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Neonatal and long-term outcomes of infants with congenital cytomegalovirus infection and negative amniocentesis: systematic review and meta-analysis

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KEYWORDS: amniocentesis; CMV; congenital cytomegalovirus infection; cytomegalovirus; meta-analysis; sequelae

CONTRIBUTION

What are the novel findings of this work?
In this systematic review and meta-analysis including studies on women with cytomegalovirus (CMV) infection during pregnancy and a negative amniocentesis result, there were 0% rates of severe neonatal symptoms, severe sensorineural hearing loss and/or neurodevelopmental impairment at follow-up and termination of pregnancy due to the presence of CMV-associated central nervous system findings or multiorgan involvement on imaging.

What are the clinical implications of this work?
A negative amniocentesis ensures the absence of any clinical complications due to CMV, even if the neonate is subsequently found to shed CMV into the urine.

ABSTRACT

Objective *Cytomegalovirus (CMV) DNA is detectable in the amniotic fluid collected by amniocentesis in cases in which the fetus has been infected. However, cases of congenital neonatal CMV infection with a negative amniocentesis result have also been reported in the literature. The aim of the present study was to compare pregnancies with a negative amniocentesis result to those with a positive amniocentesis result in terms of incidence of fetal insult and long-term sequelae.*

Methods *Observational studies that included pregnant women with CMV infection who underwent amniocentesis and that reported their results together with neonatal and/or long-term outcomes of the offspring were included. The risk of bias in included studies was assessed using the Newcastle–Ottawa Scale. The rate of severe symptoms at birth, defined as neurological symptoms or multiorgan involvement at birth, and the rate of severe sensorineural hearing loss (SNHL) and/or neurodevelopmental impairment at follow-up were the main outcomes of the study. The secondary outcome was the rate of pregnancy termination due to the presence of CMV-associated central nervous system (CNS) findings or multiorgan involvement on ultrasound/magnetic resonance imaging (MRI).*

Results *Seven studies were included in the systematic review and meta-analysis. The pooled false-negative rate of amniocentesis was 8.0% (95% CI, 5.0–13.0%). The pooled rate of severe symptoms at birth was 0.0% (95% CI, 0.0–1.0%;* $I^2 = 0\%$*) in fetuses with a negative amniocentesis result and 22.0% (95% CI, 11.0–38.0%;* $I^2 = 75\%$*) in those with a positive amniocentesis result. The pooled odds ratio (OR) was 0.03 (95% CI, 0.01–0.10;* $I^2 = 0\%$*). The pooled rate of severe SNHL and/or neurodevelopmental impairment at follow-up in fetuses with a negative amniocentesis result was 0.0% (95% CI, 0.0–1.0%;* $I^2 = 0\%$*) and, in those with a positive amniocentesis result, it was 14.0% (95% CI, 7.0–26.0%;* $I^2 = 64\%$*). The pooled OR was 0.04 (95% CI, 0.01–0.14;* $I^2 = 0\%$*). The pooled rate of pregnancy termination due to the presence of CMV-associated CNS findings or multiorgan involvement on ultrasound/MRI was 0.0% (95% CI, 0.0–2.0%;* $I^2 = 0\%$*) in fetuses with a negative amniocentesis result and 20.0% (95% CI, 10.0–36.0%;* $I^2 = 82\%$*) in those with a positive amniocentesis result. The pooled OR was 0.03 (95% CI, 0.01–0.08;* $I^2 = 0\%$*). A subgroup analysis including only pregnancies with primary CMV infection*

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and a sensitivity analysis including only prospective studies were carried out, showing very similar results to those of the main analysis.

Conclusion *A negative amniocentesis result in pregnant women with CMV infection ensures lack of fetal insult and long-term sequelae to the child, even if transmission has occurred.*

INTRODUCTION

Congenital cytomegalovirus (CMV) infection is the most common congenital infection, with an incidence of 0.2–2.2%[1,2]. CMV infection is the most common cause of non-genetic congenital deafness, accounting for approximately one-third of all cases. Neurological defects associated with congenital CMV infection affect about 8000 infants per year in the USA, which is more than the number of cases affected by several better-known childhood diseases and syndromes[3].

The reported risk of vertical CMV transmission after maternal primary CMV infection during pregnancy is approximately 40%[4]. Vertical transmission occurs through the placenta, which is the first fetal organ to be infected. The placenta temporarily acts as a barrier to the virus, but the virus eventually crosses the placenta, replicates in the tubular epithelium of the kidneys and is excreted into the amniotic fluid[5]. Therefore, if the fetus is infected with CMV, its DNA is detectable in the amniotic fluid collected by amniocentesis, allowing the diagnosis of congenital infection[6]. Prenatal diagnosis of fetal CMV infection is of paramount importance, as it determines the management of the pregnancy, including *in-utero* treatment, planning of postnatal evaluation and treatment of the newborn[7].

However, several studies have reported cases of congenital neonatal CMV infection following a negative amniocentesis result[8–10]. Explanations that have been proposed for these false-negative results include low sensitivity of the polymerase chain reaction (PCR) test and delayed transmission of CMV, after amniocentesis has been performed[9]. The clinical outcome of these cases has not been studied systematically.

The aim of the present systematic review and meta-analysis was to compare pregnancies with a negative amniocentesis result and those with a positive amniocentesis result, in terms of fetal insult and long-term sequelae.

METHODS

This meta-analysis was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement for meta-analyses and registered with PROSPERO (CRD42021290012).

Eligibility criteria

Observational studies that included pregnant women with CMV infection who underwent amniocentesis, and that reported their results together with neonatal and/or long-term outcomes of the offspring, were included in the study.

Evaluated populations included pregnant women with CMV infection in the immediate preconceptional period (up to 12 weeks prior to conception) or during pregnancy in whom amniocentesis was performed, as well as fetuses and neonates of these women for the estimation of short- and long-term outcomes.

Outcome measures

The main outcomes were the rate of severe symptoms at birth, defined as neurological symptoms or multiorgan involvement at birth, and the rate of severe sensorineural hearing loss (SNHL) and/or neurodevelopmental impairment at follow-up, as defined by the authors of primary studies.

