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(REVIEW ARTICLE)

Congenital cytomegalovirus infection: A narrative review

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Abstract

Cytomegalovirus (CMV) infection poses significant health risks, particularly for vulnerable populations including fetuses infected in utero, premature infants, and immunocompromised individuals. CMV infection is the most prevalent cause of congenital infection, affecting approximately 0.5% to 2% of all live births worldwide. Congenital transmission during pregnancy is a major concern, with a variety of fetal and neonatal outcomes ranging from asymptomatic infection to severe abnormalities, including sensorineural hearing loss, visual impairment, various neurological sequelae, growth retardation and potentially fatal consequences. Congenital transmission of CMV from mother to fetus can occur through primary infection, or reactivation of a previous infection. Diagnosis involves imaging techniques and invasive procedures to detect CMV DNA. Antiviral medications have limited data for use during pregnancy, while ganciclovir or valganciclovir demonstrates potential benefits in neonates with symptomatic disease. Routine antenatal screening is not yet recommended, but serological testing may be warranted in specific circumstances. Preventive measures focus on simple hygiene practices. Childbirth and breastfeeding present potential risks of CMV transmission, highlighting the importance of close monitoring and informed decision-making. This narrative review aims to provide a comprehensive summary of the epidemiology, transmission patterns, clinical manifestations, diagnostic approaches, treatment modalities, screening methods, preventive measures, and breastfeeding considerations related to CMV infection. This knowledge is essential for healthcare professionals to effectively manage CMV infection and improve outcomes for affected individuals and their families.

Keywords: Cytomegalovirus; Congenital Infection; Perinatal Infection; Epidemiology; Transmission; Clinical Manifestations; Diagnosis; Treatment; Prevention; Breastfeeding

1. Introduction

Cytomegalovirus (CMV), a member of the beta-herpesvirus family [1], is a widespread pathogen known for its ability to establish lifelong latent infections in humans. This ubiquitous virus, classified as the fifth human herpesvirus [2], poses significant health risks, particularly for certain populations, such as fetuses infected in utero, very low birth weight and premature infants, and immunocompromised individuals.

CMV, characterized by its double-stranded DNA structure, exhibits a unique lifecycle within the host. After initial infection, typically acquired through close contact with body fluids such as saliva or urine, the virus establishes a latent state within specific cells of the host's immune system, including monocytes and macrophages [3]. While the immune response can control active viral replication, the virus remains latent, ready for reactivation under conditions of immunosuppression or other triggers [4].

Among women of childbearing age, CMV is of particular concern due to the risk of congenital transmission during pregnancy. In developed countries, CMV infection during pregnancy is relatively common [1], with a range of potential

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fetal outcomes. These outcomes vary widely, from asymptomatic infection to the development of severe fetal abnormalities affecting multiple organ systems [1,4]. Notably, congenital CMV infection is recognized as the most common viral cause of congenital disability worldwide, with profound implications for long-term health outcomes [4]. One of the most important consequences of congenital CMV infection is sensorineural hearing loss, which can occur either at birth or later in childhood. This hearing impairment, often irreversible and progressive, significantly affects the language development and overall quality of life of affected individuals [5]. Additionally, CMV infection can lead to various neurological sequelae, including brain damage and developmental delay, further highlighting the importance of identifying and treating this disseminated viral infection [4,5].

CMV is a multifaceted pathogen with significant clinical implications, particularly with regard to pregnancy and congenital transmission. Given its impact on public health, there is an ongoing need for robust efforts to prevent and treat CMV infection, with the aim of minimizing associated morbidity and improving outcomes for affected individuals and their families. This narrative review aims to provide a comprehensive summary of the epidemiology, transmission patterns, clinical manifestations, diagnostic approaches, treatment modalities, prenatal screening methods, preventive measures, and breastfeeding considerations related to CMV infection.

2. Epidemiology

Epidemiological evidence suggests a widespread prevalence of CMV infection seroprevalence, particularly notable in developed countries, where up to 70% of the population has been exposed to the virus [3]. In the United States, a significant proportion of more than 50% of adults up to the age of 40 have experienced CMV infection [6]. The situation is even more prevalent in developing countries, where more than 90% of individuals are infected with CMV [3]. In particular, among women of childbearing age worldwide, the prevalence of CMV infection seroprevalence is estimated to be approximately 86% [2,7].

