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REVIEW

Cytomegalovirus Infection in Pregnancy – Counselling Challenges in the Setting of Generalised Testing

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ABSTRACT

Cytomegalovirus (CMV) is the most common cause of perinatal viral infection, affecting 0.2-2.2% of all neonates, with variation among different study populations. It can cause serious long-term neurological sequelae, being the leading cause of non-genetic congenital hearing loss. The risk of congenital infection is highest after primary maternal infection, varying between 30-70% and depending on the gestational age at the time of infection.

Although CMV can have serious neurodevelopmental consequences, in most developed countries current guidelines do not recommend routine screening for CMV in pregnancy, since current tests have a low predictive value for cases with serious adverse outcome and efficient therapeutic options are not standardized yet. In Romania there is a routine clinical practice to offer screening for most common causes of infections, including CMV, in the first trimester of pregnancy.

In these settings, this review summarizes the current methods of diagnosis and management of CMV infection in pregnancy.

Keywords: perinatal infection, ultrasound cerebral signs, invasive testing, seroconversion, congenital CMV, primary maternal CMV.

INTRODUCTION

Cytomegalovirus (CMV) is the most common cause of perinatal viral infection, affecting 0.2-2.2% of all neonates, with variation among different study populations (1, 2). It is the leading cause of non-genetic congenital hearing loss (3). Cytomegalovirus is a double-stranded DNA virus within the family of herpesvirus. The most common pathway of infection is through direct contact with a person excreting the virus in the saliva, urine or body fluids. For pregnant women, the main source is *via* small children in the family. Rarely, the virus can be transmitted *via* sexual exposure, transplanted organs or blood transfusion.

With different rates of maternal-fetal transmission and different approaches (4), it is important to distinguish between a primary and non-primary infection during pregnancy, which comprises reactivation of the latent CMV or reinfection with a different strain.

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Primary infection is the first exposure to the virus and 1-4% of seronegative women will acquire it during pregnancy (5). The clinical diagnosis is unreliable because 90% of infected women will be asymptomatic. When present, clinical symptoms such as fever, rhinitis, headaches, arthralgia, myalgia are not specific (6). Serological diagnosis of primary infection during pregnancy can be difficult, especially when the serological status of pregnant women at the beginning of pregnancy or before conception is unknown. Diagnosis based on immunoglobulin (Ig)M is not reliable, as IgM can either persist even one year after the primary CMV infection or become positive after reinfection or reactivation. Seroconversion documented during pregnancy can establish the diagnosis of primary infection. The appearance of CMV-specific IgG in a previously seronegative woman for 3-4 weeks after an acute episode indicates the diagnosis. CMV-specific IgG avidity may assist in timing the infection. High avidity (more than 60%) suggests past infection, more than 3-6 months, while low avidity suggests a recent infection within the last three months (7). Positive IgG and IgM levels should always be accompanied by IgG avidity determination and, if necessary, by real time PCR for CMV in blood or urine, in order to establish the diagnosis of maternal primary infection.

Primary infection

The risk of congenital infection is highest following primary maternal infection and varies between 30% in the first trimester and up to 70% in the late third trimester of pregnancy (6, 8, 9). Although vertical transmission from mother to fetus results in congenital infection, 80-90% of infected fetuses will be asymptomatic at birth (10). While the risk of maternal-fetal transmission increases with gestation, the risk for symptomatic congenital infection decreases from 20-30% in the first trimester to 9% in the second trimester (6). It has been reported that severe congenital infection with neurological sequelae was encountered following maternal primary infection acquired in the first trimester. Neonates with symptomatic congenital infection can present at birth petechiae, jaundice, hepatosplenomegaly, microcephaly, ventriculomegaly, growth retardation, or chorioretinitis (10). Paraclinical tests can show increased transaminases, conjugated bilirubinemia, and thrombocytopenia. Approximately 40% of neonates with symptomatic congenital infection will develop long term neurological sequelae such as sensorineural hearing disorder, mental retardation or psychomotor impairment (11). Also, asymptomatic congenital infection is not completely benign; so, about 8-15% of these children will develop late complications during the first two years of life, with hearing disorder being the most common (12, 13).

Non-primary infection

Although the greatest risk for congenital infection is seen following primary maternal infection, at populational level the absolute number of affected neonates results from mothers with secondary infection (reactivation of a latent virus or reinfection with a different strain) (14).

In case of secondary infection, maternal-fetal transmission will occur in only 2%, comparing to 40% after a primary infection (10). Less than 1% of neonates born from mothers with recurrent infection will be symptomatic at birth and 8% of infected neonates will develop long term neurological sequelae, mostly hearing loss (10, 15).

Diagnosis of secondary infection can be difficult. An increase in IgG titre is not reliable and invasive testing is the only way to confirm the diagnosis.

Diagnosis of fetal CMV infection

Amniocentesis with PCR analysis is considered the gold standard test for maternal-fetal transmission. At a greater risk, cordocentesis has similar sensitivity and specificity and allows additional paraclinical evaluation that could improve the prediction of neonatal outcome.

