Outcome of fetuses with congenital cytomegalovirus infection: a systematic review and meta-analysis

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What are the novel findings of this work?
The findings from this systematic review show that, in fetuses with congenital CMV infection showing no anomalies on prenatal imaging, the risk of adverse postnatal outcome is lower compared to what reported from previously published literature not considering the role of antenatal imaging assessment.

What are the clinical implications of this work?
The findings from this study show that the rate of abnormal neurocognitive delay – both mild and severe – and the incidence of hearing loss and visual defects are lower that previously reported in fetuses with congenital CMV infection and no anomalies at prenatal imaging, with the highest incidence occurring in case of first trimester infection.

ABSTRACT

Objective: To report the outcome of fetuses with congenital Cytomegalovirus (CMV) infection and normal ultrasound at the time of diagnosis.

Methods: Medline, Embase, Cinahl and Cochrane databases were explored. Inclusion criteria were fetuses with confirmed CMV infection and normal ultrasound assessment at the time of initial evaluation. The outcomes observed were anomalies detected at follow-up ultrasound scan, at prenatal magnetic resonance imaging (MRI) and at postnatal assessment, perinatal mortality, symptomatic infections at birth, neurodevelopmental outcomes, hearing and visual deficits. Random-effect meta-analysis of proportions were used to analyze the data.

Results: 26 studies (2603 fetuses) were included. The overall rate of central nervous system (CNS) associated anomalies detected exclusively at follow-up ultrasound was 4.4% (95% CI 1.4-8.8; 32/523; 15 studies), while those detected exclusively by MRI or postnatally were 5.8% (95% CI 1.9-11.5; 19/357; 11 studies) and 3.2% (95% CI 0.3-9.0; 50/660; 17 studies), respectively. The rate of extra-CNS associated anomalies detected exclusively at follow-up ultrasound was 2.9% (95% CI 0.8-6.3; 19/523; 15 studies), while those detected exclusively by MRI or postnatally were 0% (95% CI 0.0-1.7; 0/357; 11 studies) and 0.9% (95% CI 0.3-1.8; 4/660; 17 studies), respectively. Both intrauterine death and perinatal death occurred in 0.7% of cases (95% CI 0.3-14.0; 2/824; 23 studies). A symptomatic infection was shown in 1.5% (95% CI 0.7-2.7; 6/548; 19 studies) of cases and the rate of overall neurodevelopmental anomalies was 3.1% (95% CI 1.6-5.1; 16/550; 19 studies), with hearing problems affecting 6.5% of children (95% CI 3.8-10.0; 36/550; 19 studies). Sub-analyses according to the trimester at infection were affected by the very small number of included cases and lack of comparison of the observed outcomes in the original studies. Fetuses infected in the first trimester had a relatively higher risk of having additional anomalies at follow-up ultrasound and MRI, symptomatic infection, abnormal neurodevelopmental outcome and hearing problems.

Conclusions: In fetuses with congenital CMV infection showing no anomalies on both US and MRI, the risk of adverse postnatal outcome is lower compared to what reported from previously published literature not considering the role of antenatal imaging assessment. The findings from this study can enhance prenatal counselling of pregnancies with congenital CMV infection with normal prenatal imaging.

INTRODUCTION

Cytomegalovirus (CMV) is the most common congenital viral infection occurring during pregnancy, with a reported prevalence of 0.48 to 1.3% at birth.[1-4]

Maternal infection is asymptomatic in the large majority of cases, although it can sporadically present as flu-like syndrome. The chance of seroconversion depends on social, behavioral, and environmental factors[1-3] and has been estimated to be around 2% in pregnant women.[5] Maternal infection can lead to congenital CMV infection, which is caused by in utero mother to fetus transmission. The likelihood of congenital infection is higher in primary compared to non-primary maternal CMV infection, although, once acquired, the risk of symptomatic infection and long-term sequelae remains high even in non-primary maternal infection.[6] Furthermore, the risk of transmission is strongly related to the gestational age and is higher when seroconversion occurs during the third trimester of pregnancy.[7]

Parental counselling of pregnancies with congenital CMV infection is challenging and still based on old pediatric series which report that about 15-25% of newborns at birth develop short and long-term sequalae, such as abnormal neurodevelopmental outcome and hearing loss.[8-9]

