Arch Pediatr Urug 2025; 96(1): e804
doi: 10.31134/AP.96.14

Recommentions for evaluation and treatment of congenital cytomegalovirus infection

Recomendaciones de evaluación y tratamiento de la infección congénita por citomegalovirus

Recomendações para avaliação e tratamento da infecção congênita por citomegalovírus

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Abstract

Congenital cytomegalovirus (CMV) infection is the most frequent congenital viral infection. It produces important long-term sequelae, such as sensorineural deafness and psychomotor retardation, which could be reduced with timely diagnosis and early antiviral treatment.
The development of national or local guidelines for the systematic approach to this pathology, both in pregnant women and the fetus as well as in the newborn, is essential to improve perinatal and long-term outcomes, and also for health professionals to become aware of the importance of this pathology.
This publication summarizes its diagnosis, clinical follow-up, and treatment.

Keywords: Cytomegalovirus Infections
Infection/congenital

Resumen

La infección congénita por citomegalovirus (CMV) es la infección congénita viral más frecuente. Produce importantes secuelas a largo plazo, como la sordera neurosensorial y el retraso psicomotor, con su diagnóstico oportuno y tratamiento antiviral precoz podrían ser reducidas.
El desarrollo de guías nacionales o locales para el abordaje sistemático de esta patología, tanto en la mujer embarazada y el feto como en el recién nacido, resultan fundamentales para mejorar los resultados perinatales y a largo plazo, y también para que los profesionales sanitarios tomen conciencia de la importancia de esta patología.
En este documento se resume su diagnóstico, seguimiento clínico y tratamiento.

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Unpublished work.
We declare that we have no conflicts of interest.
This work has been unanimously approved by the Editorial Committee.
Received on: September 22, 2024.
Approved on: October 21, 2024.

Palabras clave: Infecciones por Citomegalovirus
Infección/congénito

Resumo

A infecção congênita por citomegalovírus (CMV) é a infecção viral congênita mais comum. Produz sequelas importantes a longo prazo, como surdez neurossensorial e atraso psicomotor, que podem ser reduzidas com diagnóstico oportuno e tratamento antiviral precoce.

O desenvolvimento de diretrizes nacionais ou locais para a abordagem sistemática desta patologia tanto na mulher grávida como no feto, bem como no recém-nascido, são essenciais para melhorar os resultados perinatais e a longo prazo, mas também para que os profissionais de saúde se conscientizem sobre a importância desta patologia.

Este documento resume seu diagnóstico, acompanhamento clínico e tratamento.

Palavras chave: Infecções por Citomegalovirus
Infecção/congênito

Introduction

Epidemiology

Worldwide, congenital cytomegalovirus (CMV) infection is common, with a prevalence that varies by region and socioeconomic level between 0.2% to 6%[1,2].

In Uruguay, there are no population data on the epidemiological profile of this disease. In a study conducted at the reference hospital *Centro Hospitalario Pereira Rossell*, the incidence of congenital CMV infection with symptomatic presentation or clinical expression between January 1, 2010, and December 31, 2018, was 0.2 per 1,000 live births[2].

Regional data, such as those reported by the Chilean Society of Infectious Diseases, show high maternal seroprevalence, with a marked difference between pregnant women of low socioeconomic status (up to 90%) and high socioeconomic status (50%)[3].

The prevalence in women of childbearing age is between 50% and 70% in the European population and North America, and 90% to 100% in Asia, Africa, and Latin America, as well as different seroprevalences within the same populations according to their income level[4-6].

Congenital CMV infection is the leading cause of non-genetic sensorineural hearing loss, which can be diagnosed at birth or developed during childhood, and approximately 50% of children with congenital cytomegalovirus (cCMV) experience deterioration or progression of their hearing disorder, making long-term follow-up essential[4]. It may also cause neurodevelopmental disorders such as cerebral palsy, seizures, and intellectual and/or visual disabilities[2].

Microbiological aspects

CMV is a member of the herpesvirus family, along with Epstein-Barr virus, herpes simplex viruses 1 and 2, varicella-zoster virus, and human herpesviruses[1-3]. CMV contains the largest genome of any human virus with a DNA of 236 kilobase pairs. Although CMV is known to be polymorphic among hosts, the source of variability remains unknown[7].

The mechanisms that determine the type, duration, and severity of clinical manifestations are poorly understood. Host factors, such as the strength of the cellular or humoral response, or both, along with viral determinants, such as viral load, may play an important role, as well as the timing of maternal infection acquisition or reactivation[7].

Genetic and immunological variability, as well as differences in *in vitro* growth characteristics, are well documented, and differences between strains can affect the virulence of human CMV (HCMV). Comparative genetic analysis of HCMV strains is mainly limited by the size and complexity of the viral genome. Its structure consists of long (L) and short (S) regions, connected by internal repeat sequences (IRL or IRS, when joined to the L and S components, respectively). The L and S regions can invert during replication, resulting in four viral genome isomers containing more than 200 open reading frames (ORFs), whose protein content has been analyzed, but only a minority of protein functions have been defined.

While studies on the DNA and protein levels suggest that different HCMV strains are 95% homologous, polymorphic sequences are observed in coding and non-coding regions of the viral genome. These genetic differences between strains are scattered throughout the genome and could explain the different forms of clinical presentation[4].

Several studies have attempted to correlate HCMV genomic variants with specific disease manifestations or sites of infectivity. The results have not established definitive associations between viral types and HCMV disease, suggesting that other variants of HCMV-encoded products, possibly in combination, may play a

role in viral pathogenesis.

The most widely studied polymorphisms to date are those related to ORF UL55, the coding locus for glycoprotein gB[8,9].

Different gB genotypes can be vertically transmitted from mother to fetus, with no type preferentially associated with *in utero* HCMV infection. However, Woo et al. and Lukacsi et al. found a high prevalence of gB-1 in babies with congenital infection, but this event was not predictive of clinical outcome.