The secondary outcome was the rate of pregnancy termination due to the presence of CMV-associated central nervous system (CNS) findings or multiorgan involvement on ultrasound or magnetic resonance imaging (MRI).

Search methods for identification of studies

Eligible studies were identified through a predefined search strategy of electronic databases. The literature was searched for observational studies reporting the results of amniocentesis in fetuses with congenital CMV infection and the neonatal and long-term outcomes of those fetuses. MEDLINE, Scopus, The Cochrane Library and 'gray literature' sources were searched. The last search was conducted in June 2022. The search and selection criteria were restricted to European languages. The search was carried out using combinations of the following terms: 'cytomegalovirus', 'congenital', 'fetal', 'maternal', 'amniocentesis', 'diagnosis' and 'symptomatic'.

Study selection

Two authors (C.C. and A.S.) independently conducted the literature search and, in the case of disagreement, a consensus was reached after discussion. Whenever a consensus could not be reached, a third author (Y.V.) was consulted. All studies were compared carefully to avoid inclusion of duplicate or overlapping samples. In cases of overlap, the study with the largest number of events was included. There was no limitation concerning the publication date.

Two reviewers (C.C. and Y.V.) independently assessed the eligibility of all identified citations according to the abovementioned criteria. Disagreements between the two reviewers were resolved by consensus.

Data extraction

Data extraction and assessment of study quality were performed independently by two authors (C.C. and K.D.).

The characteristics of each included study were assessed according to a predefined data extraction form included in the Cochrane Handbook for Systematic Reviews[11]. In case of disagreement, a consensus was reached after discussion between the two authors.

Risk of bias in individual studies

Two review authors (C.C. and A.S.) independently assessed the risk of bias in included studies using the Newcastle–Ottawa Scale (NOS), which was developed to assess the quality of non-randomized studies, including cohort studies. Each study is judged on eight items, categorized into three broad groups: the selection of the study groups; the comparability of the groups; and the ascertainment of either the exposure or outcome of interest[12]. As all individuals had the same exposure (maternal CMV infection), all included studies received the maximum number of stars for the items 'selection of the non-exposed cohort' and 'comparability'.

Synthesis of results

The data from each study were extracted, and the proportion of events in each group (positive amniocentesis and negative amniocentesis groups), with 95% CIs, for each study as well as a pooled estimate, weighted by the sample size of each study, were estimated. This was performed using the metaprop package in an open-source software R version 2.15.1 (The R Foundation for Statistical Computing, Vienna, Austria). Metaprop is used to perform the meta-analysis of proportions in R. It implements procedures that are specific to binomial data and allows computation of exact binomial CIs. In addition, the data of each study were entered into contingency tables to estimate proportions (95% CI) in each group and odds ratios (ORs) (95% CI) for each study and derive a pooled estimate, weighted by the sample size of each study. Summary effect sizes were calculated using either a random-effects or a fixed-effects model, depending on the degree of statistical and/or clinical heterogeneity. Between-study heterogeneity was assessed using the estimation of Cochran's Q and the I^2 statistic. The I^2 statistic is the ratio of between-study variance to the sum of the within- and between-study variances, and describes the percentage of the true-effect variation that is due to heterogeneity rather than chance.

The unit of analysis (denominator) for the outcomes of SNHL and/or neurodevelopmental impairment at follow-up and severe symptoms at birth was liveborn fetuses (i.e. fetuses with a positive or negative amniocentesis result after excluding cases of intrauterine loss and termination of pregnancy). The unit of analysis for the outcome of termination of pregnancy due to the presence of CMV-associated CNS findings on ultrasound or MRI was fetuses with a positive or negative amniocentesis result, regardless of pregnancy outcome.

A subgroup analysis was performed including only women with primary CMV infection, and a sensitivity analysis was performed including only studies that were conducted prospectively.

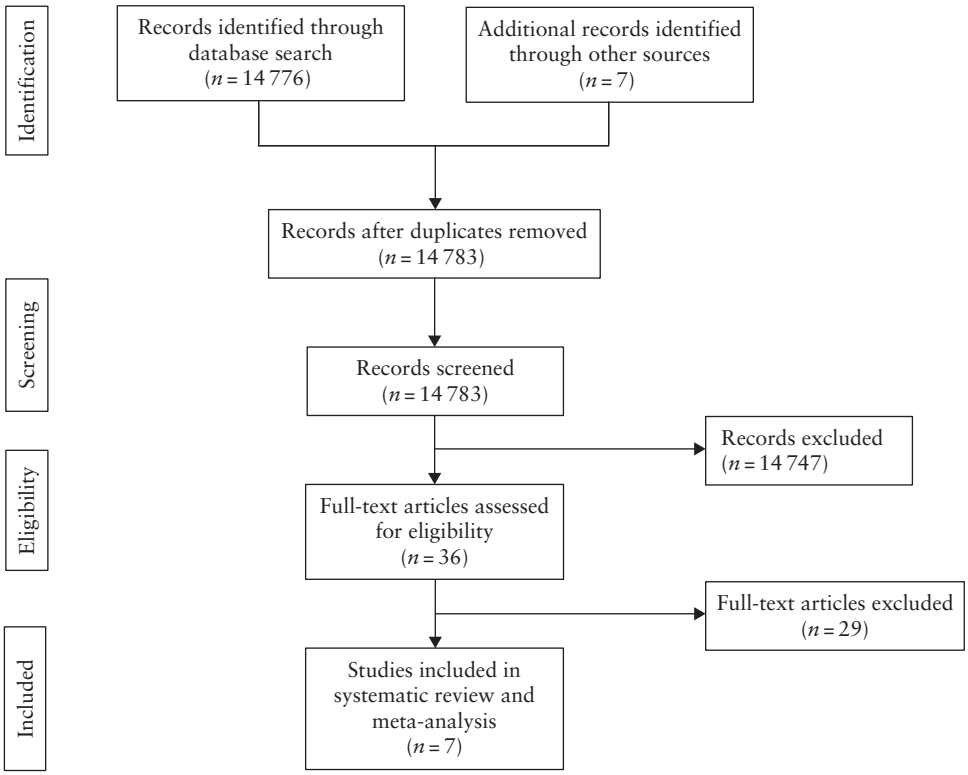

Figure 1 Flowchart summarizing inclusion of studies in systematic review and meta-analysis.

