Current evidence gaps to support systematic cytomegalovirus screening in pregnancy

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Summary

The benefits of screening for cytomegalovirus (CMV) infection during pregnancy remain a topic of debate. To date, no randomized trial has compared the impact of screening versus routine management on the prevention of severe sequelae in newborns. Furthermore, it is unclear what actions can be taken in case of a positive screening given that there is limited evidence of effective interventions as no treatments showed significant effect on the frequency of congenital cytomegalovirus infections and, as additional challenge, the window for effective treatment initiation after maternal infection is narrow, estimated to be as short as five weeks. Universal screening of all pregnant women could lead to a high number of false positives. There are also concerns regarding the cost-effectiveness of universal screening and the capacity of healthcare professionals that may struggle to manage the increased workload, and we argue that the conditions for implementing such a programme are not yet met. In this Viewpoint we aim at highlighting these challenges and stimulating the forthcoming discussion on how to fill the gaps before CMV screening in pregnancy could be adopted as a standard practice.

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Introduction

Cytomegalovirus infection is the most frequent viral congenital infection in high-income countries.[1,2] It has been recurrently suggested that screening of cytomegalovirus infection during pregnancy could be a good option to decrease the frequency of poor outcomes.[3] In 2018, the French High Council for Public Health (HCSP) performed a methodological appraisal and decision analysis[4] showing that systematic screening should not be implemented in France and that prevention of cytomegalovirus infection during pregnancy should instead be based on hygiene behaviour changes. Screening regained interest after the results of a randomised clinical trial suggested that valaciclovir might reduce the rate of foetal cytomegalovirus infection after maternal primary infection (MPI),[5] but the possible

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benefits of screening remain debated.[6,7] For instance, a group of clinicians, the European congenital infection initiative, suggested that "early and accurate maternal diagnosis through serological tests would enhance risk management and prevention strategies".[8] Other authors suggest that the evidence on treatment is insufficient to roll out a screening programme.[6] In December 2023, the HCSP reiterated that systematic screening should not be implemented.[9] In this viewpoint, we summarize the current evidence, discuss why congenital cytomegalovirus infection is a difficult target for systematic cytomegalovirus screening in pregnancy, and suggest research priorities.

Methods

Search strategy and selection criteria

We conducted a systematic analysis of the published and grey literature, using the same standard methods as for the HCSP 2018 report, and updated from 2017 to October 2022. Our search was based on PubMed/Medline, Embase, clinical.trial.gov, Cochrane and medRxiv databases, with no restriction on languages. Critical appraisal of the articles was carried by members of the group, using appropriate standards such as CONSORT, STROBE, and STARD. The GRADE framework was employed to evaluate quality of evidence across all domains relevant to a screening programme. The analysis of these domains was based on indication criteria proposed by the WHO, updated in 2020,[10] and adapted by the French High Health Authority (HAS) in 2023[11] and by the UK National Screening Programme in 2022[12] (Table 1). The latter two provide independent expertise to their government in public health decisions.

Role of funding source

The Funders had no role in study design, data collection, data analyses, interpretation, or writing of report.

Lack of evidence to justify screening

Screening is defined as the early detection of a latent disorder through testing, to allow for an early intervention to improve prognosis.[10] One of the purposes of prenatal screening is to detect diseases in the foetus and to provide parents with information about follow up, treatment and management options, so that they can make an evidence-based informed choice about whether to continue or not with pregnancy if they know that the foetus has a higher risk of having a serious condition. Any systematic screening programme, proposed as a public health intervention, must include a clear definition of the targeted disorder and population, early detection test(s), diagnostic confirmation, proposed intervention, and a description of the programme operational modalities, from the proposal of the early detection test(s) to the management of the disorder and of the consequences of testing (false positives, false negatives) and the proposed intervention (side effects of treatment ...). In addition, it must be demonstrated that this program can be effective, safe and acceptable to targeted individuals, including those without the disorder, and to the health care system, and can be delivered equitably. Ideally, the effectiveness of the screening programme in reducing mortality or morbidity, and the absence of disadvantages should be proven by high-quality randomised controlled trials.[10]

Key message: the body of evidence is not in favour of screening

At the time of writing, no randomised trial comparing the effect of screening during pregnancy versus routine management on severe sequelae of congenital cytomegalovirus infection have been published nor registered with *ClinicalTrials.gov* or WHO. In the absence of a randomized trial, we analysed all available evidence, using the above-mentioned criteria (Table 1), to verify whether conditions for an effective and safe screening were met.