Additional studies have shown that different gB genotypes do not correlate with the outcome of intrauterine infection or the development and severity of HCMV disease and symptoms at birth[10,11].

Transmission

Like other herpes viruses, CMV has the biological properties of latency and reactivation. It is transmitted through blood, urine, and secretions, demonstrating high viral loads in saliva, cervicovaginal secretions, semen, as well as in breast milk.

Children under 5 years of age, especially those under 2 years of age, appear to be a particularly important reservoir for primary infection. This is because young children who acquire CMV infection in the first months or years of life shed the virus in urine and saliva for an average of 18 months[1,2,12].

The annual infection rate in seronegative individuals is approximately 1% to 2%, but seronegative women caring for young children acquire CMV at rates 10 to 25 times higher[1,2,12].

Intrauterine transmission of CMV can occur in mothers without preexisting immunity who acquire the infection for the first time during pregnancy (primary infection), but it is more common (75%) in women with preexisting antibodies against CMV, either due to reactivation of a previous maternal infection or acquisition of a different viral strain (non-primary infections)[2,12,13]. Primary CMV infection is reported in 1% to 4% of seronegative women during pregnancy[12]. Despite being less frequent, it is associated with a higher risk of intrauterine transmission, accounting for 30%-35% of cases. Due to the persistence of viremia, fetal infection secondary to peripregnancy infections is common. There are described cases of vertical transmission when maternal infection occurred up to three months before conception (9-10 weeks before the date of the last menstrual period), with lower vertical transmission (Table 1). For reactivations or reinfections, the transmission rate is significantly lower at 1.1%-1.7%[2,12,13].

Preconceptional immunity against CMV provides a significant amount of protection against intrauterine transmission, newborn (NB) disease, and sequelae. The relatively benign course in NBs of mothers with recurrent infection is presumably due to the modulatory effect of preexisting maternal antibodies. However, this protection is incomplete as intrauterine transmission and symptomatic congenital infections also occur in neonates of women who were seropositive before pregnancy. In fact, considering the high seroprevalence in women of reproductive age, congenital CMV infection is caused by non-primary maternal infection in approximately two-thirds of infected infants[2-4,14].

The risk of intrauterine transmission depends on the timing of maternal infection during pregnancy. Fetal involvement, the presence of sequelae, and therefore the risk of having a symptomatic NB is approximately 19% to 28% in periconceptional and first-trimester infections and almost nonexistent if the fetus acquires the infection from a maternal condition in the second or third trimester (0.9% and 0.4%, respectively) (Table 1)[3,12-15].

Infection in Pregnant Women

CMV screening during pregnancy remains a topic of great interest and research, but there is still no consensus on its diagnostic and potentially therapeutic approach[12,16].

In pregnant women, the most common cause of infection is contact with children under 2-3 years of age, who, when infected, shed the virus through saliva and urine. The incubation period lasts around 3 to 4 weeks[14].

The diagnosis of maternal CMV infection cannot be established based solely on clinical symptoms, as these are nonspecific (fever, fatigue, headache, mononucleosis syndrome, lymphadenopathy) and 25% to 50% of mothers are asymptomatic. Laboratory findings may include lymphocytosis (>40%) and altered transaminases[3,17].

CMV serological tests should be performed in a pregnant woman when a viral infection not attributable to another specific infection is suspected, or when there are images suggestive of fetal CMV infection in the ultrasound[3,17].

Primary maternal infection is defined as the detection of specific antibodies against CMV in a previously seronegative woman (seroconversion).

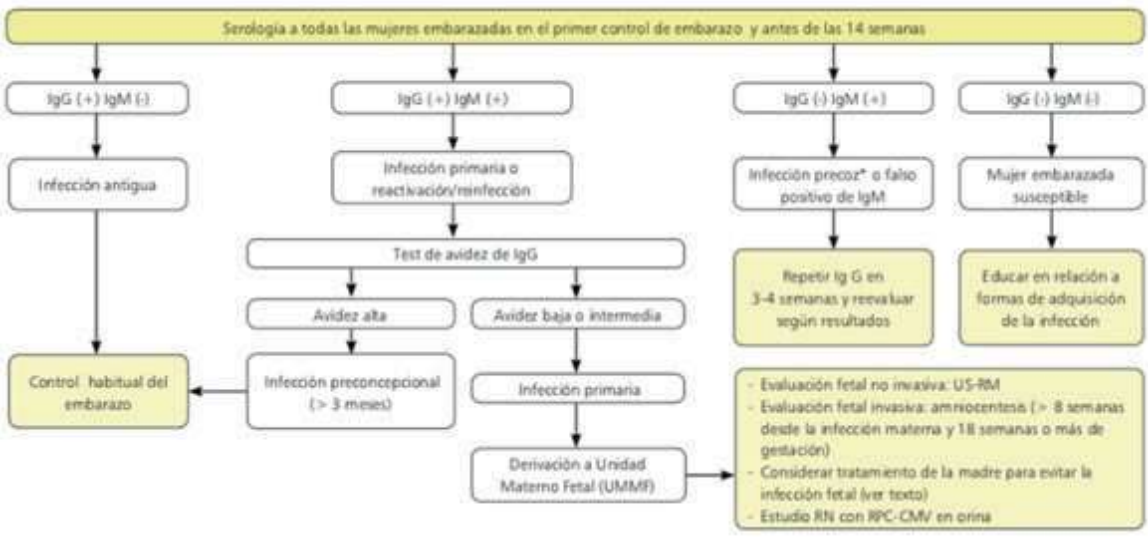
Unfortunately, seroconversion during pregnancy is not easily detected, as the preconception immunity status is usually unknown.

The serological diagnosis of primary infection is based on the determination of IgG and IgM antibodies.