However, in the last two decades advances in prenatal imaging have led to a significant improvement in the detection rate of congenital anomalies, which has allowed a more accurate prediction of the short- and long-term outcome of these children.[10] The presence of structural anomalies on ultrasound has been shown to be associated with a high risk of symptomatic infection and abnormal neurodevelopmental outcome.[11-12] Conversely, the burden of abnormal outcome in those fetuses presenting with no apparent anomalies on prenatal ultrasound has still to be quantified. The aim of this systematic review is to explore the outcome of fetuses with CMV infection and normal prenatal ultrasound at the time of diagnosis.

METHODS

Protocol, eligibility criteria, information sources and search

This review was performed according to a priori designed protocol recommended for systematic reviews and meta-analysis.[13-15] Medline, Embase, Cinahl and Clinicaltrials.gov databases were searched electronically in July 2020, utilizing combinations of the relevant medical subject heading (MeSH) terms, key words, and word variants for "cytomegalovirus" or "infection" and "outcome". The search and selection criteria were restricted to English language. Reference lists of relevant articles and reviews were hand searched for additional reports. PRISMA and MOOSE guidelines were followed.[16-18]

Study selection, data collection and data items

Inclusion criteria were fetuses with a confirmed isolated CMV infection, defined upon the presence of a positive polymerase chain reaction (PCR) for CMV on amniotic fluid or fetal blood, or neonatal urine positive to CMV during the first few days after delivery, and no associated CNS or extra-CNS anomalies detected at ultrasound at the time of diagnosis.

The outcomes observed were:

- Associated anomalies detected exclusively at follow-up ultrasound
- Associated anomalies detected exclusively at fetal magnetic resonance imaging (MRI) and missed at ultrasound
- Associated anomalies detected exclusively at postnatal imaging and missed at prenatal assessment (either ultrasound or MRI)
- Associated anomalies detected exclusively at birth, including microcephaly, cutaneous rash, elevated liver enzymes and thrombocytopenia
- Perinatal mortality, including intrauterine (IUD), neonatal (NND) and perinatal (PND) death
- Symptomatic infection at birth
- Abnormal neurodevelopmental outcome (overall, mild to moderate and severe), defined as the presence of neurological or neuropsychological anomalies
- Hearing loss

- Visual problems
- Abnormal motor function
- Abnormal cognitive function

Furthermore, we aimed to perform a sub-group analysis according to the gestational age at fetal infection (I, II and III trimester).

Data from studies reporting the incidence of these outcomes in fetuses with an isolated CMV infection, defined as CMV infected fetuses with a normal ultrasound scan at the time of diagnosis of infection, were considered eligible for analysis.

For the assessment of the incidence of associated anomalies detected only at follow-up, only cases showing no associated CNS and extra-CNS anomalies at the time of diagnosis were considered eligible for the inclusion. Likewise, the presence of additional anomalies detected only at prenatal and postnatal MRI or at birth were assessed only in fetuses with no additional anomalies; for the purpose of the analysis, associated anomalies were classified in structural malformations and abnormal signal intensity without a clear morphological anomaly. The neurodevelopmental outcome of infants with isolated CMV infection was ascertained exclusively in cases of isolated anomaly confirmed at birth.

Studies reporting cases of CMV infection presenting with associated anomalies at the first ultrasound assessment and those form which information on prenatal imaging could not be extrapolated were excluded. Autopsy-based studies were excluded on the basis that fetuses undergoing termination of pregnancy are more likely to show associated major structural anomalies. Likewise, series reporting information on CMV infection in the setting of a specific CNS or extra-CNS malformation and studies including only cases diagnosed postnatally were also excluded because they report higher rates of adverse outcomes and may not reflect the natural history of the anomaly. Finally, studies published before 2000 were also excluded, because we felt that advances in prenatal imaging techniques and improvements in the diagnosis CMV infection make them less relevant.

Only full-text articles were considered eligible for inclusion; case reports, conference abstracts, and case series with < 5 cases were also excluded to avoid publication bias.