Is congenital cytomegalovirus infection a public health issue?

At the individual level, congenital cytomegalovirus infection can be severe, due to sensorineural impairment and serious sequelae.[1,2] Congenital cytomegalovirus infections could be the cause of up to 6% of childhood hearing losses.[13] At the population level, however, severe consequences of cytomegalovirus infection are infrequent[14] (between 1 and 6 sequelae/100,000 new-borns in France[4]), as most neonates infected with cytomegalovirus *in utero* will present with no clinical sequelae, whether at birth or afterwards, in infancy and childhood.[6,13–17] In studies based on representative databases, the frequency of sequelae seems lower, even when considering terminations of pregnancy.[18] Concurrently to increased efforts towards general hygiene measures, especially during pregnancy, maternal seroprevalence of cytomegalovirus infection and the incidence of MPIs have decreased.[14,19] Uncertainties remain regarding the risk of reinfection/reactivation in women who have been infected with cytomegalovirus prior to their pregnancy.[19,20] This situation accounts for half of pregnant women in France.[19] Sequelae have the same frequency and severity in these situations as when the infection of the new-born results from a MPI.[1,6,17,20]

Were all cost-effective primary prevention interventions fully implemented?

Because screening is a secondary prevention intervention aimed at reducing the severity of the consequences of the infection, it should only be considered once all available primary prevention interventions have been implemented. Vaccine trials are ongoing[21]; the development of one vaccine was recently stopped for lack of

Criterion	Evidence
Public health importance	• Congenital cytomegalovirus infection can be severe for affected foetuses • Severe consequences are infrequent at the population level • Secondary maternal infection and consequences for the foetus are as frequent and severe after reinfections and reactivations than after primary infections
Primary prevention fully implemented	• No vaccine is available to date • General hygiene measures are effective in reducing the incidence of all infections, including cytomegalovirus • Only a minority of pregnant women report having received advice to limit the transmission
Available tests are reliable and accurate	• Interpreting serology is tricky, can be based on many available tests, and requires further examination and expert advice • Despite the good intrinsic performance of most tests, generalizing screening to all pregnant women, the vast majority of whom will not have an infection, would lead to a high number of false positives
An effective and safe treatment is available	• Lack of effectiveness of immunoglobulins has been documented in trials • One randomized trial with many flaws failed to show an effect of high-dose valaciclovir on the frequency of congenital cytomegalovirus infections and their consequences on children • The safety of valaciclovir at such a high dose in the short and long term remains uncertain
Adequacy of the preclinical phase	• Because of the time needed for first medical contact, appearance and detection of antibodies, diagnostic confirmation, and specialised consultation, there is at best 3–5 weeks between infection and when treatment could be started
Acceptability of screening to women and couples	• Observational studies suggest that the initial test is well accepted but that at least 1/3 of the women tested are subsequently lost to follow up • The anxiety caused by screening can lead to a request for an abortion or a medical termination of pregnancies, a majority of which would not result in sequelae • Acceptability of any screening tends to be lower in those most at risk of the disorder sought
Acceptability of screening to professionals and the healthcare system	• No valid medico-economic evidence is available to estimate the acceptability by the health system of routine screening for cytomegalovirus infection during pregnancy • Professionals do not seem ready to accept this overload of work and the potential ethical consequences • Additional consultations and examinations, following positive tests, are not compatible with the capacity of the professionals available to deal with such complex issues
Favourable benefit-to-risk ratio of screening program	• There are no published or ongoing randomised trials comparing the effect of screening during pregnancy with routine management on severe sequelae of congenital cytomegalovirus infection • Screening of cytomegalovirus infection during pregnancy is not recommended in any country • Many challenges could diminish the potential effectiveness of screening and lead to a lack of equity • Conditions are not met to suggest that such a programme should be considered