Table 1. Risk of vertical transmission (VT) and central nervous system (CNS) lesions in the fetus and newborn (NB), and risk of severe neurological (NL) and auditory sequelae after a primary maternal CMV infection. Source: Protocol of TORCH infections and parvovirus B19 in pregnancy, Barcelona Clinic. (Data extracted from Chatzakis et al, AJOG 2020).

Momento infección	TV	Riesgo lesiones feto /RN si TV	Riesgo secuelas a largo plazo (NL y auditivas graves)	Riesgo lesiones feto/RN si no se conoce TV
Pregestacional (hasta 10-12 sem.pre FUR)	5-6%	No datos	No datos	No datos
Perigestacional (4sem pre-6 sem post FUR)	21%	29%	No datos pero se estima > que 1T	6%
1er trimestre	37%	19%	23%	7%
2º trimestre	40%	<1%	<1%	<1%
3r trimastre	66%	<1%	0%	<1%

Figure 1. CMV study scenario in pregnant women.



IgG antibodies can be detected approximately three weeks after infection and, although their value decreases, they can remain at low concentrations for life. Therefore, their isolated finding may indicate an old infection or a reinfection/reactivation.

IgM antibodies against CMV are detectable from 7-12 days after primary infection, reach their peak level between 2-3 weeks, and then decrease to undetectable levels a few months later, persisting for 6 to 12 months[3,18].

When the exact timing of seroconversion is unknown, the avidity test is useful. It is recommended if both IgG and IgM are positive, as it can help differentiate primary infection from non-primary one. It measures the binding capacity of CMV-IgG antibodies. Low to moderate avidity is observed for 16 to 18 weeks after a primary infection. Therefore, low-moderate IgG avidity in combination with positive specific IgM antibodies supports a diagnosis of recent primary CMV infection in the previous 3-4 months, and a high avidity test indicates an old infection (>5 months)[12,19] (Figure 1).

In our setting, the recommendation of the Uruguayan Society of Gynecologic and Obstetric Ultrasound (SEGU, from its Spanish acronym) and the Gynecologic and Obstetric Ultrasound Unit of the

School of Medicine, in their 2020 edition of the Clinical Application Guide for Obstetric and Gynecologic Ultrasound[20], states that serological testing during pregnancy (IgG and IgM) is indicated in the presence of a clinical presentation compatible with maternal infection, identified risk contact, ultrasound markers suggestive of fetal infection, early fetal growth restriction (EFGR < p3 and < 28 weeks), or increased nuchal fold (> p99) persisting beyond 16 weeks with a normal karyotype/array-CGH[20].

Fetal Infection

Since in our country, as well as in most nations, universal CMV screening is not performed, the suspicion and study of infection arise from ultrasound findings suggestive of fetal involvement. As a result, only the most severe cases of fetal infection are detected, while asymptomatic or mildly symptomatic infected children, who represent the vast majority, remain undiagnosed. In addition, some of them may later develop sequelae[3].

Fetal ultrasound is of great importance for diagnosis and management during pregnancy. When the fetal condition is known, it has a sensitivity of 91% and a negative predictive value (NPV) of 96% for the detection of long-term neurological sequelae.

Alterations in fetal images may take approximately 12 weeks or more to appear after maternal infection[3,21,22].

In ultrasound, we can observe central nervous system and extracerebral alterations (Figures 2, 3, 4, and 5)[23,24].

Ultrasound markers are generally progressive, especially encephalic manifestations, and may not appear until the third trimester. Neurosonography has high sensitivity for detecting CMV-related lesions, reaching up to 80–85%. Fetal MRI performed at 32 weeks can be very useful, particularly for identifying cortical, cerebellar, and posterior fossa lesions[14].

Both techniques are complementary and used together can achieve a sensitivity close to 100% in terms of the risk of sequelae, except for auditory ones.

Encephalic alterations appear almost exclusively after primary infections acquired in the first trimester, generally associating sequelae in the NB (Figures 2, 3, 4, and 5)[23,24].

Encephalic anomalies can be classified into poor prognosis lesions (determining symptoms in the NB and associating a high risk of neurological sequelae) and lesions of uncertain prognosis[3].

Poor prognosis lesions include hydrocephalus [ventriculomegaly (VM) greater than 15 mm], microcephaly (head circumference <-3 SD, some authors <-2 SD), agenesis of the corpus callosum, cerebellar or vermian hypoplasia, increased subarachnoid space (microcephaly), destructive and hemorrhagic lesions, sulcation and gyration anomalies, periventricular hyperechogenicity (‘flare’), and porencephalic cysts (Table 2).

Lesions of uncertain prognosis are mild VM (10-14.9 mm), intraventricular adhesions or synechiae, calcifications in caudate nuclei, germinolytic cysts, hyperechogenic thalamic vessels (‘candlelight’ sign), associated hearing loss, isolated small parenchymal cysts, and increased white signal on MRI[14].

Extracerebral anomalies can appear after fetal infections in the second and third trimesters. They are generally of good prognosis (in relation to the presence of neurological sequelae in the NB), except for hydrops fetalis. When they appear in the second trimester, they precede severe encephalic alterations and associate a 30% risk of moderate and severe long-term sequelae, requiring follow-up with neurosonography and MRI[14].

The most frequent are the presence of early intrauterine growth restriction (IUGR) (before 28 weeks), hyperechogenic bowel, cardiomegaly, hepatomegaly,

Table 2. CMV infection-related fetal brain ultrasound abnormalities.

