

BMJ Open Universal screening programme for cytomegalovirus infection in the first trimester of pregnancy: study protocol for an observational multicentre study in the area of Barcelona (CITEMB study)

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ABSTRACT

Introduction Congenital cytomegalovirus (cCMV) is the leading cause of non-genetic sensorineural hearing loss and one of the main causes of neurological disability. Despite this, no universal screening programme for cCMV has been implemented in Spain. A recent study has shown that early treatment with valaciclovir, initiated in the first trimester and before the onset of signs in the fetus, reduces the risk of fetal infection. This finding favours the implementation of a universal screening programme for cCMV.

The aim of this study is to evaluate the performance of a universal screening programme for cCMV during the first trimester of pregnancy in a primary care setting.

Methods and analysis This is an observational multicentre cohort study. The study will be conducted in four primary care settings from the Northern Metropolitan Barcelona area and three related hospitals and will last 3 years and will consist of a recruitment period of 18 months.

In their first pregnancy visit, pregnant women will be offered to add a CMV serology test to the first trimester screening tests. Pregnant women with primary infection will be referred to the reference hospital, where they will continue treatment and follow-up according to the clinical protocol of the referral hospital, which includes treatment with valacyclovir. A CMV-PCR will be performed at birth on newborns of mothers with primary infection, and those who are infected will undergo neonatal follow-up for at least 12 months of life.

For the analysis, the acceptance rate, the prevalence of primary CMV infections and the CMV seroprevalence in the first trimester of pregnancy will be studied.

Ethics and dissemination Ethical approval was obtained from the University Institute Foundation for Primary Health Care Research Jordi Gol i Gurina Ethics Committee 22/097-P dated 27 April 2022.

STRENGTHS AND LIMITATIONS OF THIS STUDY

- ⇒ This is the first population study on cytomegalovirus seroprevalence in pregnant women conducted in Catalonia and Spain, prior to the implementation of a universal screening in Catalonia.
- ⇒ This is an observational multicentre study that represents general population in Catalonia.
- ⇒ In this study we will perform screening for cytomegalovirus and follow-up of the positive cases.
- ⇒ The main limitation of this study is that it will not be possible to detect those cases of congenital cytomegalovirus infection caused by reactivation of the virus or reinfection; therefore, it will not be possible to treat these cases.

INTRODUCTION

The recently estimated global seroprevalence of congenital cytomegalovirus (cCMV) was reported in 2019 as 83% in the general population and around 86% in women of childbearing age and in blood organ donors.^{1 2} Other studies report a 92%–95% seroprevalence in Chilean women.² The seroprevalence is highly dependent on geography, as shown in a systematic review (72 studies performed from 1988 to 2019 in 11 countries) where CMV IgG seroprevalence, for example, in the Middle East and North Africa region ranged from 8.7% to 99.2% (SD=38.95%).³ CMV seroprevalence in women of childbearing age was reported in a range of 45%–100%.^{4 5}

CMV infection afflicts 0.4%–5% of all live newborns depending on the country, and up to 10% will present symptoms at birth.^{5–7} In Spain, the reported prevalence is 0.47% (1 in

200 newborns).⁸ Both primary infection and secondary infection (reactivation or reinfection) during pregnancy can cause intrauterine transmission, although the risk is greater for primary infection (30%–40%) than for secondary infection (0.2%–3%).^{6,9,10} The risk of transmission increases with gestational age, although the risk of permanent postnatal sequelae is mainly driven by periconceptional and first trimester infections.⁶

CMV is the most common viral congenital infection. It is the leading cause of non-genetic sensorineural hearing loss and one of the leading causes of neurodevelopmental delay with mental or motor impairment, microcephaly,¹¹ and as a result, neonatal morbidity and mortality. It accounts for 10% of all cerebral palsy cases¹² and 8%–21% of neurosensory deafness cases at birth.^{13–15} This percentage increases to 25% at the age of 4 years old due to late-onset cases.¹⁶

