Current practices of management of congenital Cytomegalovirus infection during pregnancy and childhood: systematic review protocol

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Protocol

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Abstract

Background: Congenital CMV infection is the first worldwide cause of congenital viral infection and a major cause of sensorineural hearing loss and mental retardation. As systematic screening of pregnant women and newborns is still debated in many countries, this systematic review aims to provide the state of the art on current practices concerning management of congenital CMV infection.

Methods: We will perform electronically searches on MEDLINE, EMBASE, Cochrane Library (CENTRAL), ClinicalTrials.gov, Web of Science and hand searches in grey literature. Interventions regarding biological, imaging, and therapeutic management of infected pregnant women, fetuses and neonates/children (from birth to 6 years old) will be studied in this systematic review. Study screening will be performed in duplicate by two independent reviewers and risk of bias will be evaluated with the ROBINS-I tool.

Discussion: This review will provide the state of the art of current management of congenital CMV infection in pregnant women, fetuses, neonates and children until 6 years old, in order to have an overview of current practices of congenital CMV infection.

Systematic review registration: PROSPERO CRD42019124342

Background

Cytomegalovirus (CMV) is the first worldwide cause of congenital viral infection and its prevalence is currently estimated between 0.5 and 1% of all live births. Congenital CMV is a major cause of sensorineural hearing loss and mental retardation (1) (2) (3). CMV transmission from the mother to the fetus can occur after primary or secondary maternal CMV infection, and the risk of clinical consequence seems identical whatever the type of maternal infection (4) (5) (6). Average transmission rate of CMV from mothers to fetuses is estimated around 40% after primary infection but varies according to gestational age of maternal CMV infection (3) (7). At birth, 13% of congenitally infected neonates are symptomatic with CMV-specific symptoms including growth restriction, microcephaly, ventriculomegaly, chorioretinitis, sensorineural hearing loss, hepatitis, thrombocytopenia and a purpuric skin eruption (2) (8). Risk of long term sequelae is higher if CMV transmission occurs in the first or second trimester of pregnancy or during periconceptionnal period (7) (9) (10).

Congenital CMV infection is a public health issue. However, recommendations and guidelines to manage congenital CMV infection are scarce, even if an informal International Congenital Cytomegalovirus Recommendations Group, created in 2015, recently published consensus recommendations for prevention, diagnosis and therapy of congenital cytomegalovirus infection in pregnancy and the neonate (11). Few countries, including France, provide recommendations on screening, but management of congenital CMV infection still represents a challenge in most countries. The largest review on the subject was published in 2002 by Revello et al. but since several new diagnostic, imaging and therapeutic tools were developed and moreover, to date, no systematic review on this subject has already been published (8).

Aim

In this systematic review, we aim to collect data on current practices of CMV infection management during pregnancy and congenital CMV infection in the world. We will focus on the biological, clinical, imaging and therapeutic practices routinely used to diagnose, monitor and treat the infection. These practices will be investigated either in pregnant women infected by CMV, in fetuses, or in children congenitally infected by CMV (from neonates to 6 years old) to have an up-to-date overview of congenital CMV infection management.

Methods

Study registration

This protocol was previously registered in PROSPERO International Prospective Register of systematic reviews (http://www.crd.york.ac.uk/PROSPERO), registration number CRD42019124342.

Study design

This systematic review protocol will be conducted and reported in accordance to the Preferred Reporting Items for Systematic Review and Meta-Analysis protocols (PRISMA-P) 2015 statement (12) (13). An additional file shows this in more detail (see Additional file 1).

Eligibility criteria

Eligibility criteria are defined as followed owing to the PICOS definitions (Population – Interventions – Comparators – Outcomes – Studies):

Type of populations

We will include three categories of patients: (i) pregnant women infected by CMV (maternal infection); (ii) fetuses infected by CMV (fetal infection); (iii) neonates and young children under 6 years old congenitally infected with CMV. We will exclude studies conducted in patients with immunosuppression factors (e.g. autoimmune disease, immunosuppressive treatment, HIV infection) or in general population (non-pregnant women and adult men). We will also exclude studies focusing only on maternal CMV infection in pregnant women without mentioning fetal or child outcome.