Alteraciones graves del SNC	Alteraciones leves del SNC
Ventrículo lateral ≥ 15 mm	Ventriculomegalia > 10 mm y < 15 mm
Dilatación del 3° y/o 4° ventrículo cerebral	Adherencias intraventriculares
Hiperecogenicidad periventricular	Calcificaciones intracerebrales
Microcefalia PC < 2-3 DS	Quistes subependimarios
Cisterna magna aumentada	Quistes plexos coroideos
Hipoplasia del vermis	Calcificaciones de los vasos lenticuloestriados en los ganglios basales
Porencefalia	
Lisencefalia	
Lesiones quísticas de la sustancia blanca periventricular	
Agenesia del cuerpo calloso	

splenomegaly, meconium ileus, hydrops fetalis, ascites, oligohydramnios or polyhydramnios (less frequent), placentomegaly, and ultrasound signs of severe fetal anemia. These can be progressive over time, so serial follow-up is vital[3,14,25] (Table 3).

Fetal MRI is indicated as a complementary examination to ultrasound. Several authors report that MRI has greater sensitivity than ultrasound for detecting some alterations. Polymicrogyria and heterotopia are better detected in fetal MRI[3,26].

The diagnosis of fetal CMV infection can be confirmed by detecting the virus or viral DNA in the amniotic fluid by polymerase chain reaction (PCR). Amniocentesis for CMV study is recommended in two cases: (1) primary maternal CMV infection during pregnancy, and (2) when there are ultrasound anomalies suggestive of fetal CMV infection, along with supportive serologies (positive IgG, with positive or negative IgM)[14].

PCR for CMV has a sensitivity of 92% and specificity of 98%-100%, especially when amniotic fluid samples are collected after 21 weeks and at least 6-8 weeks after the onset of maternal infection[14].

The result can be undetectable CMV-DNA, in which case fetal infection is ruled out at that time, but the possibility of vertical transmission after amniocentesis (8%-10%) is not ruled out. In cases treated preventively with valaciclovir before amniocentesis, a neurosonography should be performed at 32 weeks, as there is a possibility of a transient false negative in amniotic fluid[14].

A positive CMV-DNA result confirms fetal infection, and the prognosis will depend on the timing of maternal infection acquisition and the severity of the fetal clinical condition. Subsequent follow-up will consist of detecting ultrasound markers of fetal involvement that may help determine the neonatal prognosis[14].

The risk of fetal loss associated with amniocentesis is 0.1%-0.2% when performed by an experienced technician in the second trimester, after 16 weeks (fusion of the amniotic membrane to the chorion). Some series report an increase in complications to 1% when the procedure is transplacental and 1%-2% if the technician is not adequately trained; in contrast, risks lower than 0.01% have been reported in highly experienced centers[3,27,28].

Cordocentesis can be performed to determine the presence of viral DNA and anti-CMV IgM in fetal blood. However, amniotic fluid sampling is generally sufficient and is the method of choice for diagnosing fetal CMV infection. Currently, there is no indication to perform cordocentesis for this pathology, as the risk of fetal loss associated with the procedure is higher than with amniocentesis (1%-3%)[3,29,30].

An interesting and little-highlighted element in the international literature is the pathological anatomy of the placenta. The study of this is a fundamental pillar. Abnormally large growth (placentomegaly) has been associated with intrauterine infection[31,32].

In a study conducted at the *Centro Hospitalario Pereira Rossell* in neonates hospitalized between January 1, 2010 and December 31, 2018 with positive CMV PCR in urine, saliva, or blood in the first three weeks of life and at least one clinical or paraclinical manifestation, pathological findings compatible with

Table 3. Extracerebral abnormalities.

Alteraciones extracerebrales
Hepatomegalia (lóbulo derecho > 40 mm)
Intestino hiperecogénico (ecogenicidad igual o mayor al hueso)
Esplenomegalia (diámetro > 40 mm en segundo trimestre)
Restricción del crecimiento fetal
Oligoamnios
Polihidramnios
Ascitis Derrame pleural Hidrops Placentonegalia > 40 mm Calcificaciones hepáticas/quiste hepatico

Figure 2. Transvaginal (TV) neurosonography. A: parasagittal section of the fetal brain, 22 weeks, abnormal periventricular echogenicity with cyst formation (arrow), and striatal artery vasculopathy (arrowhead). B: sagittal section, shows enlarged cisterna magna (cm) and fourth ventricle (v), with hypoplastic vermis (arrow).

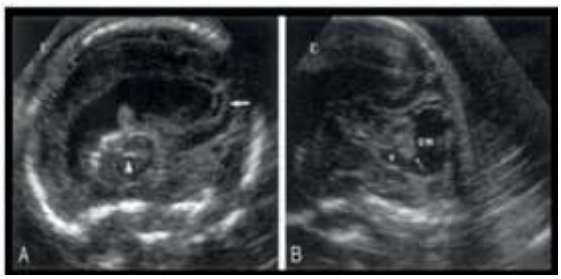


Figure 3. TV neurosonography. A: coronal section, 29 weeks, shows parenchymal foci of increased echogenicity compatible with calcifications (solid arrows) and abnormal sulcation (open arrows). B: sagittal section, shows a hypoplastic and blurred corpus callosum (CC). The genu of the CC is not observed (open arrows), the thin splenium (solid arrow). Cavum septum pellucidum (CSP). C: sagittal section, echogenic foci in the cerebellum (arrow).

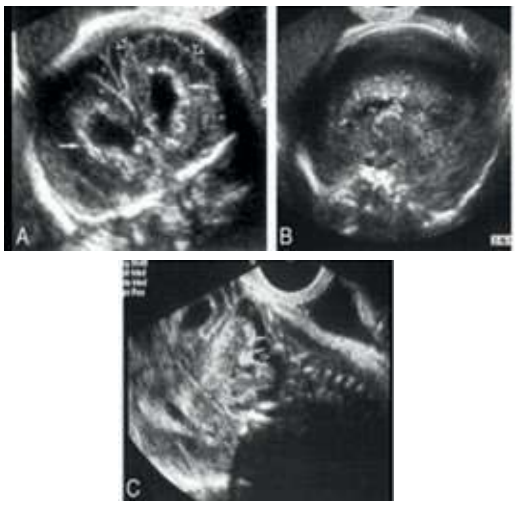


Figure 4. TV neurosonography. A: parasagittal section, 25 weeks, shows abnormal periventricular hyperechogenicity (arrows) and intraventricular adhesion (arrowhead). B: parasagittal section, 31 weeks, shows underdeveloped abnormal pre- and postcentral gyri and calcifications (arrows).