The prevention of maternal primary CMV infection is based exclusively on hygiene measures.¹⁷ Until recently, management options for cCMV infection were conservative follow-up or termination of pregnancy (TOP). However, in recent years, therapies aimed at reducing the risk of mother-to-child transmission or the severity of infection have been investigated. Studies focused on the role of hyperimmune gamma globulin remain conflicting and therefore, we cannot draw any conclusions based on clear evidence.^{18–20}

Several studies have shown that valacyclovir (8g/day) administered during the first trimester of pregnancy has been effective in reducing the risk of fetal infection. Neither toxicity nor teratogenic effects were observed.^{21–23} Acyclovir and its prodrug, valacyclovir, are DNA polymerase inhibitors.²¹ However, currently the use of valacyclovir in the prenatal setting for cytomegalovirus is off-label and based on compassionate use, as it is not indicated in the product labelling.

Acyclovir has not shown genotoxic or carcinogenic effects in vitro or in animal studies.²⁴ The rate of congenital malformations was 2% and 3.2% in records of 596 and 1561 pregnant women, respectively, exposed during the first trimester, and 2%, and 2.4% in a record of 2379 pregnant women, respectively, exposed during the second and third trimesters of pregnancy, without a specific pattern and within the same range as observed in more than 800 000 pregnancies that did not follow anti-CMV drug treatment.^{25,26} Several studies evaluating the costs of cCMV have shown that preventive treatment, as well as neonatal, was cost-effective.^{27–31}

A UK study estimated the financial cost of cCMV in the UK during 2016 to be £732 million. The long-term sequelae caused by the infection had a substantially greater financial burden than acute management of the infection.²⁷

Although most of the USA and EU guidelines do not recommend routine screening for CMV infection during pregnancy, in some areas of France, Italy, Belgium, Israel, Spain, Italy, Germany, Austria, Portugal and the Netherlands, CMV serological screening is offered.^{32,33} Since 90%

of primary maternal CMV infections are asymptomatic³³ and the majority of women are unaware of cCMV,^{32,34} universal screening would be beneficial.

In Catalonia, currently there is no routine maternal universal screening, but cases of maternal primary infection are detected by opportunistic screening or as a result of abnormal ultrasound fetal findings. Following a publication showing a reduction in fetal infection rates for women treated with valacyclovir after the first trimester infection,^{21,22} several sites have changed their clinical protocols. Although the studies showing benefit of maternal treatment are with small sample sizes, and larger studies should follow to confirm the beneficial impact, the results seem encouraging. As a result, there is a lack of consistency in clinical guidelines within public and private healthcare settings. Regarding newborn screening, the current policy includes expanded targeted newborn screening (failed hearing loss screening, microcephaly, clinical manifestations suggestive of cCMV infection, prenatal ultrasound abnormalities suggestive of CMV infection, CMV infection diagnosed during pregnancy, prematurity below 32 weeks of gestation and below 1500 g birth weight, etc).³⁵

There are three compelling reasons to initiate universal screening for CMV in the pregnant population:

1. First, long-term neurological and neurosensory impairments have been shown to be mainly due to maternal infection during the first trimester of pregnancy or during the perigestational period (up to 8–10 weeks before conception). This reduces the time window for serological screening.^{6,36}
2. Second, maternal administration of oral valacyclovir after infection during the first trimester of pregnancy significantly decreases vertical transmission.²¹
3. And third, because prognosis assessment of CMV-infected fetuses has improved in the last decade, with a high negative predictive value of fetal images obtained from 25 weeks of gestation.³⁷

Recent advances in prenatal screening and treatment have brought prenatal screening to meet the WHO screening criteria for cCMV infection due to maternal primary infection in early pregnancy, the main period in which fetal exposure can lead to long-term disability. Considerations for implementing a screening programme include the importance and prevalence of the pathology, the feasibility, reliability and acceptability of both prenatal screening and diagnostic tests, as well as the existence of a latent phase that allows prevention of infection transmission. To the classic WHO criteria (Wilson and Jungner's principles of screening, WHO 1968) we must add a very important criterion in current times, which is the patient's right to know and decide.

