

Cytomegalovirus infection in pregnancy

Infecção pelo citomegalovírus na gestação

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ABSTRACT

Congenital cytomegalovirus (CMV) infection is the leading cause of infectious congenital defects and disabilities. Its transmission can occur in primary and non-primary infections; however the transmission rate is considerably higher in primary infections. The diagnosis of congenital infection is complex, and there is a discussion concerning serological evaluation during pregnancy. This article aims to review the literature concerning CMV infection, its diagnosis and epidemiology.

Key words: pregnancy; cytomegalovirus; cytomegalovirus infections.

INTRODUCTION

Cytomegalovirus (CMV) is widely distributed among humans. As other viruses of the *Herpesviridae* family, it causes a primary infection and then remains latent in the body. Despite causing a usually harmless primary infection, CMV can be life-threatening for immunocompromised patients and can cause serious fetal damages. Hence, infection in pregnant women assumes high importance^(1,2).

Congenital CMV infection is the main cause of infectious congenital defects and disabilities, being the most frequent congenital infection in the United States^(3,4). The infection can be asymptomatic or cause severe hearing loss, microcephaly, hydrocephaly and neurological impairments^(5,6). Pregnant women can transmit the virus to the fetus in case of either a primary infection, a reactivation of a latent infection or a secondary infection⁽⁷⁾. Whereas a non-primary infection shows a rate of vertical transmission of 1%⁽⁸⁾, a primary infection has a rate of 30%-40%⁽⁹⁾.

CMV is a ubiquitous virus and its infection occurs mainly in childhood in most populations⁽¹⁰⁾. Its seroprevalence among women in reproductive age varies according to country and other epidemiological factors, with rates ranging from 40%^(11,12) in developed countries to over 90%^(10,13,14) in developing countries.

Even though cytomegalovirus infection does not have a cure and there is no vaccine available for it, the diagnosis of the

infection is important to guide the correct treatment and to enable the early detection of any sequelae.

PATHOGENESIS

CMV, also known as human herpesvirus 5 (HHV-5), belongs to the *Herpesviridae* family and is a double-stranded deoxyribonucleic acid (DNA) enveloped virus^(15,16). It is capable of infecting most of the body cells and acting in the cytoplasm and the nucleus of the infected cells, forming inclusions⁽¹⁶⁻¹⁸⁾.

CMV presents the capacity to evade the immune system⁽¹⁶⁾ and, through that mechanism, it remains latent in the body. When the host faces a situation of immunosuppression (such as pregnancy, chemotherapy, acquired immunodeficiency syndrome [Aids], amongst others)⁽¹⁹⁾, the virus can reactivate from latency and infected cells shed infectious virus.

The primary infection is often silent or subclinical, and during the period of an infection (primary or secondary), the host excretes viral particles in urine, blood, semen and saliva. Therefore, people can be easily infected (including pregnant women) by person-to-person contact, sexual contact or taking care of young infected children⁽¹⁵⁾.

Vertical transmission can either occur after a primary or a secondary infection. In both situations, the fetal infection

may occur after infected leucocytes reach the fetus through the placenta. Moreover, CMV can infect the placenta itself creating a contamination in the amniotic fluid, which is then swallowed by the fetus⁽²⁰⁾.

SCREENING AND DIAGNOSIS OF CONGENITAL INFECTION

Although the detection of maternal anti-CMV antibodies is easy to perform, there is still no consensus about serological screening during pregnancy⁽²¹⁾. While some European and Asian countries recommend it, in other countries, such as Brazil, the screening of CMV is not mandatory⁽²²⁾.

As the primary infection is commonly subclinical, it is hard to determine its outset. Normally, positive immunoglobulin class M (IgM) antibodies indicate an acute and recent infection, whereas positive immunoglobulin class G (IgG) antibodies indicate a past infection.

Furthermore, IgM can remain positive for several months making it difficult to establish the time of infection⁽²³⁾. IgM can also reappear in case of a secondary infection, a reactivation of a past infection, or in consequence of cross-reactivity to other viroses⁽²⁴⁾.

In cases with a dubious diagnosis, it is recommended to perform an IgG avidity assay. This test shows the strength with which the antibody binds to the antigen⁽²⁵⁾. At the beginning of infection, the produced IgG shows a low avidity for the virus that increases within weeks after exposure to the antigen. Thus, acute and recently produced IgG molecules show low avidity (below 35%), whereas in past infections IgG presents high avidity (above 60%)^(26, 27). Unfortunately there is still an area of uncertainty, when avidity falls into a gray zone (between 35% and 60%). Follow-up samples should be requested in order to better define the level of avidity, as it is a dynamic process and avidity values can change in three to four weeks. Therefore, the IgG avidity assay is very useful to determine the time of infection and may help to avoid unnecessary worries.

Serological evaluation is also important to identify seronegative pregnant women in order to prevent seroconversion. Although there is no vaccine available to prevent CMV infection, simple measures (such as hand washing after contact with saliva or urine, and avoiding to share glasses and cutlery amongst others)^(25, 28) are proven to be effective in order to minimize virus transmission.