Despite the high prevalence of CMV infection, the incidence of congenital CMV infection, characterized by the transmission of the virus from mother to fetus during pregnancy, varies geographically. Reported prevalence rates of congenital CMV infection range from approximately 0.5% to 2% of live births worldwide [7]. In the United States, the proportion of neonates born with congenital CMV ranges from 0.6% to 6.1% [3]. This corresponds to roughly 1 in every 200 neonates, equating to approximately 30,000 neonates affected annually in the USA alone. Conversely, in Europe, the estimated prevalence of congenital CMV infection is lower, ranging from about 0.5 to 1% per year [2]. In developing countries, documented prevalence rates of congenital CMV infection exhibit significant variation, both intra- and internationally, with reported rates reaching as high as 6–14% [8].

The high incidence of congenital CMV infection stems from the maternal ability to transmit the virus to the fetus, either through primary infection during pregnancy or reactivation of a latent infection [9,10]. The likelihood of transmission varies based on the gestational age and nature of the infection. Although only a small proportion of pregnant women experience primary CMV infection during gestation, ranging from 1 to 7% [4], such infections pose an increased risk of transmission, ranging from 30% to 40% in the first and second trimesters, and escalating from 40% to 70% in the third trimester [4,11,12]. It is known that CMV infection caused by primary infection carries a higher risk of vertical transmission and is associated with more severe cases of congenital infection [7]. Non-primary infection, which is more prevalent than primary infections, likely contributes to a greater number of congenital CMV infection cases. Approximately 30% of women who harbor the virus in a dormant state may undergo reactivation during pregnancy [2]. However, according to the CDC, the risk of transmission following non-primary infections is significantly lower, estimated at around 3% [12]. These routes of transmission underscore the importance of preventive measures to mitigate maternal CMV exposure and the implementation of strategies for early detection and treatment of congenital CMV infection to mitigate its impact on newborn health.

3. Transmission

Transmission of CMV occurs mainly through the dissemination of the virus in bodily fluids, including urine, saliva, blood, tears, semen, vaginal secretions, and breast milk [11]. Consequently, CMV spreads from infected to uninfected individuals via various routes, including [9,13]:

- Direct contact with saliva or urine, especially from newborns, and young children;
- Sexual contact, where close exposure to contaminated body secretions may facilitate transmission;
- Vertical transmission, which occurs when the virus is transmitted from mother to fetus during pregnancy or through breast milk during lactation;

- Transmission through organ transplantation and blood transfusion, where infected donor organs or blood products can transmit the virus to recipients.

During pregnancy, transmission of CMV from mother to fetus can occur through primary infection, reinfection with an alternate CMV strain, or reactivation of a previous infection [3]. In cases of congenital and perinatal infection, the virus is transmitted from mother to fetus either across the placenta or during passage through the birth canal during vaginal delivery [9,13]. Mother-to-child transmission may occur in the prenatal, perinatal, or postpartum period, but to date, only prenatal transmissions have been correlated with congenital CMV infection [2].

3.1. Intrauterine Route - Congenital Infection (Prenatal)

During pregnancy, transmission of the virus from mother to the fetus occurs mainly through the placenta [6]. Once infected, the placenta transmits the infection to the fetus, where the virus replicates in various tissues [4]. This mode of transmission occurs in about 50% of women who develop primary infection during pregnancy. Additionally, congenital infection may occur due to primary maternal infection in the preconception (3 months to 3 weeks before conception) and periconception (3 weeks either side of conception) period. Intrauterine transmission can occur at any stage during pregnancy, whether it involves reinfection or reactivation of the infection [3].

3.2. Perinatal Route - Perinatal Infection (during delivery and postpartum)

Ascending infection through the maternal genital tract is considered unusual but is possible before delivery. Perinatal transmission can result from ingestion or aspiration of vaginal secretions during the normal delivery process as the fetus passes through the mother's pyelogenital tract [4]. Additionally, perinatal transmission can occur through ingestion of breast milk after delivery. Globally, an estimated 2 to 10% of newborns or infants are infected with CMV within the first six months of life. Perinatal infection is estimated to be ten times more prevalent than congenital infection [3].