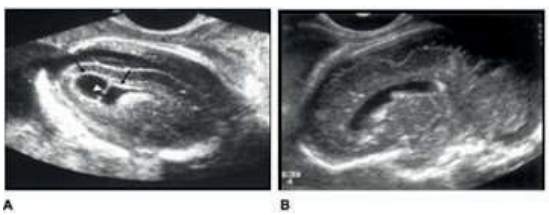
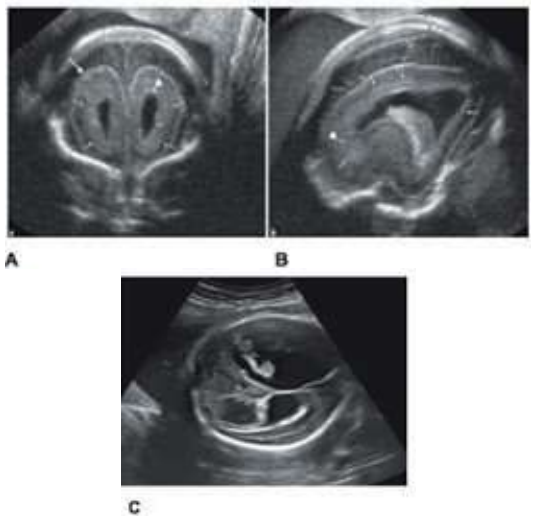


Figure 5. TV neurosonography. A and B: mild ventriculomegaly, 22 weeks. Coronal transfrontal section (a) and parasagittal section (b), showing increased subarachnoid space due to microcephaly, periventricular echogenicity (small arrows), parenchymal calcifications (arrowheads), and abnormal cortex compatible with incipient polymicrogyria (large arrow in a). C: transabdominal neurosonography. Severe asymmetric hydrocephalus, 30 weeks. Axial section shows a more dilated proximal ventricle. "Plaque" calcification on the edge of the distal portion of the ventricle.
Images taken from Malinger G, Lev D, Zahalka N, Fetal Cytomegalovirus infection of the brain, The spectrum of sonographic findings, AJNR Am J. Neuroradiol 24:28-32, January 2003, Malinger G, Lev D; Imaging of fetal Cytomegalovirus infection, Fetal Diagn ther 2011; 29: 117-26.



specific CMV infection were observed in seven out of ten patients in whom placental pathology was performed, while two suggested an infection, making it a useful tool for diagnostic orientation[2,3].

Approach and management of the newborn

The diagnosis is made by detecting CMV DNA through real-time PCR in urine, blood, or cerebrospinal fluid (CSF). Saliva determination must be confirmed with urine PCR (*gold standard*) before 21 days of life.

Diagnosis beyond three weeks of life is challenging due to the difficulty in distinguishing between congenital and postnatal acquisition, and heel blood drops collected for neonatal screening can be used to assess the presence of CMV in blood at birth[33].

CMV PCR in saliva swabs is a simple technique, obtaining the sample immediately, easily, and non-in-

vasively with a sensitivity of 97.4%-100% and a specificity of 99.9%; however, it requires confirmation with a urine sample due to the risk of false positives secondary to contamination by CMV excreted in breast milk[3]. To avoid false positives, it is recommended to obtain a saliva sample at least one hour after breastfeeding to avoid possible contamination[34-37].

If urine or saliva PCR is not available, the virus can be identified retrospectively in blood drops collected for screening, as mentioned earlier. Numerous studies in the literature report a wide dispersion in the sensitivity of this method, depending on multiple factors, such as the extraction method, the way the heel prick test is performed, and the type of amplification for PCR, with values ranging from 35% to 98%. Sensitivity is higher if it is secondary to primary infection, in selected patients, if a good extraction and amplification method is used, and a duplicated or even triplicated amplification. Specificity in all of them is consistent and reaches almost 100%, so a single negative test cannot definitively exclude a diagnosis of cCMV, with the most important application of this method being the retrospective diagnosis of infection[3,38-40].

The determination of serology (IgM and IgG) in the NB is not recommended, as the presence of positive IgM, while it may indicate an acute infection, can be falsely negative in about 50% of infected NBs. Besides, the presence of IgG is not very useful, as it reflects the passage of maternal antibodies through the placenta[3,41].

To date, it is recommended to actively search for cCMV infection in the following cases:

1. Fetuses with ultrasound and/or MRI images compatible with CMV disease.
2. Newborns with maternal history of suspected primary CMV infection during pregnancy.
3. Newborns with signs/symptoms compatible with cCMV disease, including those with compatible findings in prenatal images.
4. Confirmed sensorineural hearing loss (SNHL).
5. Newborns of mothers with HIV infection or mothers with another immunodeficiency (Izquierdo et al., Viruses 2024).
6. Symmetrical small for gestational age newborns.

There is controversy over the clinical classification of a NB with cCMV. To simplify it, work has begun on the operational definitions of "symptomatic" and "non-symptomatic".

The definition of symptomatic infection varies in different guidelines and consensus. The European consensus incorporates isolated SNHL as part of CNS involvement and suggests additional studies to evaluate other organs, unlike the American consensus which considers a NB with unilateral SNHL as asymptomatic[38,42].

The common definition of symptomatic cCMV as "a NB with clinical signs and symptoms present on physical examination" has limitations and may lead to the omission of a significant number of cases and the loss of treatment opportunities[3,38,43].