Two authors (FDA, DB) reviewed all abstracts independently. Agreement regarding potential relevance or inconsistencies was reached by consensus or resolved by discussion with a third reviewer (ML). Full text copies of those papers were obtained, and the same reviewers independently extracted relevant data regarding study characteristics and pregnancy outcome. If more than one study was published on the same cohort with identical endpoints, the report containing the most comprehensive information on the population was included to avoid overlapping populations.

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 of the outcome of interest.[19] 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 the outcome of interest was not present at start of study. Assessment of the comparability of the study includes the evaluation of the comparability of cohorts based on the design or analysis. Finally, the ascertainment of the outcome of interest includes the evaluation of the type of the assessment of the outcome of interest, length and adequacy of follow-up. According to NOS a study can be awarded a maximum of one star for each numbered item within the Selection and Outcome categories. A maximum of two stars can be given for Comparability.[19]

Statistical analysis

We used meta-analyses of proportions to combine data and reported pooled proportion (PP). Funnel plots (displaying the outcome rate from individual studies versus their precision (1 per SE) 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 <10. In this case, the power of the tests is too low to distinguish chance from real asymmetry.

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 $\geq$50% indicate a substantial level of heterogeneity. A

random effect model was used to compute the pooled data analysis. All proportion meta-analyses were carried out by using StatsDirect version 2.7.9 (StatsDirect, Ltd, Altrincham, Cheshire, United Kingdom).

RESULTS

General characteristics

354 articles were identified, 102 were assessed with respect to their eligibility for inclusion and 26 studies[10-12,20-42] were included in the systematic review (Figure 1, Table 1, Table S1). These 26 studies included 2603 fetuses affected by isolated CMV infection; out of these, 1178 (45.3%, 95% CI 43.4-47.2) showed no associated CNS or extra-CNS anomalies detected at ultrasound at the time of diagnosis.

The majority of the included studies reported data on primary CMV infection, while six[22,26,36-37,41-42] reported outcomes of both primary and secondary infection, although there were very few number of cases included.

The timing of follow-up ultrasound ranged from a minimum of two to a maximum of four weeks. Few cases in four studies[22,28,33,40] underwent prenatal therapy in some of the included cases, mainly with valaciclovir.

The results of the quality assessment of the included studies using Newcastle-Ottawa Scale (NOS) are presented in Table 2. Most of the included studies showed an overall good score regarding the selection and comparability of the study groups, and for ascertainment of the outcome of interest. The main weaknesses of these studies were their retrospective design, small sample size, heterogeneity of outcomes observed and lack of stratification of the analysis according to the gestational age at infection.

Synthesis of the results

Table 3 shows the rate of additional anomalies found at follow-up prenatal imaging or at birth in fetuses with congenital CMV infection and a normal ultrasound assessment at the time of diagnosis.

The overall rate of central nervous system (CNS) associated anomalies detected exclusively at follow-up ultrasound was 4.4% (95% CI 1.4-8.8; 32/523; 15 studies), while those detected exclusively by MRI or postnatally were 5.8% (95% CI 1.9-11.5; 19/357; 11 studies) and 3.2% (95% CI 0.3-9.0; 50/660; 17 studies), respectively (figure 2). The rate of extra-CNS associated anomalies detected exclusively at follow-up ultrasound was 2.9% (95% CI 0.8-6.3; 19/523; 15 studies), while

those detected exclusively by MRI or postnatally were 0% (95% CI 0.0-1.7; 0/357; 11 studies) and 0.9% (95% CI 0.3-1.8; 4/660; 17 studies), respectively.

An abnormal signal intensity was detected in 5.2% (21/357) of cases, although two studies[10,21] reporting postnatal outcomes of fetuses with hyperintensity at MRI found no neurological impairment in this subset of children.

Among abnormalities found exclusively at clinical examination, elevated liver enzymes (4.1% - 19/343), thrombocytopenia (2.3% - 7/343) and microcephaly (2.0% - 8/42) were the three most common conditions.

IUD and PND occurred in 0.7% (95% CI 0.3-1.4 2/824) of cases, while no cases of NND were reported in the included studies (Table 4).