Hypothesis

Universal CMV screening during the first trimester of pregnancy is feasible, is accepted by the majority of pregnant women, and allows detection of first-trimester infections, which are associated with a higher percentage of

short-term and long-term sequelae in infants. This allows to initiate early treatment in order to reduce fetal transmission and consequently the risk of negative sequelae for the infant.

Objectives

This is an observational study for the implementation in Barcelona and its metropolitan area of a universal CMV screening programme that would be performed during the first trimester of pregnancy.

The aim of this study is to evaluate a universal CMV screening programme that would be performed during the first trimester of pregnancy in a primary care setting.

Primary objectives

1. To determine CMV seroprevalence in our population of pregnant women.
2. To determine the rate of primary CMV infections during the first trimester of pregnancy.
3. To estimate the acceptance rate of CMV screening by pregnant women in our population.

Secondary objectives

4. To identify and establish the rate of vertical fetal infection detected by amniocentesis during the second trimester.
5. To identify and establish the rate of fetal sequelae (due to primary CMV infection during the first trimester) by imaging techniques (ultrasound and MRI).
6. To identify and establish the rate of neonatal infection (cCMV) within the women with a primary infection in the first trimester of pregnancy.
7. To identify and establish the rate of sequelae due to cCMV at 1 year of age within the women with a primary infection in the first trimester of pregnancy.
8. To identify and establish the rate of TOP following diagnosis of primary CMV infection in the first trimester of pregnancy.
9. To identify and establish the rate of TOP following diagnosis of fetal infection.
10. To identify and establish the rate of TOP following diagnosis of fetal abnormalities.
11. To evaluate the pregnancy outcomes (livebirths, stillbirths, miscarriages or TOP) following a primary CMV infection.
12. To identify and establish the annual cost of performing a universal CMV screening during the first trimester of pregnancy in Catalonia (Spain).

METHODS AND ANALYSIS

Study design

This is a multicentric observational study with a total duration of 3 years. The recruitment of participants is foreseen up to 18 first months of the project CITEMB, from November 2022 to April 2024. Positive cases will be followed up during the whole pregnancy and until delivery. Additionally, newborns with a positive CMV-PCR

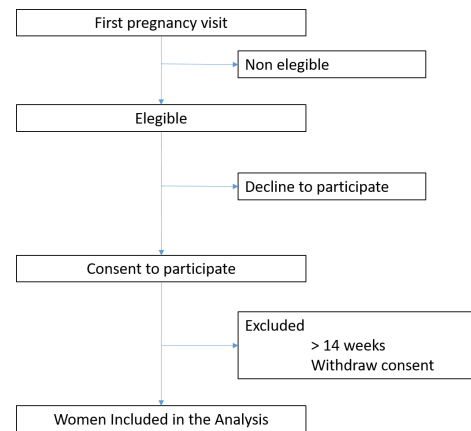


Figure 1 The CITEMB (universal screening programme for cytomegalovirus infection in the first trimester of pregnancy: a multicentre observational study in the area of Barcelona) project recruitment flowchart.

test will be followed up until 12 months of age. The study will be conducted in four primary care settings from the Northern Metropolitan Barcelona area, ASSIR (abbreviation for ASSIR in Catalan stands for primary attention centres of sexual and reproductive health) Muntanya, ASSIR Esquerra, ASSIR Santa Coloma de Gramenet, ASSIR Badalona-Sant Adrià, and three related hospitals, Hospital Universitari Vall d’Hebron, BCNatal Hospital Clinic/Hospital Universitari Sant Joan de Deu and Hospital Universitari Trias i Pujol.

Participants, inclusion and exclusion criteria

The study population will consist of pregnant women in the first trimester of pregnancy attending one of the participating sites for pregnancy follow-up.