The European consensus 2024[44] suggests that to adequately classify the NB as symptomatic or asymptomatic, it is necessary to perform adequate anthropometry, a thorough physical examination, and laboratory tests that include a complete blood count, liver function tests with bilirubin and its fractions as well as liver enzymes, and an ophthalmological and hearing evaluation. Table 4 summarizes the symptoms, signs, and laboratory abnormalities that constitute symptomatology attributable to CMV and that should be ruled out through evaluation.

In the Chilean consensus, their expert group suggests defining a "truly asymptomatic" NB as one who, after a detailed clinical, ophthalmological, hearing, laboratory, and imaging evaluation, does not present findings compatible with cCMV[3].

Most infected NBs are asymptomatic (90%). This is because most of these infections result from reactivation of the maternal virus, which implies that the NB is born with protective antibodies. The premature NB has a lower number of transferred antibodies and, therefore, a higher risk of symptomatic infection.

Symptomatic infection can manifest as pneumonitis, hepatitis, enteritis, and less frequently, lymphadenopathy or aseptic meningitis. Pneumonitis is indistinguishable from other types of atypical pneumonia in the neonate.

Hepatitis is usually not very symptomatic, manifesting in most cases as hepatomegaly or hepatosplenomegaly, mild jaundice, and moderate elevation of transaminases, although severe cases with multisystem involvement, portal hypertension, and progression to cirrhosis have been described. Transaminases usually reach their peak value at 2-3 weeks of infection, decreasing to normal values in 5-6 weeks, although they may remain elevated for months. Enteritis usually manifests with abdominal distension and pain, vomiting, and watery diarrhea. Occasionally, the clinical picture is more severe with the appearance of gastrointestinal bleeding.

CNS involvement is associated with progressive hearing loss, psychomotor developmental delay (PDD), epilepsy, cerebral palsy, and visual disturbances, in undefined percentages. The fetal brain is especially vulnerable to lesions caused by CMV due to direct cytotoxicity, inflammation, and activa-

tion of microglial cells, with one of the most characteristic features of CMV infection being periventricular echogenicity that later evolves into occipital horn cysts. The cause of PDD is believed to be due to the sensitivity of developing CNS cells to the apoptotic and lytic effects of CMV, leading to structural damage. SNHL associated with CMV infection is thought to be due to cochlear and vestibular system damage secondary to viral replication and immune response to infection[3].

Newborns with cCMV can be classified according to the severity of the disease[3,38,45].

Patients with severe disease are those with CNS involvement, evidenced by microcephaly, hearing or visual impairment, imaging abnormalities, or infection confirmation in CSF. Specific organ involvement, with significant impairment of its function, as well as infection affecting multiple parenchymas, will also be considered severe infection.

Patients with mild disease are those who generally have a compatible clinical history or are symmetrical SGA NBs, but present a normal clinical evaluation and some isolated laboratory test abnormality that resolves spontaneously in less than two weeks.

There is a third group of patients with disease referred to as moderate, whose composition is very heterogeneous. The European consensus of 2017[38] proposes classifying within this group patients with at least two mild abnormalities that persist over time.

The following table summarizes the clinical and laboratory manifestations compatible with cCMV (Table 4).

Table 4. Clinical manifestations, laboratory tests, and neuroimaging in cCMV.

Clinical manifestations
- Hepatosplenomegaly. - Petechiae, purpura or "blueberry muffin rash in a newborn". - Greenish jaundice. - Microcephaly (head circumference <-2 SD for gestational age). - Symmetrical SGA (<-2 SD for gestational age). - Unexplained seizures.
Laboratory findings
- Prolonged jaundice with elevated transaminases. - Conjugated hyperbilirubinemia. - Unexplained thrombocytopenia; consider leukopenia or anemia.
Neuroimaging
- Intracranial calcification (typically periventricular). - Intracranial ventriculomegaly with no other explanation. - Periventricular cysts, subependymal pseudocysts, germinolytic cysts, white matter abnormalities, cortical atrophy, migration disorders, cerebellar hypoplasia, lenticulostriate vasculopathy.
Ophthalmologic findings
Abnormal findings on ophthalmologic examination compatible with cCMV (chorioretinitis). Evaluate in case of congenital cataracts.
Congenital or late-onset sensorineural hearing loss
Maternal seroconversion
Consider in women with known CMV infection (known IgG seropositive at the beginning of pregnancy), particularly if symptoms or virological examination are compatible with suspected CMV reactivation/reinfection.

Clinical and laboratory evaluation of the NB with confirmed cCMV

A complete and detailed physical examination of the NB is essential, assessing skin and mucous membranes for jaundice and petechiae, visceromegalies, and ocular abnormalities. Performing a neurological examination to detect subtle findings such as lethargy, hypotonia, and hypertonia is of great importance. Also, as part of the clinical evaluation, perform anthropometry measurements and classify the NB[3,46,47].

A complete and detailed laboratory evaluation is important to detect target organ involvement and adequately categorize as symptomatic or "truly asymptomatic". It includes the following laboratory tests:

- Complete blood count with platelet count.
- Liver enzymes: AST, ALT, GGT, total and conjugated bilirubin.
- Renal function (before starting therapy): creatinine, blood urea nitrogen, complete urine.
- Hearing tests (brainstem evoked response; otoacoustic emissions are not sufficient to detect central auditory hearing loss in cCMV).
- Ophthalmic evaluation: ophthalmological abnormalities are seen in 20% of NBs with symptomatic cCMV. The main manifestation is chorioretinitis (10%-21%).
- Cranial ultrasound: It is the first-line study for the NB with cCMV due to its easy access and high sensitivity. The triad of germinolytic cysts, periventricular calcifications, and ventriculomegaly is observed in one-third of these patients. Less frequently, hydrocephalus, ventricular adhesions, and subependymal or caudothalamic groove cysts can be observed. Another frequently found lesion is lenticulostriate vasculopathy (increased echogenicity of the lenticulostriate vessels), which alone is not considered a finding compatible with cCMV[3,48].
- Brain MRI: It was classically performed on patients who previously presented abnormalities on ultrasound; however, evidence shows that there is a significant number, around 20%, who may not have evident lesions

on ultrasound but are observed on MRI. MRI can be successfully performed in NBs without the need for sedation. It is highly sensitive and free from the risks of radiation exposure associated with CT scan. It has limited capacity for detecting brain calcifications but has a much higher sensitivity than ultrasound and CT scan for detecting white matter lesions, neuronal migration abnormalities, and parenchymal lesions[48,49]. The most characteristic findings include white matter abnormalities (42%), cortical development malformations (10%), and cerebellar hypoplasia (2.8%)[49]. Currently, cranial ultrasound remains the most used and reliable imaging method for diagnosing cCMV.

- Lumbar puncture: Studies have shown detectable CMV DNA in CSF, and elevated biomarkers, such as β2-microglobulin, suggest a poor prognosis. However, others have not shown additional prognostic value of CSF samples collected in the clinical context and, although it can provide additional information, as mentioned earlier, lumbar puncture is not mandatory in these patients[3,38].

The detection of CMV DNA in CSF confirms CNS involvement, but a negative result does not rule it out. If CSF with CMV DNA is found, the NB is considered symptomatic and therefore, requires treatment initiation.

Treatment

All patients with severe or moderate disease according to the proposed classifications should receive treatment[3,38,39,44]. In the case of patients with mild presentation, each case should be discussed individually. Table 5 summarizes the treatment indications according to different guidelines and consensus.

The treatment will be with valganciclovir or ganciclovir. Valganciclovir is preferred when the patient tolerates the oral route. The duration of treatment with valganciclovir will be six months, as evidence supports that longer treatment is associated with better auditory and neurological outcomes when evaluated at two years[3,44], and at a dose of 16 mg/kg/12 hours orally. In case of using ganciclovir due to the severity of the patient or digestive intolerance, the dose will be 6 mg/kg/12 hours intravenously.

These drugs are generally safe and well-tolerated. The advantage of valganciclovir lies in its oral administration, which avoids the need for a central venous line for a prolonged period, reducing associated risks and hospital stay. It is essential to monitor the adverse effects associated with them, with a complete blood count and liver and renal function tests, initially weekly, and then spacing out after the first month of treatment. Neutropenia is observed in up to 60% of patients, generally occurring during the first month of treatment. This is reported less frequently with valganciclovir than with ganciclovir (21% vs 65%, respectively)[38]. Thrombocytopenia, anemia, elevated transaminases, and renal function abnormalities can also be found.

Some authors suggest discontinuing treatment if the number of neutrophils drops below 500 cells/mm^3 and platelets below 50,000 cells/mm^3 or reducing it to half the dose if neutrophils are below 750 cells/mm^3. Treatment should not be resumed while neutrophils are below 500 cells/mm^3, platelets below 25,000/mm^3, or hemoglobin below 8.0g/dl[3]. The use of colony-stimulating factors allows the increase of the number of neutrophils and maintaining treatment[39]. Long-term side effects in neonates treated with ganciclovir or valganciclovir have not been evaluated[34].

Follow-up

Sensorineural hearing loss is the most common sequela of cCMV infection. Approximately 22% to 65% of babies with symptomatic cCMV develop SNHL. It has been estimated that NBs with symptoms at birth are six times more likely than those without symptoms to develop SNHL[50,51].

13% of asymptomatic patients may develop SNHL and worse neurological development. Treatment with ganciclovir/valganciclovir has been shown to improve this prognosis[2].

In cCMV, the recommendation for auditory follow-up is based on long-term follow-up studies of SNHL. Frequent follow-up is suggested during the first two years of life because this is the period of greatest risk for the development of cCMV-associated hearing loss and a critical period for language development. Follow-up should continue into early childhood because hearing deterioration continues during this period.

In general, ophthalmological follow-up data are based on a few studies, with the main risk factor for poor visual prognosis being the presence of symptoms at birth, especially CNS involvement[52]. Annual ophthalmologic follow-up is recommended until five years of age[3,38].

Neurological and neurodevelopmental follow-up is recommended at 3, 6, 12, and 24 months of age in NBs with symptomatic cCMV and in the case of asymptomatic ones at 12 and 24 months. A possible association of cCMV with autism spectrum disorder, attention deficit and hyperactivity disorder, language disorders, and other neurodevelopmental disorders has been observed[3].

Table 5. Comparison of treatment indications according to different consensus.

	European Guide 2017[38]	European Guide 2024[44]	Rawlinson 2017 Australia[42]	Red Book AAP 2021-2024[64]	Chilean Consensus 2021[3]
CNS alteration, including chorioretinitis	Yes	Yes	Yes	Yes	Yes
Severe disease	Yes	Yes	Yes	Yes	Yes
Moderate disease	Yes	Yes	Yes	Yes	Yes
Mild disease	No, case-by-case assessment	Yes, 6 weeks. Do not treat isolated SGA	No	Insufficient data to recommend. Case by case	Gray area, consider case by case
Isolated uni- or bilateral sensorineural hearing loss	Yes	Yes	No	No	Yes
Asymptomatic	No	No	No	No	No

Prevention

Prevention of cytomegalovirus infection in pregnant women.

Maternal primary infection could be prevented during pregnancy through education, with simple hygiene measures and by identifying populations of pregnant women at risk such as those living with children under three years of age or working in early childhood education[38,53].

