

Clinical manifestations

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ABSTRACT

Cytomegalovirus (CMV) is the main infectious virus that leads to neurological disabilities in children such as congenital sensorineural deafness. Transmission of the virus can happen through direct contact with body fluids, saliva, urine, and blood products. Congenital infections are the result of transplacental transmission of CMV. In utero, transmission occurs in about one third of women who develop primary infection in the first trimester.

The first step for the diagnosis of infection is the laboratory confirmation, where conversion of CMV IgG antibody from negative to positive is the first thing that raises the suspicion of infection. If both IgG and IgM antibody to CMV are positive when first tested, the next step is testing for avidity of CMV IgG antibody. Low IgG antibody avidity and presence of IgM antibody is strong evidence of recent primary infection.

At present, there is no vaccine available against CMV and treatment options for pregnant women are still developing. It has been shown that in attempt to reduce the rate of primary maternal CMV infections, public health strategies based on sanitary measures can have a real impact.

Keywords: cytomegalovirus, pregnancy, infection, avidity, congenital, prevention, primary infection, amniocentesis

INTRODUCTION

Cytomegalovirus (CMV) is a part of the Herpesviridae family of viruses, which covers herpes simplex virus type 1 and 2, varicella zoster virus, Epstein-Barr virus, Roseola virus, and Kaposi's sarcoma-associated herpesvirus. It affects up to 1-2% of all live births, higher rates are seen in low-income populations, being the leading non-genetic cause of sensorineural hearing loss (SNHL) and neurological disability [1].

CMV spreads from person-to-person through body fluids such as blood, urine, saliva, semen and breast milk. Especially infants and toddlers shed high amounts of virus for months or even years and represent a substantial risk for transmitting the virus to pregnant women by saliva or urine [1].

In utero infection occurs through transplacental transmission in about one third of women with primary infection in the first trimester, being associated with more severe symptoms of congenital infection and worse neurological outcomes, compared to primary maternal CMV infection later in pregnancy [2].

During pregnancy, CMV infection can occur as a primary maternal infection, as a reactivation of a pre-existing latent CMV strain, or reinfection with a new viral strain.

Prevalence of CMV infection is approximately around 1-2% of all live births, and although the majority of infants with congenital CMV infection are normal at birth and survive without sequelae, around 15% will have damage to hearing, vision, cognition, with large variation in the severity of impairments [2,3].

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Currently, there is no CMV vaccine available, and pharmacological interventions are offered as a research protocol treatment, but there is evidence that is still growing in favor of antenatal treatment during pregnancy [4-6].

At the higher risk for primary infection are pregnant women caring for other children. Health education measures play an important role in trying to prevent primary CMV infection [2].

MATERIAL AND METHODS

We identified data in published literature, using the following search strategy (CMV, cytomegalovirus) and (pregnancy) or (infection) or (congenital). Moreover, we used recommendations from WHO (World Health Organization) and CDC (Center for Disease Control and Prevention), as well as online policies from medical societies, randomized control trials and observational studies.

EPIDEMIOLOGY

On average, the prevalence of congenital CMV infection it has been reported of 0.65% (varies from 0.2% up to 2% in countries with higher maternal seroprevalence). More than 40% up to 100% of individuals are infected with CMV throughout their lives, seroprevalence being higher in low socio-economic groups [3,4].

Behavioral interventions and avoiding intimate contacts with young children could reduce CMV seroconversion in pregnant women, hypothesis raised by two studies in USA and one in French [6].

Primary infection is defined by infection with CMV for the first time in pregnancy, while secondary infection is given either by a reactivation of prior CMV infection or by a new infection with a different strain of the virus. A metanalysis by Kenyon et al. revealed a transmission rate of 32% in primary maternal infection and a transmission rate of 1.4% in recurrent maternal infection [5].

A study was conducted in Italy to explore the usefulness of hygiene knowledge among pregnant women at risk for primary CMV infection. It made comparison between two groups of pregnant women, first group (intervention group) with CMV-seronegative pregnant women, who were given information about hygiene and were tested for CMV until giving birth, and the second group (comparison group) composed of women registered at delivery who were never informed about CMV during pregnancy neither tested. The results of the study showed that 1.2% of women (4/331) in the intervention group seroconverted, and there were 3 newborns with congenital infection, whilst in the comparison group 7.6 % (24/315) with 8 newborns

affected. Of all women enrolled 93% said hygiene recommendations worth to be told to all pregnant women [6].

CLINICAL MANIFESTATIONS

In immunocompetent people, infection with CMV is usually asymptomatic, although primary infection can include a mild mononucleosis or flu-like syndrome, occasionally associated with persistent fever, fatigue and lymph node swelling. Laboratory findings are non-specific and could show lymphocytosis and elevated liver transaminase levels [4-7].