Table 1: **Summary of evidence regarding the opportunity of screening for cytomegalovirus infection during pregnancy.**

efficacy,[22] while another candidate shows promising perspectives.[21,23] General hygiene measures are effective to reduce the incidence of all infections, including cytomegalovirus during pregnancy.[15] Promoting these hygiene measures was one of the main recommendations of the HCSP in 2018.[4] Despite the introduction of some information tools, only a minority of pregnant women report having been informed that hygiene measures limit cytomegalovirus transmission.[6,24]

Are screening and confirmation tests accurate and reliable?

Diagnosis of MPI in pregnant women is currently based on the detection of specific IgG and IgM antibodies and measurement of IgG avidity when IgM and IgG are both positive.[17] Several algorithms exist, but commercially available tests are not standardized, and interpretation requires expert advice.[17,25,26] In the absence of both IgG and IgM, an exposure to cytomegalovirus can be excluded, but a second specimen should be retested to rule out an early MPI; the presence of IgG without IgM denotes a past infection and no further serological test is required. The presence of IgM without IgG may denote an MPI but, due to a specificity of IgM serology around 50%, a rise in IgG must be documented on a new specimen, and IgG avidity tested. When both IgM and IgG are positive, MPI can be ruled out when avidity is high. When avidity is intermediate during the first trimester, an MPI is unlikely; when avidity is low, an MPI is likely and transmission to the foetus is diagnosed by seeking cytomegalovirus DNA in amniotic fluid. Tests may be difficult to interpret with low IgG

titres, yielding up to 1.6% false-positive results.[4,26,27] Some women exhibiting antibodies of low avidity may lack IgM antibodies[26] and some may transmit the virus despite a high avidity.[28,29] Moreover, no tests can identify reinfections/reactivations. Additionally, performing these tests in all women to be tested would result in a high number of false positives and a poor positive predictive value, because the vast majority of pregnant women would not have an MPI.[4] Shallow whole genome sequencing of double-stranded cell-free DNA fragments from maternal plasma might become an alternative to serological testing for MPI screening.[30] When MPI is likely, whether based on serology or ultrasound findings, amniocentesis should be performed to ascertain foetal infection.[1,6,20]

Is there a treatment whose effectiveness and safety have been demonstrated?

Currently, the only treatments that have been evaluated are hyperimmune globulins and high-dose (8 g/day) oral valaciclovir. Assessment of the effectiveness of immunoglobulins, including three randomised trials, two of which were discontinued for futility or recruitment issues, showed that this approach does not reduce congenital cytomegalovirus consequences.[31,32] Valaciclovir was evaluated in one landmark randomized trial that investigated vertical transmission of cytomegalovirus and its foetal impact.[5] In a per-protocol analysis, this trial showed a decrease in the frequency of vertical transmission, only in women who had an MPI during the first trimester. While this study is a first step towards a response to current challenges, it did not show a significant effect on the frequency of congenital cytomegalovirus infections. Further, several methodological issues question the validity of the authors' conclusions[6,32]: not all terminations of pregnancy were considered in the assessment of outcomes; recruitment modalities were not well described and were applied unevenly; definitions of MPI were vague, and changed during study and from one analysis to another; the intent-to-treat analysis and the comparison of randomisation groups were not provided; in the per-protocol comparison of groups, timing of MPI, time before and duration of treatment were different in the valaciclovir and placebo groups.