When considering abnormal postnatal outcome, a symptomatic infection was shown in 1.5% (95% CI 0.7-2.7; 6/548) of cases and the rate of overall neurodevelopmental anomalies was 3.1% (95% 1.6-5.1; 16/550), ranging from mild (1.2% - 4/471) to severe (1.9% - 8/471). Hearing problems affected 6.5% of children (95% CI 3.8-10.0) while motor and cognitive delay and visual problems were reported, respectively, in 2.3% (9/487), 1.1% (3/487) and 1.0% (1/471) of cases (table 5; figure 3).

Sub-group analysis according to the trimester of infection

Sub-group analyses according to the trimester of infection were affected by the small number of included cases and even smaller number of events which may have affected the robustness of the results.

Anomalies were detected at follow-up ultrasound assessment in 4.4% of fetuses infected in the first and in none of those in the second and third trimester of pregnancy. Likewise, the rate of associated structural anomalies detected exclusively at prenatal MRI were 6.3% in fetuses infected in the first trimester, while no additional anomaly was found at MRI in those infected in the second and third trimester of pregnancy (Supplementary Tables 2).

The incidence of abnormal neurodevelopmental outcome was 5.4% in children infected in the first and 0% in those infected in the second and third trimester. Finally, hearing problems occurred in 11.4% of children infected in the first, 7.0% of those in the second and 0% of those in the third trimester (Supplementary Tables 3).

DISCUSSION

Main findings

The findings from this systematic review show that, in fetuses with congenital CMV infection showing no anomalies on prenatal imaging, the risk of adverse postnatal outcome is lower compared to what reported from previously published literature not considering the role of antenatal imaging assessment. Additional anomalies detected exclusively at ultrasound follow-up were found in about 4% of cases, thus highlighting the need for a longitudinal evaluation of the affected fetuses through pregnancy. Likewise, the results from this study highlight the potential role of MRI even in fetuses with no anomalies, as they can be detected exclusively on MRI scan in about 6% of cases. The risk of perinatal mortality in congenitally infected fetuses was negligible. More importantly, the occurrence of symptomatic infection and abnormal neurodevelopmental outcome in fetuses showing normal prenatal imaging confirmed at birth was 1.5% and 3.1% respectively, while the occurrence of hearing problems was 6.5%. Sub-analyses according to the trimester at infection were affected by the very small number of included cases and lack of comparison of the observed outcomes in the original studies. Fetuses infected in the first trimester had a relatively higher risk of having additional anomalies at follow-up ultrasound and MRI, abnormal neurodevelopmental outcome and hearing problems.

Strengths and limitations

To the best of our knowledge, this is the first systematic review exploring the role of prenatal imaging in fetuses with congenital CMV infection. Accurate literature search, multitude of outcomes explored, and the strict inclusion criteria are the major strengths of the present review. The small number of cases in some of the included studies, their retrospective non-randomized design, lack of standardized criteria for the surveillance and follow-up examinations, the heterogeneity of the outcomes observed are the major limitations of this systematic review. Furthermore, we acknowledge that it is likely that not all these cases underwent neurosonography to evaluate fetal brain and it is well known that the rate of additional anomalies significantly depends on the quality of the sonogram and is much higher when performing only standard ultrasonography.[43] Another major limitation of the present systematic review is represented by the

very small number of included cases in the sub-group analysis according to the time at fetal infection, which can affect the robustness of the reported results. Finally, we could not stratify the analysis according to the viral load of the amniotic fluid – although it is reported that a higher viral load is associated with symptomatic fetuses or newborns[42] – and the type of maternal infection (primary vs non-primary) due to the lack of these data in the included studies. However, fetuses with a high viral load in the amniotic fluid are likely to show additional anomalies on the scan. Despite these limitations, to our knowledge this is the first and most comprehensive review specifically focusing on the outcomes of fetuses with CMV infection and normal prenatal ultrasound at the time of diagnosis.

Clinical and research implications

CMV infection is the most common fetal infection and the leading cause non-hereditary sensorineural hearing loss (SNHL) in high-income countries.[44-46] However, despite the clinical relevance of the infection, maternal serological screening has been improved and is currently offered only in few countries, such as Germany and Italy.[47]

Currently, parental counselling in pregnancies affected by congenital CMV infection is still based on observational studies that date back to many years ago. Parents are commonly counselled that - even if asymptomatic – congenital CMV infection is one of the main determinants of SNHL, delayed-onset SNHL and fluctuating SNHL[48] with an overall incidence of SNHL ranging from 15%-20% up to 44% in symptomatic children.[8,44] However, the current counselling of pregnancies complicated by congenital CMV infection does not completely take into account the role of prenatal imaging in predicting perinatal and neurodevelopmental outcome.