Inclusion criteria are maternal age 16 years or older and gestational age less than 14 weeks. *Exclusion criteria* were language barrier preventing informed consent, gestational age above 14 weeks at the time of blood sampling, and consent withdrawal.

Procedure

The general flowchart of the CITEMB study’s recruitment procedure is shown in [figure 1](#).

Recruitment

At the first pregnancy visit, which is usually scheduled between 5 and 10 weeks of gestation, and before requesting the first blood test, eligible pregnant women will be informed about the study and the benefits and risks of CMV screening. After obtaining the women’s written consent, CMV IgG and IgM serologies will be requested. Data relating to demographics, pregnancy and serologies will be entered into REDCap.³³ The recruitment will take place at primary care settings (ASSIRs) and two related hospitals (Hospital Universitari Vall d’Hebron and Hospital Universitari Trias i Pujol). The staff involved in the recruitment will be midwives and obstetricians. The number of patients who decline to participate in the study will also be calculated ([figure 1](#)).

Serology results

In the event of a positive IgG and IgM test, the laboratory will automatically determine IgG avidity and establish an alert system to notify the healthcare professional in charge of the patient. If IgM is positive and IgG is negative, the serology will be repeated within 2–3 weeks to check for seroconversion. The CMV serology (IgG and IgM) will be performed in the Microbiology Laboratories of Hospital Universitari Vall d'Hebron, Hospital Clinic and Hospital Universitari Germans Trias i Pujol. In order to ensure early management, an automated alert system has been established from the microbiology laboratory service to the clinician who requests the test, and to the physician at the referral hospital to report cases of primary infection.

Pregnancy follow-up

1. For those participants without primary infection, the follow-up will be discontinued.
2. Cases with primary infection will be referred to their tertiary referral hospital, where they will be followed up until delivery. The clinical protocols of the three tertiary hospitals include oral administration of valaciclovir 8g/day from the time of diagnosis until the amniocentesis result. This is an 'off-label' treatment and women provide written consent for this treatment. Follow-up of these pregnancies will consist of serial ultrasound examinations on a monthly basis, including neurosonography, and MRI at 32–34 weeks, or earlier if there are ultrasound abnormal findings.
 - a. *Neonatal and infant follow-up* In newborns from mothers with primary infection, a urinary CMV-PCR will be performed.³⁸ Positive cases will be followed up until 12 months of age. The neonatal evaluation includes clinical and neurological examination, blood count, liver and renal function, blood CMV-PCR, transfontanellar ultrasound, brain MRI, brainstem auditory evoked potentials, and ocular fundus. The infant follow-up includes clinical and neurological examination, weight-stature development, as well as head circumference and regular brainstem auditory evoked potentials. Antiviral treatment will be considered on a case-to-case basis.

Definitions

1. *Primary infection*. Any of the following:
 - a. IgG and IgM positive with low or intermediate IgG avidity.
 - b. IgG seroconversion if having a recent negative serology prior to the pre-conceptional period.
 - c. Seroconversion during the first trimester (if having a positive IgM and negative IgG in the first sample and positive IgM and IgG in a second sample 2–3 weeks apart).
2. *Passed infection (seroprevalence)*. Any of the following:
 - a. IgG positive and IgM negative.
 - b. IgG and IgM positive with high IgG avidity.

Variables

Details on variables of the CITEMB study are shown in online supplemental annex I.