Table 1 Characteristics of studies included in systematic review and meta-analysis

Study	*Study design*	*Patients*	*Ascertainment of maternal infection*	*Timing of infection*	*GA/time between infection and amniocentesis*	*Ascertainment of presence of symptoms at birth*	*Long-term follow-up*
Azam (2001)[13]	Retro	110 women referred for CMV serological screening, including 84 with primary infection, 16 with uncertainty regarding primary or secondary infection and 10 with abnormal US	Primary infection documented by seroconversion, CMV IgG and IgM antibodies, along with low IgG avidity	51 patients with primary infection during pregnancy, 33 patients with primary infection in periconceptional period	Mean GA at amniocentesis of 23.5 weeks, 4–19 weeks between maternal infection and amniocentesis	Eye fundus examination, auditory-evoked potentials and brain US during first days postpartum	Median follow-up of 31 months in infected and 48 months in uninfected
Bilavsky (2016)[9]	Prosp	138 infants of women with primary CMV infection	Primary infection, documented by seroconversion, CMV IgG and IgM antibodies, along with low IgG avidity	93 patients with infection in periconceptional period or first trimester, 45 patients with infection in second trimester	Amniocentesis after 21 weeks, at least 7 weeks between maternal infection and amniocentesis	Physical examination, blood tests, fundus examination, bone conduction, BERA and brain US during first days postpartum	Median follow-up of 37 months in study group and 41 months in control group
Enders (2001)[17]	Prosp	189 women with suspicious serology for maternal CMV infection, including 34 with confirmed primary infection, 41 with suspected primary infection, 46 with undetermined type of infection, 20 with suspicious serology and 48 with abnormal fetal US between 18 and 39 weeks	Primary infection documented by IgG seroconversion and rising IgM antibody titers to high levels	141 patients with suspicious serology for maternal CMV between 10 and 29 weeks (median, 20 weeks)	Amniocentesis at 14–21 weeks in 86 women, 22–39 weeks in 38 women, GA not reported in 52 women	Not reported	Median follow-up of 22.5 months (range, 3 months to 8 years)
Guerra (2000)[16]	Prosp	138 women with primary CMV infection	Primary infection documented by seroconversion, CMV IgG and IgM antibodies, along with low IgG avidity	133 women infected in first and second trimesters, five women infected in third trimester	Amniocentesis after 20–21 weeks, at least 6–9 weeks (median, 11 weeks) between maternal infection and amniocentesis	Physical examination and blood tests	Median follow-up of 32 months (range, 6–60 months)
Liesnard (2000)[18]	Prosp	237 women with CMV infection, including 139 with primary infection and 98 with uncertainty regarding primary or secondary infection	CMV IgG and IgM antibodies, along with low IgG avidity	14 women with primary CMV infection $\leq$ 8 weeks, 67 women with primary CMV infection between 8 and 20 weeks, 52 women with primary CMV infection $>$ 20 weeks	Not reported	Cerebral US, ophthalmological examination and hearing evaluation in most infants and systematically when CMV infection diagnosed	Follow-up for at least 2 years

Continued over.

Table 1 *Continued*

Study	*Study design*	*Patients*	*Ascertainment of maternal infection*	*Timing of infection*	*GA/time between infection and amniocentesis*	*Ascertainment of presence of symptoms at birth*	*Long-term follow-up*
Lipitz (1997)[14]	Prosp	63 women with suspected maternal primary CMV infection	Primary infection documented by seroconversion, CMV IgG and IgM antibodies, along with low IgG avidity	34 women with abnormal serology during pregnancy, including 20 in first half of pregnancy and 12 women with abnormal serology performed owing to abnormal second-trimester US (detailed timing provided for affected fetuses)	Amniocentesis after 21 weeks, mean of 7 weeks between maternal infection and amniocentesis	Clinical evaluation during first 2 weeks, eye fundus examination, neonatal brain US, TEOAE and BERA	Testing repeated every 3–4 months until 1 year of age, then twice annually until 3 years of age
Picone (2013)[15]	Retro	238 women with primary CMV infection	IgG seroconversion or positive IgM with low IgG avidity	34 women with preconceptional infection, 78 women with periconceptional infection, 72 women with first-trimester infection, 15 women with third-trimester infection	Amniocentesis after 21 weeks, at least 6 weeks between maternal infection and amniocentesis	Clinical examination	Not reported

Only first author of each study is given. No treatment was used in any study, apart from Bilavsky *et al.*[9], in which no treatment was used during pregnancy, but valganciclovir was used in symptomatic infants. BERA, brainstem evoked response audiometry; CMV, cytomegalovirus; GA, gestational age; IgG, immunoglobulin G; IgM, immunoglobulin M; Prosp, prospective; Retro, retrospective; TEOAE, transient-evoked otoacoustic emissions; US, ultrasound.

RESULTS

Study selection

The electronic search from the databases yielded 14 783 potential studies, of which 14 747 were excluded based on their title/abstract, leaving 36 studies for full-text review. After the full-text review, seven studies were included[9,13–18] (Figure 1). The excluded studies, with reasons for exclusion, are shown in Table S1, and the characteristics of the included studies are shown in Table 1.

Overall, five studies were conducted prospectively[9,14,16–18], and two were conducted retrospectively[13,15]. Long-term follow-up for sequential manifestations of the infection was reported in six studies[9,13,14,16–18]. In four studies[9,13,17,18], the result of amniocentesis was confirmed at birth, and the pooled false-negative rate of amniocentesis (i.e. neonates who shed CMV into urine despite a negative amniocentesis result) was 8.0% (95% CI, 5.0–13.0%).