The findings from this study show that the rate of abnormal neurocognitive delay – both mild and severe – and the incidence of hearing loss and visual defects are lower that previously reported in fetuses with congenital CMV infection and no anomalies at prenatal imaging, with the highest incidence occurring in case of first trimester infection. In this scenario, parents whose pregnancy has been complicated by a congenital CMV infection can be counselled on the low risk of symptomatic infection and severe neurodevelopmental outcome in case of normal prenatal imaging, although the risk of hearing problems cannot be completely rule out by ultrasound.

Fetuses with isolated subtle CNS anomalies, such as ventriculomegaly, are commonly referred to prenatal MRI assessment in order to rule out additional anomalies which can significantly impact the prediction of postnatal outcome.[43,49] Despite this, there is still insufficient evidence on whether prenatal MRI should be offered to fetuses with congenital infections. In the present review, the overall rate of additional findings detected exclusively at MRI was about 6%, and an abnormal hyperintensity represented another 6%. Of note, no anomalies at birth and no significant neurological sequelae were found in studies reporting postnatal outcomes of fetuses with abnormal signal intensity.[10,21] Moreover, the clinical significance and the prognostic value of an hyperintense signal at MRI is still uncertain, particularly when affecting the frontal and parieto-occipital white matter, while an hyperintensity in the temporal lobe is more likely to be associated to an adverse neurological outcome.[50] In this scenario, prenatal MRI should always be considered in the diagnostic work up of fetuses with congenital CMV infection, even when no anomalies are detected on ultrasound. Nevertheless, parents might be reassured that the risk of detecting associated anomalies at MRI is low when a thorough sonographic assessment has been performed before.

Finally, timing of maternal infection is another peculiar issue during the management of congenital CMV infection. A recent systematic review showed that severe fetal impairments are rare after infection in the first trimester of pregnancy,[51] and these results are concordant with the findings from our study, as we found that fetuses infected in the first trimester had a relatively higher risk of additional anomalies at follow-up ultrasound and MRI, symptomatic infection, abnormal neurodevelopmental outcome and hearing problems, although the strength of this association was affected by the small number of included cases.

Conclusion

In fetuses affected by congenital CMV infection showing no anomalies on prenatal imaging, the risk of adverse postnatal outcome - particularly in terms of hearing loss and neurodevelopmental impairment - is lower than previously reported not considering the role of antenatal imaging assessment. The findings from this study can enhance prenatal counselling of pregnancies with congenital CMV infection with normal prenatal imaging.

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Figure legend

Figure 1. Systematic review flowchart.

Figure 2. Graphical representation of the occurrence of central nervous system (CNS) anomalies detected at prenatal or postnatal imaging.

Figure 2. Graphical representation of the occurrence of abnormal postnatal outcomes.

Supplementary Material

Supplementary Table 1. Excluded studies and reason for the exclusion

Supplementary Table 2. Pooled proportions (95% confidence intervals) for the occurrence of anomalies at prenatal imaging and at birth in fetuses with congenital CMV infection and normal ultrasound assessment at the time of diagnosis according to the trimester at maternal infection

Supplementary Table 3. Pooled proportions (95% confidence intervals) for the occurrence of anomalies at prenatal imaging and at birth in foetuses with congenital CMV infection and normal ultrasound assessment at the time of diagnosis according to the trimester at maternal infection

