Clinical and epidemiological features of congenital cytomegalovirus infection globally

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Human cytomegalovirus (CMV) is the most common non-genetic cause of congenital disability. As a herpesvirus that infects the majority of the population, CMV is able to establish a lifelong latent infection in the host. Any time during pregnancy, a primary CMV infection, reactivation of latent CMV or a new viral strain can infect the placenta and the developing foetus, resulting in congenital CMV infection. Each year, an estimated 2000 children are born with congenital CMV infection in Australia, leaving ~500 children with permanent disabilities such as hearing or vision loss, or mental disability. Despite the clinical importance of congenital CMV, there is limited awareness and knowledge in the medical and general community about congenital CMV infection. This article reviews the global epidemiology and clinical features of maternal and congenital CMV infections.

Human CMV infection

Human CMV is a member of the Herpesviridae family of viruses, which includes Herpes simplex virus type 1 and type 2, Varicella zoster virus, Epstein-Barr virus, Human herpesvirus 6A, Human herpesvirus 6B, Human herpesvirus 7, and Human herpesvirus 8. The genome of human CMV is ~235 kbp and is one of the largest among the Herpesviridae.

Human CMV infects most individuals in the world and can be acquired anytime during life: as a foetus, neonate, toddler, child or an adult. Initial infection (also known as primary infection) occurs following close personal contact. CMV is typically transmitted via body fluids, particularly breast milk, urine, genital secretions, and blood. In addition, CMV can infect the placenta and the developing foetus. Once infected, the human body does not clear the virus. CMV is able to persist in a latent form in either low or undetectable levels in peripheral blood mononuclear cells (CD14+) and bone marrow cells (CD34+ and CD33+). Stimuli such as inflammation, immune impairment due to pregnancy, medical treatment with immunomodulating agents such as corticosteroids, chemotherapy, and immunosuppressive therapy post organ transplantation may stimulate reactivation and growth of latent CMV.

Considering CMV secretion in urine and cervical-vaginal fluids increases during pregnancy with increasing gestational age, hormonal changes related to pregnancy may also stimulate reactivation of CMV.

Epidemiology of maternal and congenital CMV infections

CMV is a common cause of infections worldwide. Antibodies to CMV, representing a previous infection, can be detected in 45 to >90% of women of reproductive age. The percentage of women that are infected with CMV varies between countries and tends to be the lowest in Western Europe, Australia, Canada and the United States and the highest in South America, Africa and Asia. Particularly, in Australia, the average seroprevalence rate of CMV for women between the ages of 14 to 44 years is 58%. However, even within countries the rate of CMV infected women varies by socio-economic status and ethnicity.

Approximately 1–2% of initially uninfected pregnant women will acquire CMV by the time of delivery. A possible source of CMV for these women is young children whose saliva and urine contain high levels of CMV. In addition, a partner who is infected with CMV is an additional possible risk factor for infection during pregnancy, as CMV is present in semen, and can be transmitted sexually. Among the women who acquire a primary infection during pregnancy 32% transmit CMV to the foetus via the placenta, resulting in congenital CMV (cCMV) infection. Only a percentage of cCMV infected children will exhibit symptoms at birth or develop CMV associated symptoms later in life, as further described in detail below.

The foetus can also be infected by a woman’s latent virus or re-infection with a different strain of CMV (secondary infection). The risk of transmitting CMV to the foetus is reported to be higher when a pregnant woman acquires a primary infection during the first half of the pregnancy compared to secondary infections, or infection in
the second half of pregnancy. Kenneson reported 1.4% of secondary infections lead to foetal infection. However, considering the high seroprevalence of CMV, it is estimated that more than two-thirds of CMV infected children are born to mothers who were already infected with CMV.

Intrauterine CMV infection occurs in 0.2 to 2% (average of 0.64%) of live births in the United States, Australia and Western Europe (Table 1). In addition, the limited studies of regions in Latin America, Africa, and Asia have reported a birth prevalence of cCMV infection ranging from 0.6 to 6.1% of pregnancies. Based on the number of live births per year and reported cCMV prevalence, this translates to an estimated ~0.12 million cCMV infections in developed countries per year, and ~0.7 million to 4.5 million cCMV infections annually in developing countries. Particularly in Australia, an estimated ~2000 children are born with cCMV infection in Australia each year (Table 1). Nonetheless, in practice, most congenital CMV infections remain undiagnosed.

Clinical features of maternal CMV infection

The majority of CMV infections in immunocompetent individuals do not cause symptoms; however, clinical manifestations could include glandular fever (mononucleosis) syndrome characterised by flu-like symptoms, or occasionally persistent fever. Several studies reported that pregnant women, who acquired a primary CMV infection, experienced mononucleosis, fever, fatigue, and headache. Nigro observed a significantly higher number of pregnant women with primary CMV infection presenting with symptoms compared to pregnant women with recurrent or latent CMV infection. A review of congenital CMV cases in Australia reported more than half of the mothers had evidence of, or could recall experiencing symptoms of fever during pregnancy. In addition to clinical symptoms, laboratory examination may show an increase in lymphocytes in the blood and increased serum levels of liver enzymes (alanine transaminase and aspartate transaminase). Since all of these clinical manifestations are not only observed upon a CMV infection, they do not represent specific indicators of maternal CMV infection. However, collection of the clinical history and laboratory examination may be extremely useful for dating the onset of infection to determine the risk of CMV transmission to the foetus and risk of cCMV disease.