Outcome measures

1. Screening acceptance rate: number of women who consent to participate/number of eligible women (figure 1).
2. Prevalence of primary CMV infection in the first trimester of pregnancy or in the periconceptional period: number of cases that are IgG positive and IgM positive with low or intermediate IgG avidity/total number of serologies performed.
3. Prevalence of seroconversion during the first trimester: number of cases having a positive IgM and negative IgG in the first sample and positive IgM and IgG in a second sample 2–3 weeks apart/total number of serologies performed.
4. CMV seroprevalence in the first trimester of pregnancy: (number of cases that are IgG positive and IgM negative+IgG positive and IgM positive with high IgG avidity)/number of serologies performed.
5. Fetal infection rate at the second trimester amniocentesis: number of positive PCR-CMV in the amniotic fluid/total number of amniocentesis performed.
6. Rate of fetal sequelae by imaging techniques (ultrasound and MRI) after first trimester/periconceptional CMV infection: ultrasound or MRI abnormalities attributable to CMV/total number of primary infections (IgG positive and IgM positive with low or intermediate IgG avidity).
7. Neonatal infection rate (cCMV): number of PCR-CMV in neonatal urine/total number of primary infections (IgG positive and IgM positive with low or intermediate IgG avidity).
8. Rate of cCMV sequelae at 1 year of life: number of symptomatic cases at 1 year of life/total number of primary infections (IgG positive and IgM positive with low or intermediate IgG avidity).
9. Rate of TOP following the primary infection: number of TOP before amniocentesis among cases of primary infection/total number of primary infections (IgG positive and IgM positive with low or intermediate IgG avidity).
10. Rate of TOP following diagnosis of fetal infection: number of TOP after positive PCR-CMV in amniotic fluid and without fetal involvement/total number of primary infections (IgG positive and IgM positive with low or intermediate IgG avidity).
11. Rate of TOP following diagnosis of fetal abnormalities: number of TOP after positive PCR-CMV in amniotic fluid and with fetal involvement/total number of primary infections (IgG positive and IgM positive with low or intermediate IgG avidity).

Sample size estimation

Sample size calculations will be performed taking into consideration data on pregnant women who visited four

primary care settings last year. If we consider a fairly high rate of acceptance to participate in this screening programme of around 90%, and an 11% fetal infection rate according to the clinical assessment for valacyclovir in the study published by Shahar-Nissan and colleagues.²¹

During 18 months, these four sites will care for approximately 12 700 pregnancies. We believe that 90% of pregnant women will accept the screening, which means 11 430 pregnant women will be included in the study. Assuming that 2% of pregnant women will have a primary infection during the first trimester, there will be 229 pregnant women requiring follow-up according to the protocol. Of these, we would expect to find 25 positive cases in the amniotic fluid (11% in cases treated with valacyclovir). A 30% of fetuses infected during the first trimester will be symptomatic (n=8), and 70% (n=18) asymptomatic. A 45%–65% (n=5) of symptomatic and a 15% (n=3) of asymptomatic fetuses will present long-term sequelae, resulting in a total of seven infants presenting long-term sequelae. It should be considered that in a majority of fetuses with severe involvement and in some fetuses that are infected showing minor or no involvement, the pregnant woman will likely opt for a TOP. The estimations were performed for the most optimistic scenario (we could not estimate participants that do not pass inclusion/exclusion or drop out from the study follow-up due to changing the residence or passing to the private medical centres, etc).

Ethics and dissemination

Study participants will be informed about the objectives of the study and the interventions linked to their participation. They will receive a written information sheet with details about the study and will be asked to provide a written informed consent. Samples will be anonymised using a numeric coding system. The confidentiality and anonymity of the data will be ensured in accordance with current regulations (Organic Law 3/2018, of 5 December, on Personal Data Protection and Guarantee of Digital Rights). The study will be conducted in accordance with the articles pertaining to the Declaration of Helsinki, agreed at the 64th General Assembly in 2013. The project is under the tutelage of the Clinical Research and Ethics Committee (CEI) of the participating sites: ASSIR-Instituto Universitario de Investigación en Atención Primaria (IDIAPJGol ref 22/097-P approved 27 April 2022), Hospital Universitari Vall d'Hebron (Comité de Ética de Investigación con Medicamentos y comisión de proyectos de investigación del Hospital Universitari Vall d'Hebron (CEIm-VHIR) (ref. PR(AMI)307/2022 approved 5 July 2022)), Hospital Universitari Germans Trias i Pujol (CEIC CITEMB22/097P approved 22 July 2022), Hospital Clínic (CEIm HCB/2022/0807 approved 2 December 2022) and incorporates its recommendations and suggestions.