Supplementary Funnel plots

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

Author	Year	Country	Study design	Study period	Type of infection	Pre-natal imaging	GA at infection	Ultrasound follow-up	Time of follow-up	Prenatal therapy	Fetuses (n)
Lipitz[20]	2019	Israel	Retrospective	2011-2018	Primary	US+MRI	I trimester	3-4 weeks	2y (6m-10y)	No	123
Dimb[illegible]m[21]	2017	Israel	Retrospective	2011-2014	Primary	US+MRI	NS	3-4 weeks	48m (27-64)	No	81
Leruez-Ville[22]	2016	France	Retrospective	2008-2013	Primary and secondary	US	I,II,III trimester	NS ("serial")	24 m (1-53)	Yes[b]	82
Leyder[12]	2016	Belgium	Prospective	1996-2012	Primary	US	I-II trimester	4 weeks	NS	No	69
Cannie[23]	2016	Belgium	Retrospective	2004-2014	Primary	US+MRI	I-II trimester	NS	4.4 y (0.6-9.7)	No	121
Amir[24]	2016	Israel	Retrospective	2007-2013	Primary	US	I-II trimester	NS	32m (12-83)	No	98
Lavattoni[25]	2015	Italy	Prospective	1995-2010	Primary	US+MRI	I trimester	NS	6y	No	46
Picone[26]	2014	France	Retrospective	2004-2013	Primary and secondary	US+MRI	NS	2 weeks	NS	NS	69
Garcia-Flores[27]	2013	Spain	Retrospective	2008-2012	Primary	US+MRI	NS	NS	1y	NS	7
[illegible][28]	2011	Israel	Retrospective	2001-2007	Primary	US+MRI	NS	3-4 weeks	11-81m	Yes[c]	69
Feldman[29]	2011	Israel	Retrospective	2000-2006	Primary	US+MRI	NS	3-4 weeks	18m	No	118
Lipitz[10]	2010	Israel	Prospective	2004-2009	Primary	US+MRI	I-II-III trimester	3-4 weeks	6-55m	No	38
Doneda[30]	2010	Italy	Retrospective	2000-2008	Primary	US+MRI	II-III trimester	NS	1m-8y	NS	38
Simonazzi[31]	2010	Italy	Prospective	2007-2008	Primary	US	NS	NS	NS	No	218
Picone[32]	2008	France	Retrospective	1991-2002	NS	US+MRI	NS	NS	23 m (0-72)	No	38
[illegible][33]	2008	France	Retrospective	2000-2007	Primary	US+MRI	III trimester	2 weeks	NS	Yes[d]	49
Benoist[34]	2008	France	Retrospective	2000-2006	Primary	US+MRI	III trimester	NS	NS	No	73
Ginde[35]	2008	Israel	Prospective	1998-2005	Primary	US	III trimester	2 weeks	36m (6-36)	No	21
Romanelli[36]	2008	France	Retrospective	2005-2006	Primary and secondary	US+MRI	I-II trimester	2 weeks	NS	NS	13
Guerr[illegible][11]	2008	Italy	NS	1996-2006	Primary	US	NS	NS	NS	No	650
Yinon[37]	2006	Israel	Retrospective	1997-2004	Primary and secondary	US	I-II trimester	NS	36m (4-72)	No	40
Lipitz[38]	2002	Israel	Prospective	1999-2000	Primary	US+MRI	I-II-III trimester	3-4 weeks	32 m (6-96)	No	51
Gouarin[39]	2002	France	Retrospective	1992-1999	Primary	US	II trimester	NS	NS	NS	30
Enders[40]	2001	Germany	Retrospective	1988-2000	Primary	US	I-II-III trimester	NS	22.5m (3m-8y)	Yes[e]	189
Azar[41]	2001	Switzerland	Prospective	1989-1998	Primary and secondary	US	I-II-III trimester	4 weeks	39 m (14-76)	No	26
Lazzarotto[42]	2000	Italy	Prospective	1994-1998	Primary and secondary	US	NS	NS	NS	No	246

NS, not specified; US, ultrasound; MRI, magnetic resonance imaging; GA, gestational age

a: valaciclovir in 49 cases with non-severe US anomalies; b: valaciclovir in 37 cases; c: in 4 cases; d: valaciclovir in 17 cases; e: therapy in 2 cases

Table 2. Quality assessment of the included studies according to Newcastle-Ottawa Scale (NOS) for case-control study. 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.