Fetal infection is usually diagnosed after ultrasound abnormalities are seen or after maternal infection is confirmed.

The gold standard method for fetal infection diagnosis is the detection of viral DNA by polymerase chain reaction (PCR) of the amniotic fluid. However, amniocentesis is an invasive procedure and can only be performed after 18 weeks of gestation and 6-8 weeks after seroconversion, time it takes the fetus to excrete the virus through the urine^(24, 29).

It is important to note that virus detection alone in the amniotic fluid does not determine whether the fetus is going to show signs of infection. Following up with ultrasounds is important to observe if there are any central nervous system abnormalities. After delivery, otologic evaluation is necessary to investigate hearing impairment, which is the most common sequela of CMV.

TREATMENT

The treatment of congenital infections is complex and controversial. Available antiviral drugs, such as ganciclovir, cidofovir and foscarnet, are commonly used in immunocompromised patients, but their toxicity (especially renal and hematological) and teratogenic effects restrict their use during pregnancy⁽²⁴⁾.

Recently, a pilot study performed in France assessed the pharmacological efficacy of oral valgacyclovir in cases of congenital infection. The drug was able to reach therapeutic levels in both maternal and fetal blood and also had effect on the viral load in fetal blood⁽³⁰⁾. Although the study aim was not to evaluate therapeutic effects, its results are encouraging.

An Italian study analyzed the efficacy of a treatment with CMV hyperimmune globulin for maternal primary CMV infection showing promising results for prevention and treatment of congenital infection with no signs of side effects^(24, 31). The study has also shown that hyperimmune globulin has immunomodulatory effects that can decrease the pathogenic effects of CMV⁽³¹⁾.

In spite of those evidences, more controlled trials with larger number of patients are needed to properly evaluate treatment in this scenery.

EPIDEMIOLOGY

Although CMV is widely distributed, CMV epidemiology is diverse. As its transmission is deeply related to low sanitarian conditions and high population density, higher seroprevalence is expected to be found in developing countries⁽³²⁾.

A German study carried out in 1996-2010 showed a 42.3%⁽³³⁾ seroprevalence among pregnant women. In the United States a seroprevalence of 50% has been reported in the general population⁽¹²⁾. Following the same trend, a study with pregnant women in France reported an overall seroprevalence of 51.5%⁽³⁴⁾.

Concerning the low income countries, overall seroprevalence is higher than that found in developed countries. A cross-sectional study conducted in Iran found 97.7% seropositivity⁽³⁵⁾. A similar rate was found in Turkey, where a retrospective observational study showed 94.9% seropositivity⁽³⁶⁾.

When women's origin was taken into consideration, seroprevalence among pregnant women of low socioeconomic level was 95%; among pregnant students, 69.9%, according to a cross-sectional study undertaken in Chile⁽³⁷⁾. Those findings are similar to what is found in Brazil, where a study conducted with low- and medium-income pregnant women showed seroprevalence of 92.9%⁽¹⁰⁾. Controversially, a study among high-income pregnant women in Brazil showed a seroprevalence of 84%⁽³⁸⁾. Two other studies performed in Brazil in different demographic regions demonstrated seroprevalences of 75.1%⁽³⁹⁾ and 76.6%⁽⁴⁰⁾ among pregnant women, highlighting the variety of seroprevalence that may be found in the country.

It is also important to emphasize that in a same country one may find great differences in seroprevalence depending on socioeconomic status, ethnicity and geographical region. For instance: two studies performed in Japan reported CMV

seroprevalences of 66%⁽⁴¹⁾ and 87.3%⁽⁴²⁾. Such disparity shows how complex CMV epidemiology can be. Accordingly, an Italian study also correlated socioeconomic status and seroprevalence, showing that seroprevalence was 62.5% in non-immigrant women, while in immigrant women it was 91.4%⁽¹⁴⁾.

FINAL CONSIDERATIONS

Since CMV is present everywhere, people are normally exposed to the virus, what increases the risk of primary infections in pregnancy when women are seronegative. In countries where seroprevalence is high, secondary infection and reactivation can still occur.

Despite being controversial, the screening of CMV during pregnancy can be effective in order to implement preventive measures or diagnosis of fetal infection. In those cases, diagnosis is important to perform the correct treatment and follow-up of the infected child. Moreover, recent researches have shown promising results concerning treatment and prevention, what enhances the importance of diagnosis.

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RESUMO

A infecção congênita pelo citomegalovírus (CMV) é a principal causa de deficiências congênitas infecciosas. Sua transmissão pode ocorrer em infecções primárias (cuja taxa de transmissão é consideravelmente mais alta) e não primárias. O diagnóstico da infecção congênita é complexo e existe controvérsia sobre a avaliação sorológica durante a gravidez. Este artigo tem como objetivo revisar a literatura acerca da infecção por CMV, seu diagnóstico e sua epidemiologia.

Unitermos: gestantes; citomegalovírus; infecções por citomegalovírus.

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