CONGENITAL CMV TRANSMISSION

Transmission of CMV from mother to child (vertical transmission) can occur *in utero*, intrapartum, or during breastfeeding. Intrauterine transmission is thought to be the result of transplacental crossing of virus, which then replicates in multiple embryonic or fetal tissues [4].

Congenital CMV is the prime cause of non-hereditary sensorineural hearing loss, also can cause fetal death *in utero*, neonatal death, intrauterine growth restriction, preterm birth and maternal pregnancy complications, including preeclampsia.

Even though most newborns appear asymptomatic at birth, neurological sequelae may develop after months or even years after [5]. Of all newborns with congenital CMV infection 10% will have symptoms like low birth weight, rash, intrauterine growth restriction, seizure, hepatosplenomegaly and about 40% up to 60% of these newborns will have long term health problems such as hearing loss, intellectual disability, seizure [8].

DIAGNOSIS

Although American College of Obstetricians and Gynecologists (ACOG) recommendations are that every pregnant woman should be educated about CMV infection, they have not approved routine screening in pregnancy, but for women that are planning to get pregnant, routine CMV screening can help them to understand how careful they must be to prevent infection [9].

Less than 25% of pregnant women with primary infection are reported to be symptomatic and most CMV infections are asymptomatic even during the acute stage.

Diagnosis of primary infection is based on IgG antibody seroconversion or positive IgM. However, reactive CMV IgM antibodies may be detected upon both primary and non-primary infections and may persist for months or even years in some women. Additional for detection of reactive CMV-specific IgM, the avidity of CMV IgG antibodies should be determined [7]. Pregnant women with primary infec-

tion have low avidity between 0- and 3-months post-infection, intermediate avidity between 4 and 5 months, and high avidity by month 6 [10,11].

Fetal diagnosis

A common indication for testing for CMV is fetal abnormalities seen on ultrasound (US). There are a few things seen on ultrasound that can indicate a possible infection with CMV, as hyperechogenic bowels, ascites, growth restriction with an estimated fetal weight below 10th percentile, ventriculomegaly and any other brain anomaly [11].

Laboratory findings are non-specific and sometimes can show fetal elevated GGT and fetal platelet count < 100,000/ul.

A study was published on February 2017, at Emory University in Georgia, comparing US alone as a diagnostic tool and the combination of ultrasound and laboratory findings (fetal thrombocytopenia) at the time of prenatal diagnosis. The results were 79% positive predictive value and 91% non-predictive value (NPV) in predicting any symptoms at birth or at the termination of pregnancy, while US alone reached 93% NPV, similar to those of US and magnetic resonance imaging executed during the third trimester [12].

Magnetic resonance imaging (MRI) is recommended when fetal intracranial abnormalities are detected by ultrasound and should be performed during the third trimester. Severe outcomes for infected fetuses are excluded by negative MRI findings, concomitant with negative US results [12].

More studies show the role of CMV cell mediated immunities (CMIs). A study made on rhesus macaque primates showed that CD4⁺ T-cell depletion in infected pregnant rhesus macaques led to more severe outcomes compared with those of immunocompetent pregnant primates, thus suggesting a protective role of CD4⁺ T cell. In a study of a cohort of 80 pregnant women with active CMV infections, researchers showed that pregnant women with primary infections had significantly higher CMV T-cell immune responses compared with those with nonprimary infections. Additionally, the maternal CMV-specific T-cell immunity positively correlated with congenital transmission in primary-infected case [13].

In a recent study published on March 2021, in the Department of Obstetrics and Fetal Medicine, Hospital Necker, Paris, it was analyzed the viability of amplification of the viral genome by polymerase chain reaction (PCR) analysis of trophoblast samples obtained by chorionic villus sampling (CVS). This study was carried out between October 2019 and October 2020 following CMV serology screening in early pregnancy. CVS was performed in 37 pregnancies, between 11- and 14-weeks gestational

age, resulting that CMV-PCR in chorionic villi was positive in three and negative in 34 cases. CMV-PCR following amniocentesis, performed at a median gestational age of 17.6, was positive for the three cases which were positive following CVS and of the 34 patients with a negative finding following CVS, amniocentesis was negative in 31 and positive in three. An important thing to mention is that all cases underwent secondary prevention with Valacyclovir as soon as maternal primary infection with CMV was diagnosed [14].

TREATMENT

Currently there is no accepted or recommended treatment to prevent fetal infection after maternal primary infection, but options are still evolving, and for now recommendations for antenatal therapy should only be proposed as part of a research study [14].