Neither this randomised trial[5] nor any observational study[32] showed that valaciclovir would favourably impact the occurrence of sequelae in children infected *in utero*. Proponents of systematic cytomegalovirus screening in pregnancy argue that a decrease in maternal–foetal transmission after MPIs should logically result in a decrease in sequelae in children infected *in utero*,[3,33] but this has not been demonstrated. Combined with uncertainties about the safety of high-dose valaciclovir in the short and long term, these elements do not currently allow to conclude on a favourable benefit-risk balance. Three years after the trial was published, no further information has been provided about the impact of the intervention on sequelae, prognostic factors, and terminations of pregnancy.

Is the preclinical stage long enough to allow a diagnosis and an early intervention?

The time between MPI and the development of possible serious consequences must be known and long enough to perform the screening test, to obtain its result, to implement a treatment and for it to have time to have a positive effect. Most MPIs are asymptomatic.[20] IgM appear 3–5 days after the onset of clinical signs and usually disappear within 4–18 weeks, but can persist for months or even years, depending on the host and the technique used. IgG appear about 5–7 days after the onset of clinical signs and persist for life. Theoretically, for screening to be of interest, MPIs would have to be detected before 13 weeks of pregnancy to allow at least 7 weeks of treatment. When MPIs occur later than 13 weeks of pregnancy, they are less likely to cause severe sequelae of congenital cytomegalovirus infection[1,14,34] and treatment would be less valuable. Based on the natural history of cytomegalovirus infection and the valaciclovir trial data,[5] intervention should be initiated within a maximum of 8 weeks after infection. In practice, the time needed for first medical contact, appearance and detection of antibodies, diagnostic confirmation, and specialised consultation would make it difficult to start treatment before 3–5 weeks from MPI. The window of opportunity for therapeutic intervention is therefore very short,[34] and does not fit the follow-up schedule of pregnant women, including timing of amniocentesis.

Would all steps of screening be acceptable to expectant women and parents?

Acceptability is poorly documented.[6,24] The initial test is well accepted but at least one third of the women tested are subsequently lost to follow up. Patients' organisations, interviewed by the HCSP,[9] reported that in France, as in other countries, cytomegalovirus serology is prescribed to women by some practitioners, although this is not recommended. They also report heterogeneities in responses made by healthcare professionals to the serology result, a source of uncertainty for patients. Several patient organisations are opposed to the implementation of systematic screening programmes if they have not been proven to be useful.[9] The anxiety caused by screening procedures can lead to a request for a termination of pregnancy.[6,20,25] Data from other screening programmes indicate that acceptability tends to be lower in those most at risk of the condition sought.[35]

Would modalities and resources needed to implement the programme be acceptable to professionals and the healthcare system?

Published medico-economic analyses are based on modelling without real-world data collection.[16] They

focus their cost-effectiveness estimation on the cost of managing the consequences and are mainly limited to direct medical costs. A French study indicated that the current situation of screening without any recommendation is inefficient,[36] compared to a hypothetical generalized screening, but was based on the valaciclovir trial,[5] assuming that the per-protocol effectiveness on infection can be interpreted as an intent-to-treat effectiveness on sequelae. Several international studies suggest that routine prenatal screening may not be cost-effective, especially if there are only few cases.[16] Furthermore, the number of additional visits and examinations, following positive tests, does not appear to be clearly compatible with the capacity of the professionals available to deal with such complex issues, especially when considering the need for an amniocentesis, interpreting its results, and weighting all options, including termination of pregnancy. This is in line with the studies of acceptability by professionals who do not seem ready to accept the overload of work and the potential ethical consequences.[25,37] The current situation where screening of cytomegalovirus during pregnancy and treatment of MPI may be offered to pregnant women against the current guidelines should also be considered from an ethical point of view to make sure that such an attitude does not lead to unjustified terminations of pregnancy.

