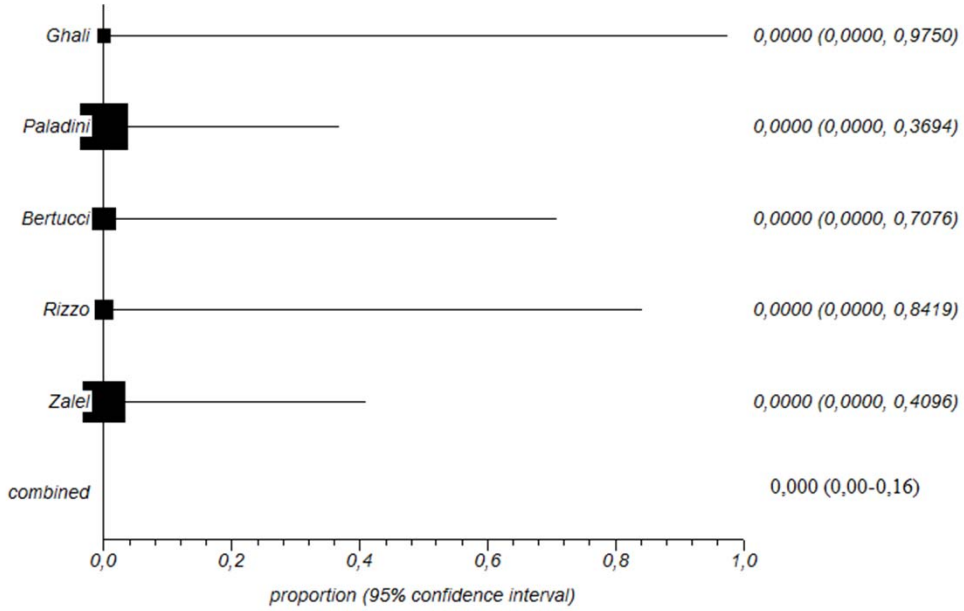
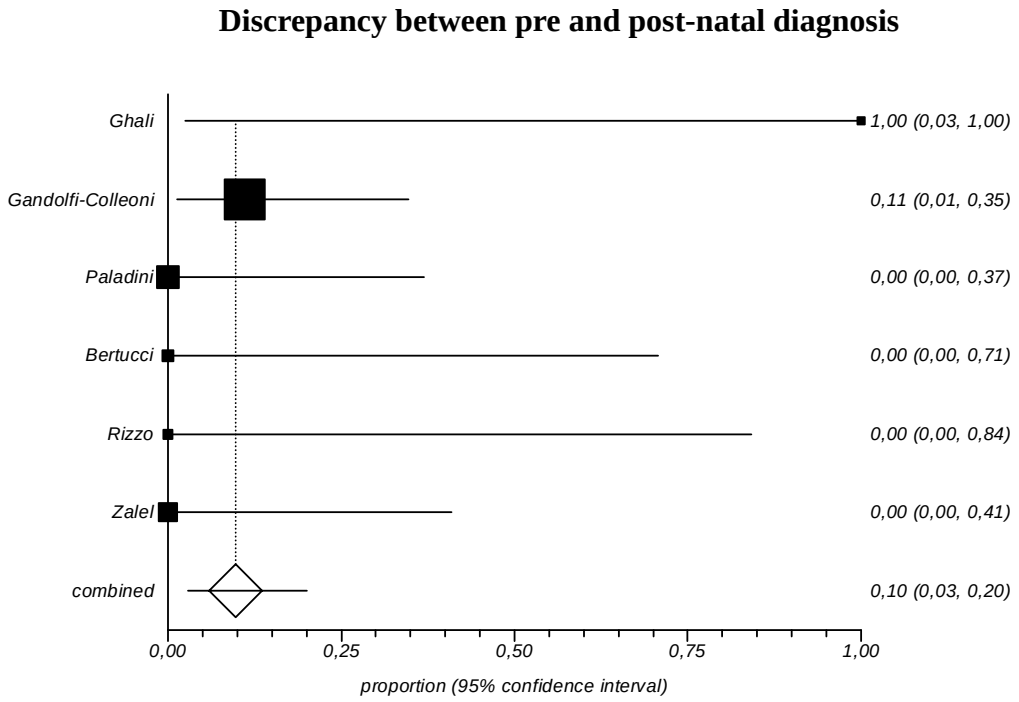
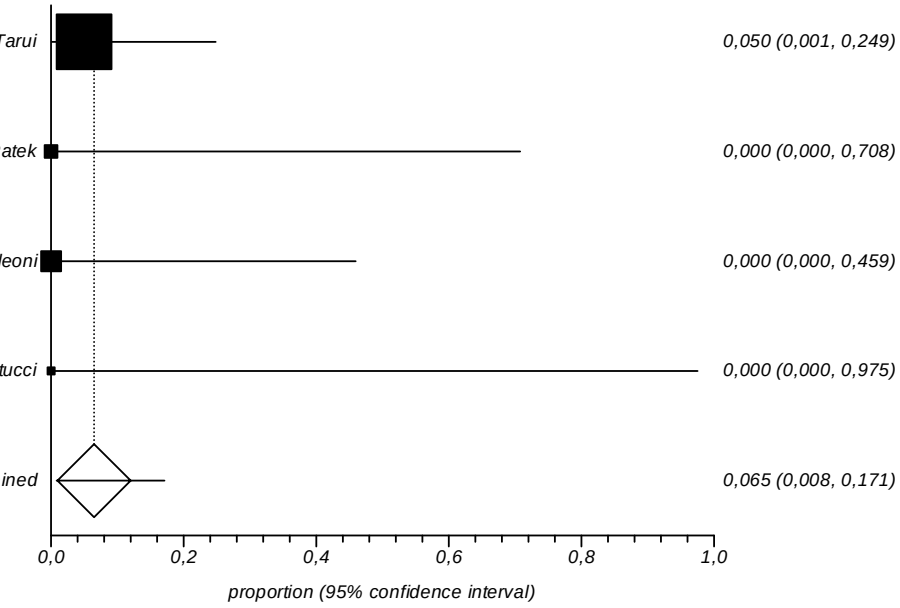