Author	Year	Selection	Comparability	Outcome
Lipitz[20]	2019	★★★	★	★★
Birnbaum[21]	2017	★★★	★	★★
Leruez-Ville[22]	2016	★★★	★	★★
Leyder[12]	2016	★★★	★	★★
Cannie[23]	2016	★★★	★	★★
Amir[24]	2016	★★★	★	★★
Zavattoni[25]	2015	★★★	★	★★
Picone[26]	2014	★★★	★	★★
Garcia-Flores[27]	2013	★★★	★	★★
Farkas[28]	2011	★★★	★	★★
Feldman[29]	2011	★★★	★	★★
Lipitz[10]	2010	★★★	★	★★
Doneda[30]	2010	★★★	★	★★
Simonazzi[31]	2010	★★★	★	★★
Picone[32]	2008	★★★	★	★★
Benoist[33]	2008	★★★	★	★★
Benoist[34]	2008	★★★	★	★★
Gindes[35]	2008	★★★	★	★★
Romanelli[36]	2008	★★★	★	★★
Guerra[11]	2008	★★★	★	★★

Yinon[37]	2006	★★★	★	★★
Lipitz[38]	2002	★★★	★	★★
Gouarin[39]	2002	★★★	★	★★
Enders[40]	2001	★★★	★	★★
Azam[41]	2001	★★★	★	★★
Lazzarotto[42]	2000	★★★	★	★★

Table 3. Pooled proportions (95% confidence intervals) for the occurrence of anomalies at prenatal imaging and at birth in fetuses with congenital CMV infection and normal ultrasound assessment at the time of diagnosis.

Outcome		Studies (n)	Fetuses (n/N)	I^2 (%)	Pooled proportions (95% CI)
Anomalies detected exclusively at follow-up ultrasound					
•	CNS anomalies	15	32/523	74.4	4.35 (1.4-8.8)
•	Extra-CNS anomalies	15	19/523	68.2	2.93 (0.8-6.3)
Anomalies detected exclusively at prenatal MRI					
•	Structural anomalies	11	19/357	68	5.77 (1.9-11.5)
•	CNS anomalies	11	19/357	68	5.77 (1.9-11.5)
•	Extra-CNS anomalies	11	0/357	0	0 (0-1.7)
•	Abnormal signal intensity	11	21/357	70.8	5.24 (1.5-11.0)
Anomalies detected exclusively at postnatal imaging					
•	CNS anomalies	17	50/660	89.3	3.23 (0.3-9.0)
•	Extra-CNS anomalies	17	4/660	0	0.91 (0.3-1.8)
Anomalies detected exclusively at clinical examination					
•	Microcephaly	16	8/442	0	2.01 (0.1-3.5)
•	Rash	10	2/308	0	1.03 (0.2-2.5)
•	Elevated liver enzymes	11	19/343	77.8	4.05 (0.5-
•	Thrombocytopenia	11	7/343	2	
		10	3/326	0	