In order to achieve an accurate result, it is recommended to perform the invasive testing (that is, amniocentesis) at six weeks following primary infection and after 21 weeks' gestation. While a positive result obtained before 20 weeks confirms the infection, a negative result has a high false negative rate and requires a second testing after 21 weeks' gestation (16). A negative PCR result at either 21 weeks or six weeks post-infection has a specificity between 97% to100% (16, 17).

Documentation of fetal infection by amniocentesis is not equivalent with symptomatic infection at birth, and prenatal prediction of prognosis for affected fetuses is challenging and generally

based on timing of maternal infection, presence of ultrasound markers of fetal infection and paraclinical changes (18).

Ultrasound imaging

Ultrasound changes alone are not a diagnostic test for congenital CMV infection and predict symptomatic infection in only a third of cases (19). Additionally, ultrasound findings are seen in less than 50% of affected fetuses (19). This aspect might be an issue in the setting of current guidelines to indicate the screening for CMV only for cases with clinical suspicion of CMV infection. Contrary, a fetus with confirmed CMV infection following an invasive test and associating ultrasound changes, especially cerebral signs, might be at increased risk of long- term neurological consequences.

Although there are no pathognomonic signs of CMV infection, the common ultrasound findings which can rise the suspicion of fetal infection are classified into CNS signs and extracerebral signs. The proposed classification by Leruez-Ville *et al*. is presented in Table 1 (18).

Sonographic signs are seen in Figures 1 and 2.

The main sonographic prognostic indicator is fetal cerebral abnormalities (Figure 1), with ventriculomegaly being the most common one (19). Among extracerebral signs as consequence of the affinity of the virus to endothelial and epithelial cells, hyperechogenic bowel is reported to be the most common finding. Ultrasound changes at the time of diagnosis by amniocentesis are of great value in counselling and consecutive management of pregnancy. In some cases, brain lesions are progressive and severe signs will become apparent later in the third trimester. Around 7% of cases with a positive amniocentesis at 23 weeks and normal ultrasound examination or with non-severe findings might progress to a severe brain abnormality later during pregnancy, which is important in patient counselling when deciding to continue or terminate the pregnancy (18).

In an attempt to improve the prediction of adverse outcome following confirmed fetal infection, recent studies investigated the value of paraclinical tests such as platelet concentration in combination with the viral load in fetal blood. Both in univariate and bivariate analysis, ultrasound signs, viral load in amniotic fluid and fetal platelet count were independent predictors of symptomatic infection at birth or at the time of termination of pregnancy (18). Paraclinical examination improved the predictive value achieved by ultrasound findings alone. In case of platelet count less than 114.000/mm^3 or viral load in amniotic fluid above 4.93 log10 IU/mL, more than 50% of neonates will present symptomatic infection at birth (18).

Fetal magnetic resonance imaging (MRI) may be considered at 32 weeks as a complementary evaluation in case of inconclusive ultrasound examination. If there are clear ultrasound abnormalities, additional value of fetal MRI is limited. When both evaluations are normal, the neonatal prognosis is generally considered to be favourable (20).

Prevention and treatment

Currently there are no efficient therapies available for the treatment of maternal or fetal CMV infection. Aiming to prevent maternal infection or

CNS signs		Extracerebral signs
Severe abnormalities	**Mild abnormalities**	
Ventriculomegaly ≥15 mm	Ventriculomegaly 10-15 mm	Hyperechogenic bowel
Periventricular hyperechogenicity	Intraventricular adhesions	Hepatomegaly (≥ 40 mm)
	Intracerebral calcifications	Splenomegaly (≥ 40 mm)
Hydrocephalus	Subependymal cysts	Growth restriction <5th centile
Microcephaly	Choroid plexus cysts	Oligohydramnios
Mega cisterna magna ≥ 8 mm	Calcifications of lenticulostriate vessels in basal ganglia	Polyhydramnios
Vermian hypoplasia		Ascites, pleural effusion, hydrops
Porencephaly		Placentomegaly
Lissencephaly		Intrahepatic calcification

TABLE 1. Ultrasound abnormalities related to CMV infection (18)