Assessment of risk of bias

The methodological quality of the included studies based on the NOS is summarized in Table 2. All studies had adequate outcome assessment methods, ascertainment of exposure and incidence of disease. Six studies had adequate follow-up for long-term complications[9,13,14,16–18].

Primary outcomes

Data from six studies[9,13,14,16–18] ($n = 694$) were used in the evaluation of severe symptoms at birth. The pooled rate of severe symptoms at birth in fetuses with a negative amniocentesis result was 0.0% (95% CI, 0.0–1.0%; $I^2 = 0\%$). The pooled rate of severe symptoms at birth in fetuses with a positive amniocentesis result was 22.0% (95% CI, 11.0–38.0%; $I^2 = 75\%$). The pooled OR was 0.03 (95% CI, 0.01–0.10; $I^2 = 0\%$) (Figure 2).

Data from all seven studies[9,13–18] ($n = 767$) were used to compare the rate of severe SNHL and/or neurodevelopmental impairment at follow-up between the two groups. The pooled rate of severe SNHL and/or neurodevelopmental impairment at follow-up in fetuses with a negative amniocentesis result was 0.0% (95% CI, 0.0–1.0%; $I^2 = 0\%$). The pooled rate of severe SNHL and/or neurodevelopmental impairment at follow-up in fetuses with a positive amniocentesis result was 14.0% (95% CI, 7.0–26.0%; $I^2 = 64\%$). The pooled OR was 0.04 (95% CI, 0.01–0.14; $I^2 = 0\%$) (Figure 3).

Secondary outcome

Data from six studies[13–18] ($n = 732$) were used in the evaluation of the rate of pregnancy termination due to the presence of CMV-associated CNS findings or multiorgan involvement on ultrasound or MRI. The pooled rate

Table 2 Risk of bias assessment of studies included in systematic review and meta-analysis according to Newcastle–Ottawa Scale

	Selection					*Outcome*		
Study	*Representativeness of exposure cohort**	*Selection of non-exposed cohort†*	*Ascertainment of exposure‡*	*Incidence of disease§*	*Comparability¶*	*Assessment of outcome***	*Length of follow-up††*	*Adequacy of follow-up‡‡*
Azam (2001)[13]	Truly representative	Concurrent controls	Secure record	Yes	Controls for most important factor	Independent blind assessment	Yes	Complete follow-up
Bilavsky (2016)[9]	Truly representative	Concurrent controls	Secure record	Yes	Controls for most important factor	Independent blind assessment	Yes	Complete follow-up
Enders (2001)[17]	Truly representative	Concurrent controls	Secure record	Yes	Controls for most important factor	Record linkage	Yes	Small loss to follow-up
Guerra (2000)[16]	Truly representative	Concurrent controls	Secure record	Yes	Controls for most important factor	Independent blind assessment	Yes	Complete follow-up
Liesnard (2000)[18]	Truly representative	Concurrent controls	Secure record	Yes	Controls for most important factor	Independent blind assessment	Yes	Small loss to follow-up
Lipitz (1997)[14]	Truly representative	Concurrent controls	Secure record	Yes	Controls for most important factor	Record linkage	Yes	Complete follow-up
Picone (2013)[15]	Somewhat representative	Concurrent controls	Secure record	Yes	Controls for most important factor	Record linkage	No	No statement

Only first author of each study is given. Each item was categorized as follows: *Truly representative of average cytomegalovirus (CMV)-infected pregnant woman; somewhat representative of average CMV-infected pregnant woman; selected group; no description of derivation of cohort. †Drawn from the same source as intervention cohort (concurrent controls); drawn from a different source (historical controls); no description of derivation of non-exposed cohort. ‡Secure record (e.g. hospital record); structured interview; written self-report; no description. §Demonstration that outcome of interest was not present at start of study: yes or no. ¶Study controls for the most important factor; study controls for any additional factor; not carried out or not reported. **Independent blind assessment; record linkage; self-report; no description. ††Follow-up long enough for outcomes to occur: yes or no. ‡‡Complete follow-up, all subjects were accounted for; subjects lost to follow-up were unlikely to introduce bias because small numbers were lost, > 90% had follow-up or description was provided of those lost; follow-up rate < 90% and no description of those lost; no statement.

of termination of pregnancy in fetuses with a negative amniocentesis result was 0.0% (95% CI, 0.0–2.0%; $I^2 = 0\%$). The pooled rate of pregnancy termination in the fetuses with a positive amniocentesis result was 20.0% (95% CI, 10.0–36.0%; $I^2 = 82\%$). The pooled OR was 0.03 (95% CI, 0.01–0.08; $I^2 = 0\%$) (Figure 4).

Subgroup analysis

A subgroup analysis was carried out including only pregnancies with primary CMV infection. Data from six studies[9,13,14,16–18] ($n = 526$) were used in the evaluation of severe symptoms at birth in pregnancies with primary CMV infection. The pooled rate of severe symptoms at birth in fetuses with a negative amniocentesis result was 0.0% (95% CI, 0.0–1.0%; $I^2 = 0\%$). The pooled rate of severe symptoms at birth in fetuses with a positive amniocentesis result was 19.0% (95% CI, 14.0–26.0%; $I^2 = 0\%$). The pooled OR was 0.07 (95% CI, 0.02–0.24; $I^2 = 0\%$).

Data from seven studies[9,13–18] ($n = 599$) were used in the evaluation of the presence of severe SNHL and/or neurodevelopmental impairment at follow-up in pregnancies with primary CMV infection. The pooled rate of severe SNHL and/or neurodevelopmental impairment at follow-up in fetuses with a negative amniocentesis result was 0.0% (95% CI, 0.0–1.0%; $I^2 = 0\%$). The pooled rate of severe SNHL and/or neurodevelopmental impairment at follow-up in fetuses with a positive amniocentesis result was 16.0% (95% CI, 8.0–29.0%; $I^2 = 63\%$). The pooled OR was 0.05 (95% CI, 0.02–0.16; $I^2 = 0\%$).