It is expected to publish at least two full articles in open access journals for this study and present the results on national and international conferences. The results will

be disseminated to the relevant stakeholders (Catalonian and Spanish Ministry of Health) and to other relevant stakeholders (primary care settings, reproductive clinics, both public and private, etc) and citizens. The dissemination of results will also be conducted via social media platforms such as Twitter, LinkedIn or ResearchGate.

Data storage and safety

1. Type and format of data collected/generated during the study.

All data will be pseudo-anonymised by coding the identifying variables collected and managed using REDCap (Research Electronic Data Capture)³⁹ hosted at IDIAP Jordi Gol as electronic data capture tool. REDCap is a secure, web-based software platform designed to support data capture for research studies, providing (a) an intuitive interface for validated data capture; (b) audit trails for tracking data manipulation and export procedures; (c) automated export procedures for seamless data downloads to common statistical packages and (d) procedures for data integration and interoperability with external sources. Access to REDCap for researchers is individual and protected by individual usernames and passwords. Each patient will be assigned an identification number for the study by the REDCap tool. The correspondence between the medical record number and the study identification number will be collected in a separate and encrypted database for each site. Only data necessary to achieve the study objectives will be collected. The necessary variables are listed in the Methods section.

In accordance with Regulation 14/2007, the biological samples of each participant will be collected directly from the participant within a usual procedure for pregnant women in the primary care settings and related hospitals in accordance with the procedure set out in the regulations on the use of biological samples for clinical care.

2. Procedure provided to access data (who can access data, and how and when), data ownership, repository to deposit data.

The necessary variables will be obtained directly from the participants by means of a self-completed form. Exploratory variables, biological samples and complementary explorations will be obtained by accredited personnel. All variables and data obtained will require the prior consent of the participants, in accordance with the provisions of Articles 6.1.a and 9.2.a of the GDPR, as well as additional provision 17.2.d of the LOPD-GDD.

The Catalan Institute of Health (ICS), the IDIAP Jordi Gol Research Institute and the Germans Trias i Pujol Research Institute are the data controllers. The project database will be stored in the computers of the ICS's Unitat de Suport a la Recerca Metropolitana Nord, which will be the data processor. International data transfer is not expected at this stage.

3. Procedure planned to ensure compliance with specific ethical and legal requirements.

The database will be created and stored on a physical computer where the organisation has installed the



corresponding software and therefore, it is only accessible from computers with a trusted connection via VPN and secure credentials (certificates, RSA keys or complex passwords). This computer follows the security standards set by the ICS in compliance with current regulations.

Patient and public involvement

For the design of the project, the association of families affected by CMV infection was contacted in order to incorporate the vision of those affected by the disease in the screening programme. We will count on their opinions also for the discussion of the results and their further dissemination to communities.

Expected outcomes and data analysis plan

The study variable collection plan is described in Section Methods / Variables.

For the descriptive analysis, all categorical data will be reported as absolute and relative frequencies (percentage). Proportions will be reported with 95% CI. Continuous variables will be described as mean and SD or median and IQR depending on whether or not the variable follows a normal distribution. All the outcome measures will be reported as absolute frequency and percentage with 95% CI.

The analysis will be performed according to the approved protocol. The outcome measures will be stratified by ethnic origin and maternal age, grouped in <20 years, 20–30 years, 30–40 years and >40 years old. If we have sufficient number of cases, we will stratify the results taking into account the treatment (maternal and, if needed, neonatal) status.

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Contributors MAS-D and NM conceived the project. MAS-D, NM, CM, AG, MAF, GF-P and RG drafted the project protocol. LL drafted the first version of the manuscript with assistance from CV and NM. MAS-D, JB-P, RG, AMZ, IV, EV, OG, AR, NS, MN, CM, AG, MAF, MG-M, PT, GF-P reviewed have reviewed subsequent versions of the manuscript and approved the final version.

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