4. Clinical manifestations

CMV infection in newborns is the most prevalent cause of congenital infection, affecting approximately 0.5% to 2% of all live births [7]. Approximately 75-90% of newborns with congenital CMV infection have no symptoms at birth. However, nearly 10-25% of these asymptomatic neonates may subsequently develop neurological symptoms, such as sensorineural hearing loss, delayed psychomotor development, and visual dysfunction [1,14]. On the other hand, roughly 10-50% of newborns born to mothers with primary CMV infection exhibit overt symptoms, compared to 1% of neonates born to mothers with non-primary infection [7]. These clinical manifestations may include intrauterine growth restriction, low birth weight, microcephaly, hepatosplenomegaly, petechiae, jaundice, chorioedema, thrombocytopenia, seizures, or anemia [1,4,10]. Additionally, approximately 30% of these symptomatic neonates may not survive [4]. Miscarriage and intrauterine death are also recognized as complications of congenital CMV infection [1,4,10].

Primary infection in pregnant women during the third trimester is associated with an increased rate of transmission to the fetus, although outcomes for the neonate are usually favorable [11]. Complications are more pronounced in fetuses when the primary infection occurs during the first trimester [12].

Finally, CMV infection can also occur intrapartum or postnatally through exposure to cervical secretions during vaginal delivery or through breastfeeding. However, these types of infection rarely cause symptoms or complications in full-term neonates [6,7].

5. Diagnosis

The diagnosis of congenital fetal CMV infection involves the following methods:

5.1. Imaging Techniques

These include ultrasound and magnetic resonance imaging (MRI), which reveal various abnormalities such as intrauterine growth restriction [15], hydronephrosis, ascites [4], intracranial calcifications (10%), hydrocephalus (10.5%), heterogeneous parenchymal appearance, microcephaly [15], intra-abdominal adhesions [16], hepatic calcification, hepatomegaly, and hyperechogenic bowel pattern [4,12]. Central nervous system findings usually occur after weeks, and severe brain involvement often indicates poor prognosis, with microcephaly being the only finding that actually predicts an adverse outcome in up to 95% of cases [7].

5.2. Invasive Procedures

a. Collection of amniotic fluid after 21-22 weeks of gestation for polymerase chain reaction (PCR) testing to detect CMV DNA. This diagnostic approach should take into account the potential risks for pregnancy [6,13].

b. Collection of umbilical fetal blood for the detection of CMV-specific IgM antibodies and quantification of viral load. However, this method is not recommended for the diagnosis of fetal infection due to its low sensitivity, because infected fetuses do not develop specific IgM until late in gestation, and associated risks [17].

5.2.1. Diagnosis of CMV Infection in Neonates

Congenital CMV infection is diagnosed by detection of CMV DNA in urine, saliva (preferred samples) or blood [14], within three weeks after birth [13-15]. Tests that detect antibodies against CMV are not reliable for the diagnosis of congenital infection. Additionally, samples collected after the third week of life cannot distinguish between congenital infection and infection acquired during or after delivery [12,13].

6. Treatment

Currently, there is no established treatment for congenital CMV infection. Consequently, parents are often faced with the challenging decision of whether to terminate the pregnancy following confirmation of fetal CMV [18].

6.1. Antiviral Medicines

Antiviral agents such as ganciclovir, valganciclovir, cidofovir, foscarnet, and valacyclovir demonstrate limited efficacy in the treatment of CMV infection in adults, particularly in immunocompromised individuals, and have not been proven effective in preventing or treating congenital CMV infection. Furthermore, their use during pregnancy is not recommended due to their teratogenic and toxic effects, with the exception of valacyclovir [4,19]. Recent findings from a multicenter, open-label phase II study evaluating the efficacy of high-dose oral valacyclovir (8 g daily) in pregnant women carrying moderately CMV-infected fetuses show promising results. Nevertheless, given study limitations, such as sample size and study design, further investigation of this treatment option is warranted before considering antiviral therapy in pregnant women [2].

Antiviral treatment for the newborn is warranted when there is evidence of central nervous system involvement or severe organic disease (e.g., hepatitis, pneumonia, thrombocytopenia). Ganciclovir is the cornerstone of antiviral therapy in neonates with congenital CMV infection, demonstrating safety and efficacy. Ganciclovir proves beneficial in the management of severe, localized organ impairment in neonates and infants. In a randomized controlled trial, it demonstrated long-term neurodevelopmental benefits for neonates with congenital CMV infection [3,5]. Treatment should be initiated in the first month of the newborn's life. A six-week course of intravenous ganciclovir is recommended, with close monitoring for toxicity, particularly neutropenia [5,18]. Despite completion of treatment, neonates continue to excrete CMV in urine and saliva. It is worth noting that antiviral drug use in asymptomatic neonates with congenital CMV infection at birth is not recommended [1,5]. However, all neonates diagnosed with congenital CMV infection should undergo regular hearing and vision screening, as early detection and intervention can significantly improve outcomes [6,11].