Type of interventions

We will include studies relating to biological, clinical, radiological, therapeutic interventions to diagnose, predict and treat congenital CMV infection in the three populations of interest described above.

We will not include interventions and measures to prevent maternal CMV infections (such as hygiene-based behavioral interventions or hypothetical vaccine), interventions to improve knowledge of CMV

infection pathophysiology and interventions that are no longer available in current practice, particularly concerning biologic assays.

Comparator

Presence of a comparator group is not relevant for this systematic review. Therefore, this review will be excluded studies comparing congenital CMV infection with other congenital infections or other pathologies.

Type of outcome measures

Outcomes that will allow characterize the following items related to congenital CMV infection should be available:

- Pregnancy outcome and termination of pregnancy;
- Mortality and morbidity;
- Economic costs and quality of life;
- Guidelines and current practice of management;
- Treatments efficacy;
- Prenatal and at birth clinical signs;
- Prognosis of congenital CMV infection;
- Adverse effects of different interventions;
- Adverse effects of treatments (short, medium and long term);
- Acceptability of congenital CMV infection management.

Type of studies

We will include all study designs (randomized controlled trials, controlled trials, observational studies, prospective and retrospective cohort studies, guidelines…), except review articles, letters, case reports and case series of less than or equal to 10 patients, with no restriction on the study duration, study period or date of publication.

Search strategy

We will perform electronically searches on the following databases: MEDLINE, EMBASE, the Cochrane Library, including the Cochrane Central Register of Controlled Trials (CENTRAL), ClinicalTrials.gov, Web of Science until September 6th, 2019. Relevant medical subject heading (MeSH) terms and key words relating to “Cytomegalovirus infection”, “congenital” will be used as restricting criteria. Grey literature with non-published studies (thesis, congress abstracts) will also be analyzed. Studies will be restricted to English and French languages. In **Figure 1**, we present our search strategy developed for MEDLINE, then

translated for other databases. All references will be registered in Zotero (Version 5.0.60) and duplicates will be removed.

Study screening

In a first step, two teams of reviewers (CPD and CVF / CPD and OP) will independently screen titles and abstracts to identify relevant studies meeting the pre-specified PICOS inclusion criteria. In a second step, the same reviewers will examine the full text of the selected studies according to the inclusion and exclusion criteria. We will solve discrepancies after discussion with the three reviewers. A flowchart diagram will be generated to document the study selection process (14) and the inter-observer agreement between reviewers will be calculated using kappa coefficient (15). A kappa coefficient higher than 0.6 will indicate an acceptable agreement between reviewers.

Data extraction

Data extraction will include information on the population, interventions, outcomes and study designs. Data will be extracted by CPD using a structured Excel sheet and another reviewer (CVF or OP) will quality check. This will be conducted on twenty percent of articles and discrepancies will be solved through discussion with a third team member when necessary.

Data will be extracted for the following:

- Country
- Study characteristics: design of study, sample size
- Participants: age, demographic characteristics
- Interventions: method of diagnosis of CMV, imaging, amniocentesis, neonatal screening, therapeutic, follow up
    - frequency of interventions
    - circumstances of diagnosis (clinical sign, systematic screening, …)
- Outcomes:
    - pregnancy outcome
    - mortality/morbidity
    - sensitivity/specificity of diagnosis tools
    - clinical symptoms, prognosis
    - quality of life
    - side effects
    - costs
    - adherence of pregnant women to interventions

If necessary, in case of missing data, we will contact the authors for complementary information.

Assessment of risk of bias in included studies

The risk of bias will be assessed by the ROBINS-I tool: "Risk Of Bias In Non-randomized Studies – of Interventions assessment tool" (16). We will analyze seven domains of bias:

- Confounding;
- Selection of participants into the study;
- Classification of interventions;
- Deviations from intended interventions;
- Missing data;
- Measurement of outcomes;
- Selection of reported results.

Using this ROBINS-I tool, we will classify each of the seven bias domains according to a risk of bias judgment. Included studies will be classified according to the overall risk of bias: Low / Moderate / Serious / Critical risk of bias.