Clinical features of congenital cytomegalovirus disease

A minority (~10%) of cCMV infected children present symptoms at birth (Table 2). Physical signs such as petechiae, jaundice, and hepatosplenomegaly are common and have been observed in 28 to 50% of children with cCMV infection. Neurological abnormality, including microcephaly and intracranial calcification has been reported to occur in 18–38% of cCMV infected children. The majority of these affected children develop sensorineural hearing loss, mental disability, motor deficits, chorioretinitis and seizures.

A significant amount (~15%) of initially asymptomatic CMV infected children will encounter developmental difficulties, neurological problems, or hearing loss before the age of five. Among those with hearing loss ~40% of children may develop severe to profound

Table 1. Estimated annual number of cases of cCMV infection in Australia, United States, Western Europe, Latin America, Africa, and Asia.

<table>
<thead>
<tr>
<th>Region</th>
<th>Live births per year (in 1000s) (LB)</th>
<th>Estimated rates of CMV infection per 100 live births (R)</th>
<th>Estimated number of live births with cCMV infection (N = R*LB)</th>
<th>Symptomatic cCMV infection at birth (S = N*10%)</th>
<th>Asymptomatic cCMV infection at birth – later symptoms (AS = N*15%)</th>
<th>Estimated total number of live births with cCMV associated symptoms (t = S + AS)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Australia</td>
<td>~308B</td>
<td>0.64%</td>
<td>1971</td>
<td>197</td>
<td>296</td>
<td>493</td>
</tr>
<tr>
<td>United States</td>
<td>~4334C</td>
<td>0.64%</td>
<td>27 737</td>
<td>2774</td>
<td>4160</td>
<td>6934</td>
</tr>
<tr>
<td>Western Europe</td>
<td>~1900C</td>
<td>0.64%</td>
<td>12 160</td>
<td>1216</td>
<td>1824</td>
<td>3040</td>
</tr>
<tr>
<td>Latin America</td>
<td>~11 746C</td>
<td>1.9%</td>
<td>223 174</td>
<td>22 317</td>
<td>33 476</td>
<td>55 794</td>
</tr>
<tr>
<td>Africa</td>
<td>~41 024C</td>
<td>3.4%</td>
<td>1 394 816</td>
<td>139 482</td>
<td>209 222</td>
<td>348 704</td>
</tr>
<tr>
<td>Asia</td>
<td>~79 738C</td>
<td>3.95%</td>
<td>3 149 651</td>
<td>314 965</td>
<td>472 448</td>
<td>787 413</td>
</tr>
</tbody>
</table>

AAverage percentage rates based on data from Kenneson and Cannon, McMullan et al, Munro et al and Lanzieri et al.

B2013 data from the Australian Bureau of Statistics.

CData from World Population Prospects: The 2012 Revision.
impairment of both ears. Other neurological complications such as microcephaly, neuromuscular defects, and chorioretinitis may also develop in initially asymptomatic CMV infected children, but at a lower rate compared to symptomatic infection.

Congenital CMV infection may also result in adverse pregnancy outcomes, as cCMV has been associated with fetal death in utero, neonatal death, preterm birth and maternal pregnancy complications, including preeclampsia.\textsuperscript{29–33}

### Concluding remarks

CMV continues to be the leading infectious cause of congenital malformation in developed countries. More children may be affected by CMV than by any other childhood disorder, such as down syndrome, fetal alcohol syndrome, and spina bifida. Each year in Australia, an estimated 2000 children are born with cCMV infection, leaving ~500 children with permanent disabilities such as hearing or vision loss, or mental disability. Even though the rates of maternal and cCMV infection are still lacking for many parts of the world, which likely underestimates the global impact of cCMV infection, the importance of cCMV infection and disease as a large public health problem is self-evident.

### References


In Focus
Human cytomegalovirus (CMV) is the leading non-genetic cause of fetal malformation in developed countries. Congenital CMV infection can cause serious clinical sequelae, and in severe cases result in fetal or neonatal death. Despite the clinical and social importance of congenital CMV there is currently no standardised management strategy to prevent or treat maternal/fetal CMV infection during pregnancy and no evidence-based therapeutic for prenatally diagnosed CMV infection or disease. For pregnant women with a primary CMV infection during pregnancy, standard medical practise remains to offer no treatment or the option to terminate pregnancy. If intervention is requested, pregnant women may be offered a narrow range of medical therapies with limited evidence for efficacy and some with high risks of toxicity. However, there are several experimental and novel anti-CMV therapeutics currently being investigated that may provide a safe and effective therapeutic for use during pregnancy to prevent both fetal infection and reduce the risk of congenital CMV disease developing in the fetus once infected in utero.

Established anti-CMV therapeutics

Valaciclovir

To date, the only established CMV antiviral to undergo investigations during pregnancy is valaciclovir, the prodrug of the nucleoside