When infection with CMV is confirmed by amniocentesis or by fetal growth restriction and structural abnormalities, mostly brain abnormalities, serial ultrasounds are recommended during pregnancy.

In a study in 2007, made by a group of French medical doctors, observational data was brought about the utility of using Valacyclovir at a high-dose for fetuses with congenital CMV infection. Study included 20 pregnant women with 21 fetuses, and management involved collection of a blood sampling at the time of diagnose, and between 4 and 6 weeks later, to establish the platelet count and gamma-glutamyl transpeptidase plasma concentration in the beginning and their variations in time. Biomarkers of a symptomatic fetal infection were believed to be fetal thrombocytopenia (under 100,000/dl) and/or raised levels of gamma-glutamyl transpeptidase. Therapeutic concentration of the drug was achieved in both maternal and fetal blood, and a decrease of viral load in fetal blood was associated with better end-result. Comparing with a group of 24 pregnancies with symptomatic intrauterine CMV infection, no distinction regarding poor results was noticed, before Valacyclovir treatment was proposed or refused [15].

Years later, the same research group studied afterwards oral Valacyclovir 8 g/day in a trial named "In Utero Treatment of Cytomegalovirus Congenital Infection with Valacyclovir". Administration of Valacyclovir was associated with an importantly proportion of neonates born asymptomatic, enhancing the outcome of the fetuses. This study was the first one that has managed to show the performance of an antiviral drug on treating cytomegalovirus-infected fetuses, even though is not a randomized controlled trial [16].

In a randomized placebo-controlled study, was described the efficacy of hyperimmunoglobulin (HIG) to prevent maternal-fetal transmission, at a dose of 100 IU/kg following every 4 weeks after primary maternal infection, but only a reduced rate of congenital infection of the newborns was noted in the treatment group, and this was not significantly lower than that in the placebo-control group. Furthermore, in the HIG group the number of obstetric side-effects was above the ones in the placebo group [17].

In another multicentric Spanish study was established that the rate of the congenital infection was not affected in pregnant women that followed CMV-specific HIG treatment for primary CMV infection. Nevertheless, a recent non-randomized study admits that biweekly up to 20 weeks of pregnancy, using a dose of 200 UI/kg CMV-specific HIG, can prevent maternal-fetal transmission. This information that are strikingly different need to be further investigated [15-17].

MANAGEMENT OF INTRAUTERINE CMV INFECTION

Intrauterine CMV infection remains one of the most frequent non-genetic cause of severe malformation in the newborn, and a significant global health concern.

The most extensively used procedure for screening of infection with CMV in pregnant woman remains testing for anti-CMV IgM antibodies, but this only can be a starting point in further advanced diagnostic investigation, such as anti-CMV IgG avidity testing. CMV IgG avidity testing has emerged as a powerful tool for distinguishing primary from past CMV infection and has been successfully utilized in a variety of clinical settings [18].

Considering there is growing consensus that first-trimester maternal infection is the sole source of fetal CMV infection and related to neurological impairment and hearing loss and that a high viremia is responsible for both syncytiotrophoblast and cytotrophoblast viral invasion, the diagnosis of

CMV fetal infection through CVS at a median of 13 weeks of pregnancy and the Valaciclovir antiviral treatment can be important tools in the management of the disease and can have a real impact in society.

Both the CMV vaccine and antiviral medication for pregnant women are still under development, and recent studies have concentrated on passive immunization of pregnant women with CMV infection with hyperimmune globulin to reduce the rate of vertical CMV transmission, but they still need further investigation [7].

Congenital cytomegalovirus is the leading infectious cause of childhood hearing loss and brain damage worldwide. Guidelines recommends discussing education and hygiene measures to prevent CMV infection with all patients, regardless of serologic status, before conception and through pregnancy [18].

CONCLUSIONS

It has been shown that women who contract primary CMV infection after conception are at higher risk of intrauterine transmission of cytomegalovirus than the ones that had proof of infection before conception. Studies show that CMV IgG avidity measurement can determine if we are dealing with a recent primary infection, and consequently with a higher risk for vertical transmission of the virus.

Amniocentesis and detection of CMV DNA with qPCR is now the gold standard for diagnosis of fetal infection, although several studies show the importance of chorionic villus sampling.

At present, infection with CMV during pregnancy has no approved treatment, and pharmacological interventions are offered as a research protocol treatment in different studies, although there is important evidence of the use of Valaciclovir.

Until an effective therapy is available, education of women regarding hygiene measures that can help prevent CMV transmission is the best preventive strategy for CMV.

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