6.2. Human Hyperimmune Globulin (HIG)

Currently, HIG is not routinely recommended for the treatment of women with primary CMV infection during pregnancy, as conflicting study results exist. Its use should be reserved for investigational purposes, particularly if the infection occurred within weeks before delivery, is a recent primary infection, and treatment is initiated promptly [11].

7. Screening

Routine screening for CMV does not currently meet the criteria for an effective screening test. Primarily, there is lack of proven effective treatment options during pregnancy. Therefore, routine antenatal screening is not recommended, except within the context of research protocols. Both the UK National Screening Committee (UK NSC) and leading medical organizations, such as the American College of Obstetricians and Gynecologists (ACOG) and the Centers for Disease Control and Prevention (CDC), do not advocate for routine maternal screening for CMV [10]. However, serologic testing for CMV may be warranted in pregnant women under certain circumstances, including:

- Those who have experienced flu-like symptoms or glandular fever-like symptoms, with negative test results for Epstein-Barr virus, or hepatitis, with negative test results for hepatitis A, B, and C during pregnancy.
- Cases in which routine ultrasound detects fetal abnormalities suggestive of possible CMV infection, including ventriculomegaly, microcephaly, calcifications, intra-abdominal adhesions, intracranial hemorrhage, peritoneal cysts, cerebellar hypoplasia, cortical anomalies, echogenic bowel, small for gestational age fetuses, pericardial effusion, ascites, and hydatidiform mole [10].

8. Preventive Measures

Currently, there are no vaccines available to prevent CMV infection [3]. Therefore, adopting simple hygiene practices remains the most effective strategy [2,20]. These measures mainly include hand washing after contact with urine or saliva, and avoiding sharing utensils, drinks, or food with young children, as they are often carriers of the virus [3,21]. Furthermore, pregnant women engaged in professions that involve regular contact with young children, should be made aware of the increased risk of CMV infection and its potential consequences for the unborn child [3]. Moreover, pregnant women who require blood transfusion should receive blood from donors who have tested negative for CMV to reduce the risk of infection [3].

9. Childbirth and Breastfeeding

While CMV infection does not typically necessitate a cesarean section, it should only be performed when medically indicated, in accordance with obstetric guidelines. However, a study by Jie Chen et al. (2023) reported a higher rate of postpartum infection after vaginal delivery compared to cesarean section, at 62.6% versus 29.9% [22].

Although breastfeeding is widely encouraged for its numerous benefits, it is important to note that CMV-positive mothers shed the virus in their breast milk [21], at a rate of approximately 80.5% [23] for up to 12 weeks postpartum [17]. This poses an elevated risk of infection for infants, particularly with regard to preterm neonates, where the incidence of postnatal CMV infection through breastfeeding has been recorded at approximately 20.7% [23]. To reduce the risk in preterm or low birth weight neonates, the breast milk can be pasteurized [7]. Notably, a study involving very low birth weight neonates in intensive care units found that postnatal CMV infection through breast milk significantly increased the risk of mortality and bronchopulmonary dysplasia [17]. However, long-term consequences of CMV infection transmitted through contaminated breast milk have not been reported [24]. A recent study by Midgley et al. (2020) has reported that, compared to formula feeding and caesarean section, breastfeeding and vaginal delivery respectively increase the likelihood of postnatal CMV infection (OR=3.801, 95% CI: 2.474-5.840, $p<0.001$; OR=1.818, 95% CI: 1.190-2.196, $p<0.001$) [25].

Following delivery, neonates should undergo follow-up, with particular attention to developmental milestones and especially hearing, which should be closely monitored [13,21].

10. Conclusions

Cytomegalovirus (CMV) infection remains a significant public health concern, particularly due to its impact on vulnerable populations. Despite the high prevalence of CMV infection globally, there is considerable variation in the incidence of congenital CMV infection, which highlights the need for targeted prevention strategies and early detection efforts. Congenital CMV infection can lead to severe neurological sequelae and long-term health complications, emphasizing the importance of early diagnosis and treatment. Comprehensive understanding of CMV infection is crucial to mitigate its impact on affected individuals and improve outcomes for both neonates and their families. Continued research efforts are needed to further elucidate the epidemiology and pathogenesis of CMV infection and to develop more effective prevention and treatment strategies.

Compliance with ethical standards

Disclosure of conflict of interest

All authors declare that they have no conflicts of interest.

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