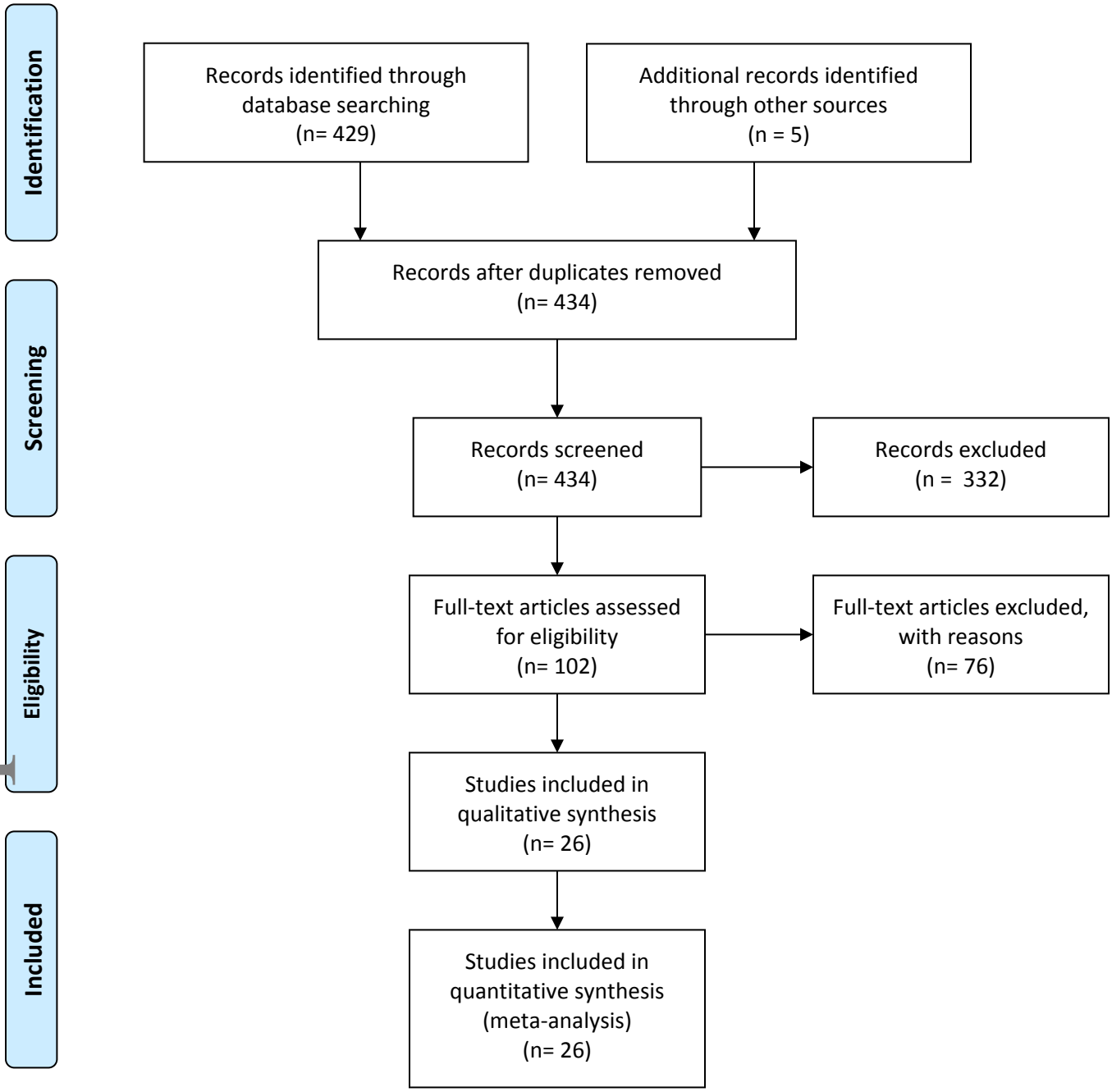
•	Chorioretinitis				10.1) 2.25 (1.0-4.1) 1.39 (0.4-2.9)

Table 4. Pooled proportions (95% confidence intervals) for the occurrence of intra-uterine (IUD), neonatal (NND) and perinatal (PND) death in fetuses with congenital CMV infection.

Outcome	Studies (n)	Foetuses (n/N)	I^2 (%)	Pooled proportions (95% CI)
IUD	23	2/824	0	0.74 (0.3-1.4)
NND	23	0/824	0	0 (0-1.4)
PND	23	2/824	0	0.74 (0.3-1.4)

Table 5. Pooled proportions (95% confidence intervals) for the occurrence of abnormal postnatal outcome in fetuses with congenital CMV infection.

Outcome	Studies (n)	Foetuses (n/N)	I2 (%)	Pooled proportions (95% CI)
Symptomatic infection	19	6/548	22.1	1.49 (0.7-2.7)
Abnormal neurodevelopmental outcome (overall)	19	16/550	22.1	3.10 (1.6-5.1)
• Abnormal mild neurodevelopmental outcome	17	4/471	0	1.19 (0.4-2.3)
• Abnormal moderate neurodevelopmental outcome	17	0/471	0	0 (0-1.7)
• Abnormal severe neurodevelopmental outcome	17	8/471	0	1.90 (0.9-3.3)
Visual problems	18	1/471	0	0.95 (0.3-2.0)
Hearing problems	19	36/550	48.8	6.54(3.8-10.0)
Cognitive delay	18	3/487	0	1.14 (0.4-2.3)
Motor delay	18	9/487	0	2.28 (1.2-3.8)
Other neurological anomalies	18	2/487	0	1.10 (0.4-2.2)



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