Data from six studies[13–18] ($n = 531$) were used in the evaluation of the rate of termination of pregnancy owing to the presence of CMV-associated CNS findings or multiorgan involvement on ultrasound or MRI in pregnancies with primary CMV infection. The pooled rate of termination of pregnancy in fetuses with a negative amniocentesis result was 0.0% (95% CI, 0.0–2.0%; $I^2 = 0\%$). The pooled rate of termination of pregnancy in fetuses with a positive amniocentesis result was 16.0% (95% CI, 7.0–32.0%; $I^2 = 82\%$). The pooled OR was 0.05 (95% CI, 0.02–0.15; $I^2 = 0\%$).

A sensitivity analysis was carried out including only prospective studies. The results of this analysis were identical to the main results, showing rates of 0% for severe symptoms at birth, severe SNHL and/or neurodevelopmental impairment at follow-up and termination of pregnancy owing to the presence of CMV-associated CNS findings or multiorgan involvement on ultrasound or MRI in pregnant women with CMV infection during the pregnancy and a negative amniocentesis result.

DISCUSSION

Summary of evidence

Pooling data from seven observational studies, we found that pregnant women with CMV infection during pregnancy and a negative amniocentesis result had a zero rate of severe SNHL and/or neurodevelopmental impairment at follow-up. Moreover, the rates of severe symptoms at birth and termination of pregnancy owing to the presence of CMV-associated CNS findings or multiorgan involvement on ultrasound or MRI were also 0% in the same population.

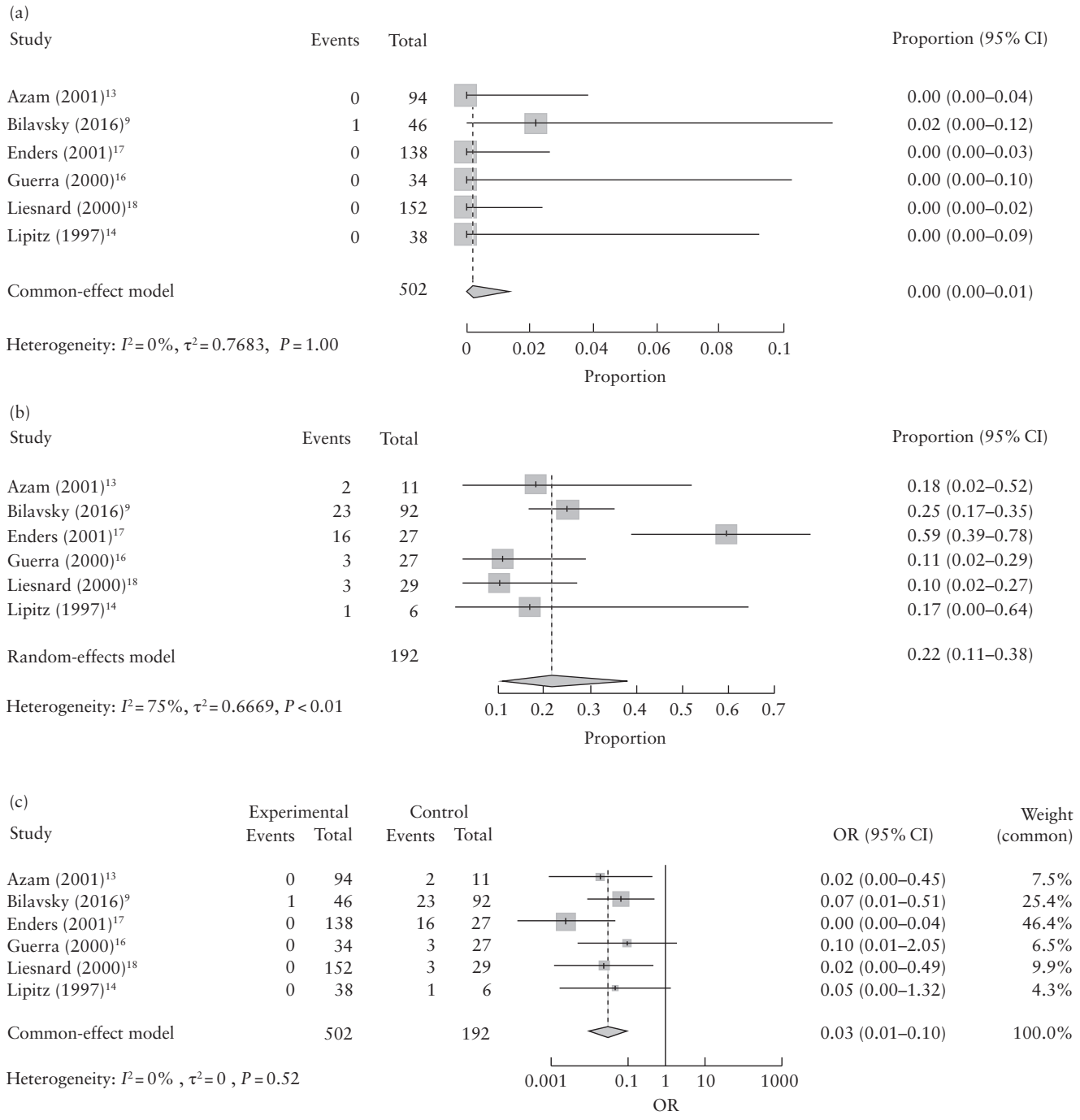

Figure 2 Forest plots for presence of severe neonatal symptoms, defined as presence of neurological symptoms or multiorgan involvement at birth, among liveborn fetuses following maternal cytomegalovirus infection. (a) Proportion (95% CI) of cases with a negative amniocentesis result. (b) Proportion (95% CI) of cases with a positive amniocentesis result. (c) Odds ratio (OR) (95% CI) for outcome following a negative *vs* positive amniocentesis result. Only first author of each study is given.