Discussion

Ideally, the effectiveness of the screening programme in reducing the risk of severe consequences in foetuses and children should be proven by high-quality randomised controlled trials.[10–12] The relevance of such trials, however, is questionable as long are there is not an identified effective and safe treatment or other intervention. The feasibility of a population-based trial is also unclear, given the continuing uncertainty regarding the shortness of the preclinical phase and the acceptability of all stages of the screening programme. Given the difficulties of conducting such trials, the potential benefit-risk ratio of a screening strategy should be assessed in evidence-based models comparing screening to current practice.[10] Such simulations can consider the natural history and compare the frequency of relevant outcome in the presence and absence of screening, and consider the evolution of prevalence and incidence of the infection when promoting hygiene measures. These models must consider all components of the program, including initial testing, confirmation strategy, treatment, and acceptability of all stages.

Randomized trials will still be key to assess the effectiveness of new drugs active on cytomegalovirus. Ideally, these new treatments should be applicable earlier and have a faster effect. The possibility of treating all pregnant women, as is has been proposed for the prophylaxis of neurological malformation with folic acid,[38] should be also discussed and evaluated. All trials should include a long-term follow up of treated women and their children, in terms of safety and effectiveness on sequelae. The relevance of treating all seropositive women should also be explored. Imputation of reported side effects, however, is difficult, as some, such as deafness, are similar to consequences of the infection.

We did not find representative cohorts, including comparative cohorts, to validly estimate the incidence of early and late severe sequelae, the impact of infection and moderate sequelae on children's psychomotor development, and identify potential prognostic factors and high-risk pregnancies.[37] These representative cohorts with a comparator group, ideally with a follow up of children from early pregnancy to at least schooling age, are needed to document the magnitude of consequences of congenital cytomegalovirus infection.[14,16,37] These data will also be useful to estimate the maximum size of the benefits attainable by an intervention and compute the number of pregnant women to include in trials or to carry simulations.

Research is also needed on the effect of hygiene measures on reinfection and on interventions that can improve information by professionals and the appropriation of hygiene measures by all pregnant women.[15] This should also include representative studies on how hygiene promotion is actually done in real life. Research on candidate vaccines and their effectiveness and safety remains a priority.[21]

Apart from the results of quality-assuring of laboratories,[39] there is a lack of dedicated, large-scale studies, representative of the actual conditions of routine management of pregnancy, on the accuracy and reliability of tests in the early period of cytomegalovirus infection in women in early pregnancy. Although shallow whole genome sequencing of double-stranded cell-free DNA fragments[30] seems promising, its applicability on a universal basis needs to be assessed in real-life conditions.

The acceptability of all stages of screening should be assessed in studies using representative sampling techniques, not just opinion polls. Ideally, this should be done in cohorts documenting barriers to acceptability and their determinants at each stage of follow up of pregnant women. Such studies are also needed to document how often pregnant women are requesting testing, and to what extent this results from testing promotion by some clinicians. We also need representative surveys and cost-benefit analyses to assess the ethical acceptability of providing or not a pregnant woman with knowledge that could have more reproductive choices, especially because prediction of sequelae is difficult.

Outstanding questions

In conclusion, strengthening the evidence on screening for cytomegalovirus during pregnancy needs further

research. Reporting of the long-term follow up of children from the randomised trial of valaciclovir[5] is urgently needed. Besides, vaccine trials and representative cohorts and surveys should be supported.

Contributors

ABV contributed to the design and conduct of the work reported, and to the writing and reviewing of this article; she had direct access to and checked the accuracy of all the data reported in the manuscript.

BH contributed to the design and conduct of the work reported, and to the writing and reviewing of this article; he had direct access to and checked the accuracy of all the data reported in the manuscript.

LRS contributed to the design and conduct of the work reported; he drafted the first version of this article and reviewed the final version; he had direct access to and checked the accuracy of all the data reported in the manuscript.

EB, PD, KG, VHF, PM, BPa, BPo, MR, contributed to the design and conduct of the work, and reviewed the manuscript.

All authors read and approved the final version of the manuscript.

Declaration of interests

EB received support for attending conferences from MSD, Gilead and ViiV; PD received honoraria for lectures by Norgine and Exeltis, and for manuscript writing by Biocodex and a grant from the Ministry of Health for the ePPOP id study. The rest of the authors declare no conflict of interests.

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