Data synthesis

We will provide a systematic narrative synthesis of the findings from the included studies, structured around the type of intervention, study design, intervention content and outcome of interest. The different interventions will be reported according to the following items: sensitivity analysis, specificity, frequency and evaluation of the outcomes measured regarding management of congenital CMV infection. Subgroups will be established based on the following three circumstances of congenital CMV diagnosis: maternal CMV infection discovered during pregnancy, presence of ultrasound abnormalities and congenital infection diagnosed at birth The impact of including studies assessed as high risk of bias will be considered in a sensitivity analysis.

Discussion

This review will provide global overview current practices of congenital CMV infection concerning pregnant infected women, fetuses, neonates and children until 6 years old. The systematic review will describe interventions performed according to the country, the prevalence of congenital CMV infection and the clinical situation (maternal infection, ultrasound abnormalities, screening after birth). To date, this will be the first systematic review assessing management of congenital CMV infection.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Availability of data and materials

Not applicable.

Competing interests

The authors declare that they have no competing interests.

Funding

We declare no funding source.

Authors' contributions

CPD, CVF and OP are the three investigators for screening of studies. CPD is the main investigator for data extraction and was a major contributor in writing the manuscript. CPD, DB, CL, CVF and OP represent the discussion team members in case of screening or extraction discrepancies. All authors read and approved the final manuscript.

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Not applicable.

Abbreviations

CMV: Cytomegalovirus

CENTRAL: Cochrane Central Register of Controlled Trials

MeSH: Relevant medical subject heading

PICOS: Population – Interventions – Comparators – Outcomes – Studies

PRISMA-P: Preferred Reporting Items for Systematic Review and Meta-Analysis protocols

ROBINS-I: Risk Of Bias In Non-randomized Studies – of Interventions

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Figures

1	"Cytomegalovirus Infections"[MeSH] OR Cytomegalovirus[TiAb] OR CMV[TiAb]
2	congenita*[TW] OR "Congenital Abnormalities"[MeSH]
3	#1 AND #2
4	"Sensitivity and specificity"[MeSH] OR predict*[tw] OR diagnos*[tw] OR accura*[tw]
5	"cohort studies"[MeSH] OR "case-control studies"[MeSH] OR "comparative study"[pt] OR "risk factors"[MeSH] OR "cohort"[tw] OR "compared"[tw] OR "groups"[tw] OR "case control"[tw] OR "multivariate"[tw] OR "prospective"[TiAb] OR "case series"[ALL] OR "case repor*"[pt]
6	"randomized controlled trial"[pt] OR "clinical trial"[pt] OR "clinical trials as topic"[MeSH] OR "random allocation"[MeSH] OR "double-blind method"[MeSH] OR "single-blind method"[MeSH] OR "clinical trial"[pt] OR "research design"[MeSH:noexp] OR "comparative study"[pt] OR "evaluation studies"[pt] OR "follow-up studies"[MeSH] OR "prospective studies"[MeSH] OR "cross-over studies"[MeSH] OR "clinical trial"[tw] OR placebo*[tw] OR random*[tw] OR "control"[tw] OR "controls"[tw] OR prospectiv*[tw] OR volunteer*[tw]
7	"consensus development conference"[pt] OR "practice guideline"[pt] OR "guideline*"[TiAb] OR "clinical guideline"[TW] OR "evidence based"[ti] OR "evidence-based medicine"[mh] OR "best practice*"[ti] OR "evidence synthesis"[tiab]
8	"burden"[ALL] OR "Costs and Cost Analysis"[MeSH] OR "economic*"[TiAb] OR "cost"[TiAb] OR "costs"[TiAb] OR "costly"[TiAb] OR "costing"[TiAb] OR "price"[TiAb] OR "prices"[TiAb] OR "pricing"[TiAb] OR "pharmacoeconomic*"[TiAb] OR "quality-of-life"[TiAb]
9	#4 OR #5 OR #6 OR #7 OR #8
10	#3 AND #9
11	animals[MeSH] NOT (humans[MeSH] AND animals[MeSH])
12	English[LA] OR French[LA]
13	#10 NOT #11 AND #12

Figure 1

MEDLINE database retrieval strategy

Supplementary Files

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