Interpretation

Approximately 7 weeks elapse between the first maternal contact with CMV and the onset of placental and fetal infection[19]. The placenta is the first fetal organ to be infected, as virions spread to the cytotrophoblasts in floating and anchoring villi, and infect the syncytiotrophoblast[20,21]. If the virus crosses the barrier of the placenta, it gets transmitted to the fetus, replicates in the tubular epithelium of the fetal kidney and is excreted into the amniotic fluid[5]. This explains why the International Society of Ultrasound in Obstetrics and Gynecology recommends that amniocentesis should be delayed for at least 8 weeks after the initial maternal infection and should be performed after 18–20 weeks' gestation[22].

However, cases of neonatal congenital CMV infection after maternal infection with a negative amniocentesis result have been reported. The prevalence of such cases ranges from 4.1% to 15.6% in the literature (pooled rate of 8.0% in our meta-analysis), even though amniocentesis

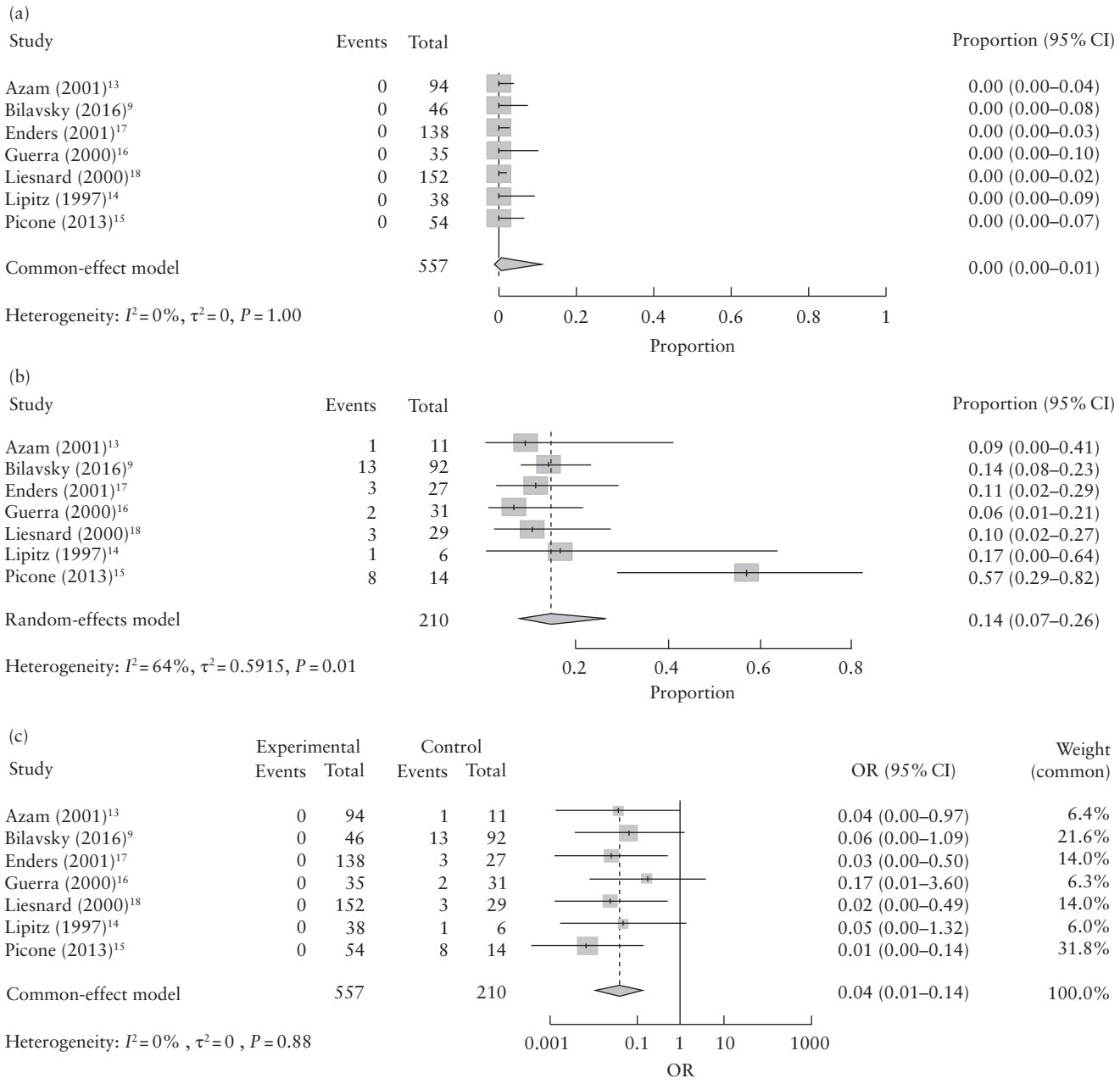

Figure 3 Forest plots for presence of severe sensorineural hearing loss and/or neurodevelopmental impairment at follow-up among liveborn fetuses following maternal cytomegalovirus infection. (a) Proportion (95% CI) of cases with a negative amniocentesis result. (b) Proportion (95% CI) of cases with a positive amniocentesis result. (c) Odds ratio (OR) (95% CI) for outcome following a negative *vs* positive amniocentesis result. Only first author of each study is given.

was performed at least 7 weeks after maternal primary infection and after 21 weeks' gestation in those studies[9,10]. A possible explanation for these findings is that vertical transmission was delayed at the level of the placenta, therefore fetal infection occurred later and the viral load in the amniotic fluid was too low to be detected by PCR. In a recent meta-analysis, we showed that fetal insult and long-term sequelae develop only when maternal primary infection with CMV occurs in the periconceptional period or the first trimester[4]. The results of the present meta-analysis show that, if transmission to the fetus is delayed to the extent that amniocentesis gives a (false-) negative result, fetal infection has happened too late to have any clinically relevant consequences. This also corroborates the findings of recent research showing that negative chorionic villus sampling in the first trimester excludes any clinically significant infection, even if transmission eventually occurs later[23].