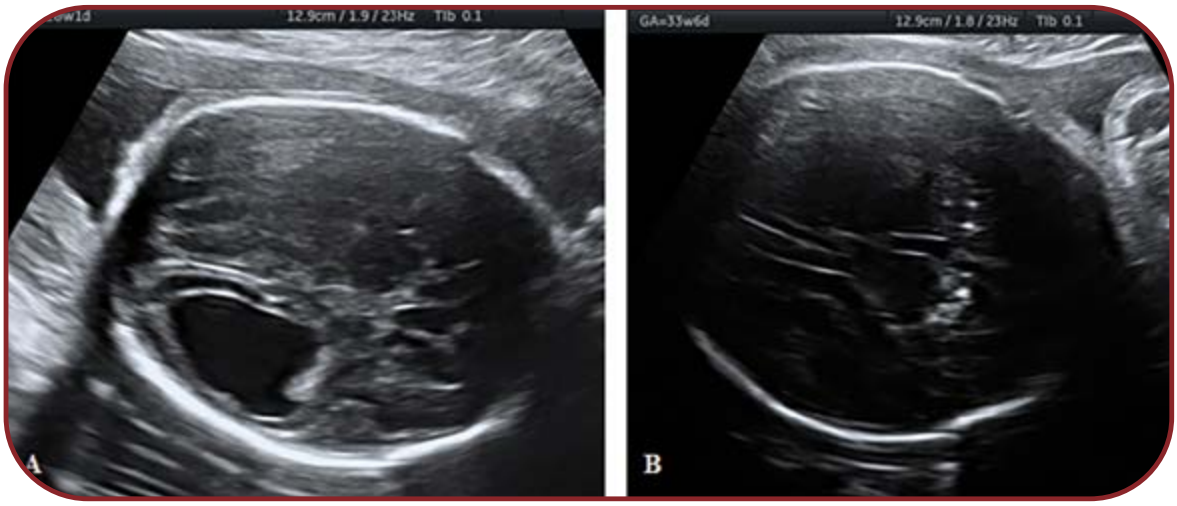

FIGURE 1. A) Severe ventriculomegaly (arrow); B) brain calcification bilaterally (arrows)

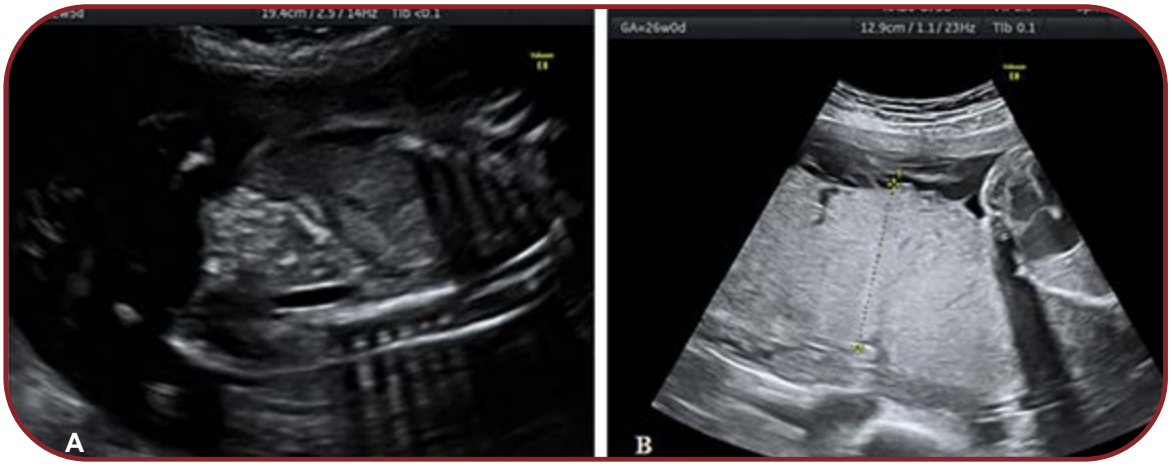

FIGURE 2. Extracerebral findings. A) Hyperechogenic bowel (arrow); ascites; B) placentomegaly, oligohydramnios

transmission and reduce the severity of clinical implication in case of vertical transmission to fetus during pregnancy, promising medical alternatives are subject of current research studies.

Hygienic measures remain the most efficient way to prevent a maternal CMV infection during pregnancy. A CMV vaccine for primary prevention has been tested in a phase II trial, but has not been approved by FDA for clinical use due to its limited efficacy of only 50%, similarly with simple hygienic measures (21).

The next level of prevention is concerning mother-fetal vertical transmission, once the primary maternal infection has been detected in the first trimester. Passive immunization with CMV-specific hyperimmune globulin (HIG) is currently under investigation as a potential means of preventing congenital CMV infection. Initial results of a non-randomised study showed a lower rate of congenital infection following HIG administration (16% vs 40%) (22). These promising results have not been proved to be statistically significant in the first randomised study by Ravelo *et al*, with 30% transmission rate in the treatment group and 40% in the control group (23). Later, the study has been criticized in terms of power calculation and interval of HIG administration and a two-week rhythm has been proposed. Recently, a prospective observational study on 40 pregnant women with primary CMV infection reported that the transmission rate following HIG administration every two weeks, starting from 14 weeks until 20 weeks, has been reduced to 7% and none of the neonates were symptomatic at birth (24).

Finally, once fetal transmission has occurred, several attempts have been made to reduce the risk of long-term sequelae and neurological impairment. HIG may still be considered for preven-

tion of a symptomatic infection at birth. Non-randomised studies on a limited number of cases reported a reduction from 43% to 13% (25). Alternatively, although not standardized, antiviral therapy may represent an option. A phase II open label trial reported that oral valaciclovir 8 g/day (16 pills/day) improved the outcome of moderately symptomatic infected fetuses and increased the rate of asymptomatic infection at birth (82% with treatment versus 43% without treatment) (26). Antiviral therapy can be continued postpartum, and intravenous ganciclovir administered for six weeks can improve cognitive development (27, 28). ❑

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