**Additional extra-CNS anomalies detected only post-natally**

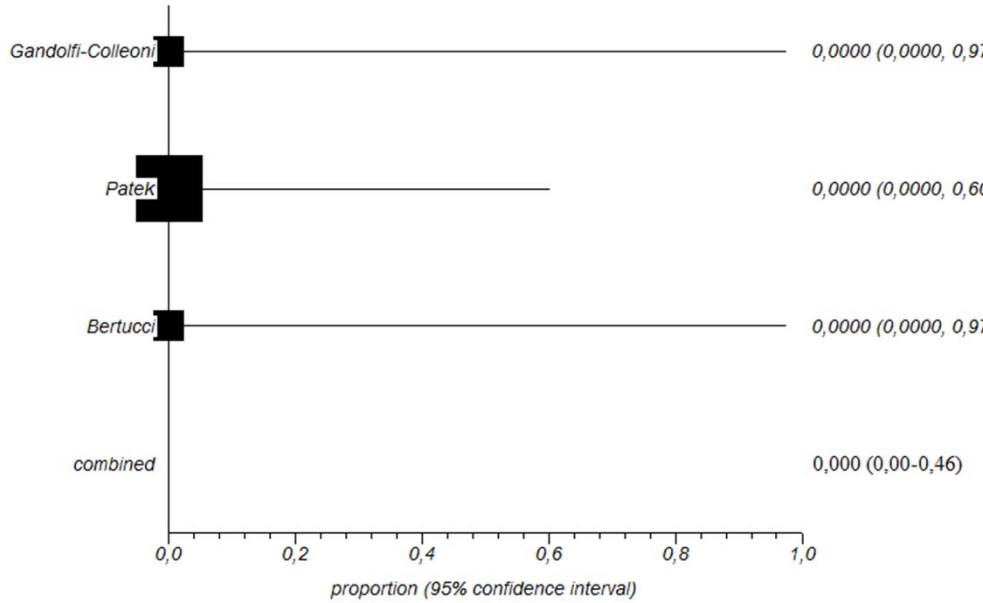




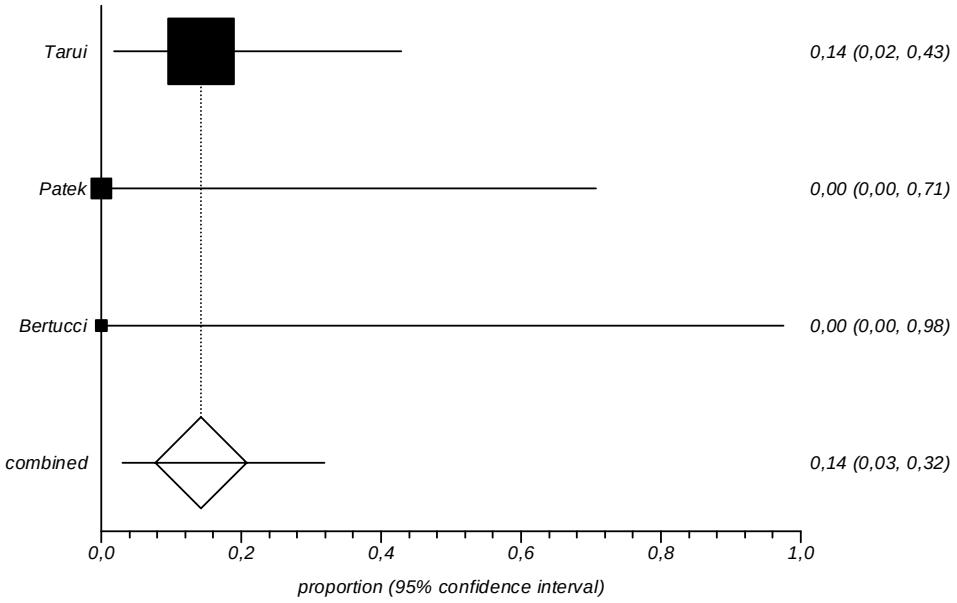
**Chromosomal anomalies**




**Additional anomalies detected only at prenatal MRI**



**Additional CNS anomalies detected only post-natally**




**Additional extra-CNS anomalies detected only post-natally**