Strengths and limitations

In order to assess the feasibility of quantitative synthesis, we thoroughly examined the definition criteria for the fetal insult (prenatal or symptoms at birth) in each of the examined studies. Furthermore, studies reporting results for SNHL and/or neurodevelopmental impairment were

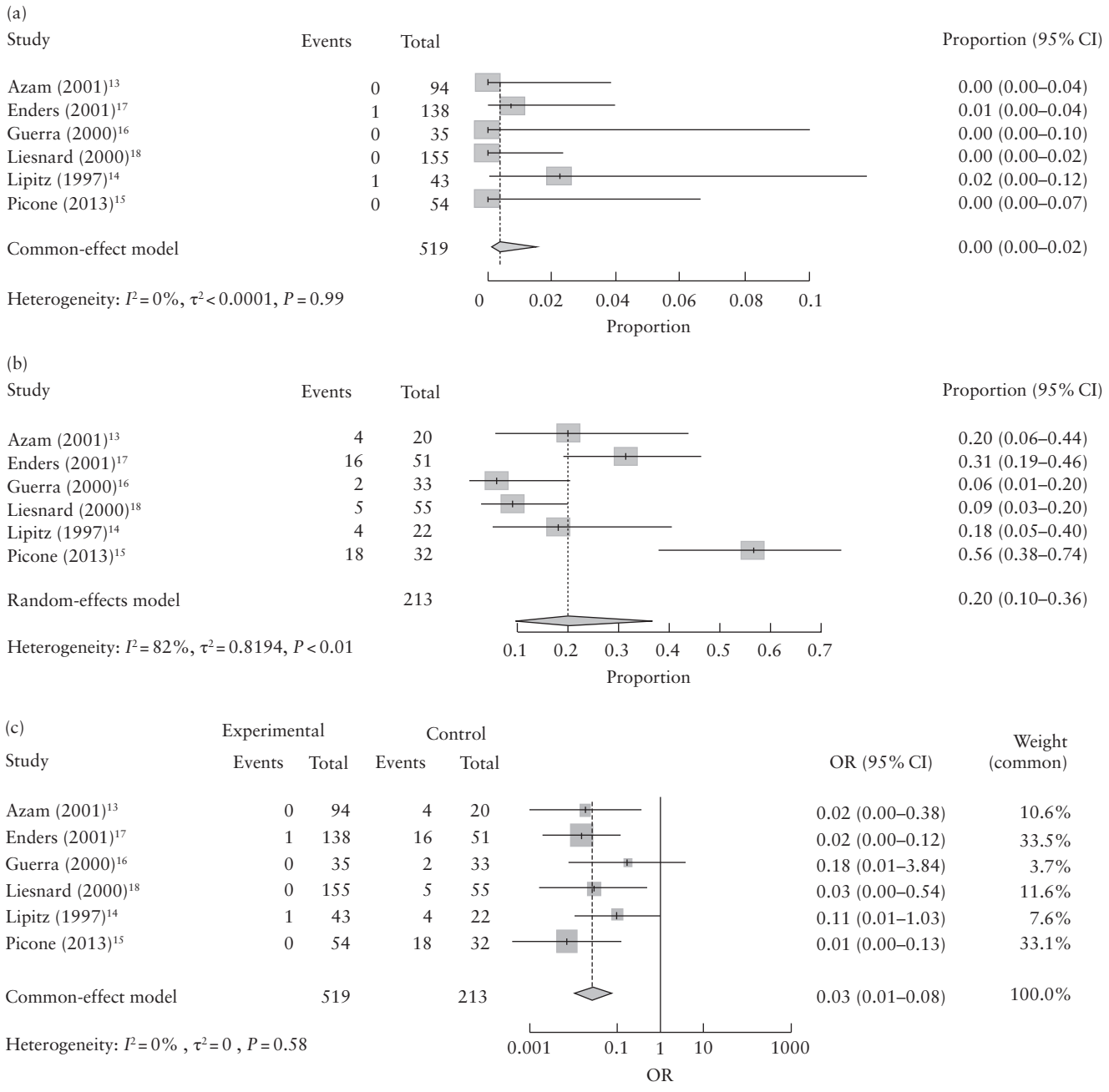

Figure 4 Forest plots for occurrence of termination of pregnancy due to presence of cytomegalovirus (CMV)-associated central nervous system findings or multiorgan involvement on ultrasound or magnetic resonance imaging among all included fetuses following maternal CMV infection. (a) Proportion (95% CI) of cases with a negative amniocentesis result. (b) Proportion (95% CI) of cases with a positive amniocentesis result. (c) Odds ratio (OR) (95% CI) for outcome following a negative *vs* positive amniocentesis result. Only first author of each study is given.

evaluated based on the diagnostic methodology they used and the length of the follow-up (Table 1).

Even though the prevalence of congenital CMV infection due to secondary maternal infection is low[24], a subgroup analysis including only cases with primary CMV infection was conducted in order to eliminate the potential confounding effect of mixing together primary and secondary maternal CMV infection. In addition, we conducted a sensitivity analysis including only the prospective studies.

The pooled rate of fetuses with a negative amniocentesis result who shed CMV into the urine at birth (i.e. false negative) was 8% in our meta-analysis. Although delayed vertical transmission is the most likely explanation for this result, not all maternal infections in the included studies occurred in the first trimester, which introduces a degree of heterogeneity into the mechanics of placenta crossing.

An additional limitation of the study is that we could not formally assess the presence of abnormal ultrasound or MRI findings in the neonates with a negative amniocentesis result. However, owing to the 0% pooled rates of symptoms at birth and long-term sequelae in these cases, we can speculate that there were no ultrasound or MRI findings in these cases.

Conclusion

A negative amniocentesis result in pregnant women with CMV infection ensures lack of fetal insult and long-term sequelae to the child, even if transmission has actually occurred.