There are four types of CMV vaccines in development: live-attenuated virus vaccines, inactivated vaccines, viral vector-based vaccines, and DNA/RNA-based vaccines and, to date, three vaccines undergoing early-stage clinical trials in humans[54,55]. The main difficulty in achieving efficacy in a CMV vaccine lies in the virus's own characteristics, and the vaccine must be able to control both primary infection and reactivation or reinfection episodes[56].

Prevention of fetal infection

Passive immunization, based on the administration of anti-CMV immunoglobulin to women at risk of transmitting CMV to the fetus, is currently an area of clinical research. Its usefulness is based on the presence of neutralizing antibodies that would reduce the passage of CMV through the placenta. This is due to the high concentration and avidity of CMV IgG antibodies and the immunomodulatory effect against placental and fetal organ inflammation generated by CMV[50,57,58].

With the currently available evidence, the systematic use of immunoglobulin for the prevention of fetal infection cannot be recommended[59,60].

Regarding antiviral drugs for the prevention of fetal infection, in pregnancy, the alternatives are reduced due to the potential risk of teratogenicity. Ganciclovir and its prodrug valganciclovir are the most effective antivirals in the treatment of CMV, but since they generate genotoxicity *in vitro*, they belong to category C of the Food and Drug Administration (FDA). There are no data to date on their use to prevent fetal infection[61]. Acyclovir and valacyclovir have an adequate safety profile for use during pregnancy (category B, FDA) with a fetal malformation rate equivalent to the general population. The Chilean consensus recommends treatment with valacyclovir in the case of demonstrated primary infection in the first trimester at 2g/6 hours (8g/day) dose[3].

The dosing regimen of valacyclovir to prevent renal complications, although infrequent (reversible acute kidney injury, secondary to drug-induced crystal precipitation in the proximal renal tubule), is at 8g/24 hours in four doses, with high bioavailability when administered orally[14].

Valacyclovir is recommended to prevent vertical transmission in pregnant women who acquired the infection in the first trimester or in the perigestational period and with serological diagnosis before 14 weeks. Treatment should be started as soon as possible after diagnosis and maintained until the amniocentesis result is available, with weekly renal function monitoring initially and then every two weeks until the end of preventive treatment[3,14].

Follow-up with a complete blood count and liver function tests (transaminases) the first week after initiation, and then every two weeks is recommended.

Contraindications for drug administration are the

presence of liver or kidney disease, allergy to valacyclovir, and hyperemesis gravidarum.

In the case of confirmed fetal infection, there are no publications of randomized, controlled studies evaluating this treatment scenario to date. Treatment with valacyclovir can be considered in cases of demonstrated fetal infection, without deep lesions in fetal neuroimaging regardless of gestational age[3]. The use of Ig-CMV immunoglobulin for the treatment of demonstrated fetal infection is not recommended[3].

Future Projection

For future vaccination and prevention strategies, it is essential to understand the virological, immunological, and other risk characteristics associated with intrauterine transmission in women with non-primary CMV maternal infection.

CMV education programs are necessary to raise awareness and provide accurate information about CMV to both mothers and healthcare providers. Additional studies are needed to evaluate the effectiveness of brief behavioral interventions during pregnancy to reduce maternal CMV risk behaviors and, therefore, cCMV infections[62].

States and numerous hospitals have developed specific CMV screening protocols within NB hearing screening programs. However, without universal CMV screening, most children with cCMV will go unnoticed, and it will not be possible to identify NBs with cCMV who are at risk of late-onset SNHL[62].

Currently, universal CMV screening is not routinely performed. Several states and hospitals have proposed targeted CMV screening for NBs who fail the hearing test as a strategy to identify babies with CMV-related SNHL at birth. However, findings from a large multicenter study showed that only 57% of CMV-infected babies with confirmed SNHL during early childhood would be identified through a selective CMV screening approach. These findings support universal CMV screening of all NBs for early detection and timely interventions. Moreover, a universal approach would identify infants with cCMV who are at higher risk of late-onset SNHL[62].

The time for universal CMV screening is now. Although both targeted and universal CMV screening have been shown to be cost-effective, universal screening provides greater net savings and the greatest opportunity for targeted care.

The prevalence of congenital CMV infection, its associated sequelae, the availability of a simple saliva screening tool, available antiviral treatment, and targeted therapies for hearing impairment demand that that we act now to make universal screening a reality[63,64].

In conclusion, long-term storage of dried blood spots is essential, as these samples can be useful and cost-effective diagnostic tools for long-term biobanks, enabling the diagnosis of major infectious diseases, including cCMV[33].

Conclusions

Despite the significant long-term impact of cCMV infection, there is limited evidence on which to base many treatment decisions in clinical practice. In an era of improved perinatal screening, fetuses and NBs are increasingly tested for CMV after abnormalities are detected during routine ultrasound or maternal serology.

Given its frequency and disabling consequences, it is striking that cCMV is less known to the general population than other conditions with lower prevalence, such as Down syndrome, fetal alcohol syndrome, and spina bifida.

This lack of awareness is problematic since currently, the only way to prevent fetal infection is through careful hygienic practices, such as handwashing and avoiding potential sources of CMV.

The development of national or local guidelines for the systematic approach to this pathology in both pregnant women and fetuses, as well as in NBs, is essential not only to standardize care and improve perinatal and long-term outcomes but also to raise awareness among healthcare professionals about the importance of this pathology and how it can, in many cases, cause severe morbidity and mortality if not suspected early.

It is difficult to conclude this review without referring to the need to develop a national program for the systematic search for cCMV in all NBs, or at least initially in those at high risk. There are various examples of screening, both universal and targeted, such as the Chilean case, or some states in the United States, from which to learn and advance. The evidence, as mentioned, is increasingly compelling in the need to move forward in this direction.

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Data availability
The dataset supporting the results of this study is NOT available in open-access repositories.

Authors contribution
All authors of this manuscript contributed to its conception and critical revision, and approved the final version for publication.

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