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Table S1 Excluded studies with reasons

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Resultados neonatales y a largo plazo de lactantes con infección congénita por citomegalovirus y amniocentesis negativa: revisión sistemática y metaanálisis

RESUMEN

Objetivo. El ADN del citomegalovirus (CMV) es detectable en el líquido amniótico recogido por amniocentesis en los casos en que el feto ha sido infectado. Sin embargo, también se han descrito en la literatura casos de infección neonatal congénita por CMV con un resultado negativo de la amniocentesis. El objetivo del presente estudio fue comparar los embarazos con un resultado negativo de la amniocentesis con los embarazos con un resultado positivo en cuanto a la frecuencia de lesiones fetales y secuelas a largo plazo.

Métodos. Se incluyeron los estudios observacionales que incluían a mujeres embarazadas con infección por CMV sometidas a amniocentesis y sobre las que se informó de sus resultados junto con los resultados neonatales y/o a largo plazo de la progenie. El riesgo de sesgos en los estudios incluidos se evaluó mediante la escala Newcastle-Ottawa. Los principales resultados del estudio fueron la tasa de síntomas graves al nacer, definidos como síntomas neurológicos o afectación de múltiples órganos al nacer, y la tasa de pérdida auditiva neurosensorial grave (SNHL, por sus siglas en inglés) y/o trastornos del desarrollo neurológico durante el seguimiento. El resultado secundario fue la tasa de interrupción del embarazo debido a la presencia de hallazgos asociados al CMV en el sistema nervioso central (SNC) o afectación de múltiples órganos observada en ecografía o imágenes por resonancia magnética (IRM).

Resultados. En esta revisión sistemática y metaanálisis se incluyeron siete estudios de cohortes. La tasa conjunta de falsos negativos fue del 8,0% (IC 95%, 5,0–13,0%). La tasa conjunta de síntomas graves al nacer fue del 0,0% (IC 95%, 0,0–1,0%; I^2 =0%) en los fetos con un resultado negativo de la amniocentesis y del 22,0% (IC 95%, 11,0–38,0%; I^2 =75%) en aquellos con un resultado positivo de la amniocentesis. La razón de momios (RM) conjunta fue del 0,03 (IC 95%, 0,01–0,10; I^2 =0%). La tasa conjunta de SNHL grave y/o trastornos del desarrollo neurológico durante el seguimiento en fetos con un resultado negativo de la amniocentesis fue del 0,0% (IC 95%, 0,0–1,0%; I^2 =0%) y, en aquellos con un resultado positivo de la amniocentesis, fue del 14,0% (IC 95%, 7,0–26,0%; I^2 =64%). La RM conjunta fue del 0,04 (IC 95%, 0,01–0,14; I^2 =0%). La tasa conjunta de interrupción del embarazo debido a la presencia de hallazgos en el SNC o afectación de múltiples órganos asociados a CMV en una ecografía/IRM fue del 0,0% (IC 95%, 0,0–2,0%; I^2 =0%) en fetos con resultado negativo de la amniocentesis y del 20,0% (IC 95%, 10,0–36,0%; I^2 =82%) en fetos con una amniocentesis positiva. La RM conjunta fue del 0,03 (IC 95%, 0,01–0,08; I^2 =0%). Se realizó un análisis de subgrupos que incluía sólo embarazos con infección primaria por CMV y un análisis de sensibilidad que incluía sólo estudios prospectivos, que mostraron resultados muy similares a los del análisis principal.

Conclusión. Un resultado negativo de la amniocentesis en embarazadas con infección por CMV garantiza la ausencia de lesiones fetales y de secuelas a largo plazo para el niño, aunque se haya producido la transmisión.

先天性巨细胞病毒感染和羊膜穿刺术阴性的新生儿和长期结局：系统综述和荟萃分析

摘要

目的：在胎儿已感染的情况下，通过羊膜腔穿刺术采集的羊水中可检测到巨细胞病毒(CMV)DNA。但羊水穿刺结果阴性的先天性新生儿CMV感染病例也有文献报道。本研究的目的是比较羊膜穿刺术结果为阴性的妊娠与羊膜穿刺术结果为阳性的妊娠在胎儿损伤和长期后遗症的发生率方面的差异。

方法：观察性研究，包括接受羊膜腔穿刺术的CMV感染孕妇，并报告其结果以及新生儿和/或后代的长期结局。采用Newcastle—Ottawa量表评估纳入研究的偏倚风险。研究的主要结局为出生时重度症状（定义为出生时神经系统症状或多器官受累）的发生率以及随访时重度感音神经性聋(SNHL)和/或神经发育障碍的发生率。次要结局是由于存在CMV相关中枢神经系统(CNS)结果或超声/磁共振成像(MRI)显示多器官受累导致的妊娠终止率。

结果：7项研究纳入系统评价和meta分析。羊膜腔穿刺术的合并假阴性率为8.0%(95%CI，5.0-13.0%)。羊膜腔穿刺结果阴性胎儿出生时严重症状合并率为0.0%(95%CI，0.0-1.0%；I2 = 0%)，羊膜腔穿刺结果阳性者出生时严重症状合并率为22.0%(95%CI，11.0-38.0%；I2 = 75%)。合并比值比(OR)为0.03(95%CI，0.01-0.10；I2 = 0%)。羊膜穿刺术结果阴性胎儿随访时严重SNHL和（或）神经发育障碍的合并率为0.0%(95%CI，0.0-1.0%；I2 = 0%)，羊膜穿刺术结果阳性者为14.0%(95%CI，7.0-26.0%；I2 = 64%)。合并OR为0.04(95%CI，0.01-0.14；I2 = 0%)。羊膜穿刺术结果阴性胎儿因存在CMV相关CNS表现或超声/MRI多器官受累而终止妊娠的合并率为0.0%(95%CI，0.0-2.0%；I2 = 0%)，羊膜穿刺术结果阳性胎儿为20.0%(95%CI，10.0-36.0%；I2 = 82%)。合并OR为0.03(95%CI，0.01-0.08；I2 = 0%)。我们进行了仅包括原发性CMV感染妊娠的亚组分析和仅包括前瞻性研究的敏感性分析，显示了与主要分析非常相似的结果。

结论：CMV感染孕妇的羊膜穿刺术结果为阴性，保证了对胎儿无伤害和对患儿的长期后遗症，即使已发生传播。