

# Why a generalized serological screening in early pregnancy for CMV is just not justifiable?

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## ABSTRACT

*Infections acquired during pregnancy add up to the overall perinatal rate of mortality and morbidity. Because it has the potential to be screened in all pregnant women, infection with cytomegalovirus continues to raise awareness among obstetricians and healthcare providers, given the perinatal complications involved, but also because not all parturient women are equally informed about the impact of the disease. A significant possibility of vertical transmission is attainable if primary infection is acquired in pregnancy, especially in the first trimester, when the risk of developing a congenital neonatal disease is higher. Even so, there are many more steps to be taken into consideration in order to fully understand the consequences of the infection, given the fact that the leading consequence of the congenital disease is the sensorineural hearing loss in the neonates, thus raising an important question: why a generalized serological screening in early pregnancy for CMV is just not justifiable?*

**Keywords:** cytomegalovirus, serological screening, pregnancy, congenital infection, sensorineural hearing loss

## OBJECTIVE AND METHOD

In the current systematic review it was aimed to re-assess the background, clinical aspects, screening and prevention of cytomegalovirus infection in pregnant women, calling into question the lack of rationalization of a generalized serological screening in early pregnancy. Literature was searched via Pubmed using key words such as pregnancy, cytomegalovirus, serological screening, sensorineural hearing loss, congenital infection.

## BACKGROUND

A double-stranded DNA virus, a component of the *Herpesvirales* order, *Herpesviridae* family, *Betaherpes-*

*viridae* subfamily, known as herpesvirus 5, cytomegalovirus (CMV) found in humans (HCMV) is one of the most surveyed unit of cytomegaloviruses [1]. Coming from the Greek terms “cyto” (cell) and “megalo” (big), cytomegalovirus is transmitted through mucosae or blood, dissemination of the virus emerging after replication [1]. Infection is transmitted by lineal contact with body fluids such as urine, breastmilk or blood among others, as listed in table 1 [1]. All body cells could act like hosts for cytomegalovirus, liver and spleen remaining the leading subsidiary habitats, the three main cells involved in the dissemination of the virus being the monocytes, the macrophages and the endothelial cells [2].

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**TABLE 1.** Body fluids involved in transmission of cytomegalovirus

Blood
Lacrimal fluid
Saliva
Maternal milk
Urine
Vaginal secretions

According to Smithers et al., neonates with cytomegalovirus viremia and coming from seropositive women, suggesting a congenital disease, have a high risk to develop neurological impairment, such as cerebral palsy or sensorineural hearing loss [2]. In a literature review published in 2010, it was noted that cytomegalovirus infection prevalence is higher in women pertaining to a lower income class, patients in the reproductive age group being seropositive between 45 and 100% [3]. Some European states and The United States of America registered a lower prevalence rate in comparison to other countries belonging to South America or Asia [3].

Primary and nonprimary infection are described as the main types of cytomegalovirus infection. Primary infection is identified in women without previous exposure to CMV and thus acquired through direct contact with secretions such as saliva and urine, women with children under two years old having propensity to this situation as a result of a habitual mundane activity such as the contact with urine from wet diapers [4]. Nonprimary infection could be an indicator of reinfection or reactivation of a past infection [5]. The key of this entire process consists in the presence of antibodies as a response to altered cytomegalovirus glycoproteins or to different viral strains as studies have shown that reinfections between breastfeeding patients and their children is possible without identification of a distinctive virus strain [6].

## CLINICAL ASPECTS OF CYTOMEGALOVIRUS INFECTION

The classification of the infection with cytomegalovirus, as displayed in table 2, shows that hearing loss remains one of the most important consequences of the congenital disease and it can also be found in asymptomatic neonates [7]. Foulon et al, in a paper that studied the association between pregnancy trimester in which primary infection was acquired and the incidence of sensorineural hearing loss (SNHL), included 28 neonates diagnosed with congenital cytomegalovirus disease that were screened for sensorineural hearing loss [7]. The results have shown that sensorineural hearing loss was not identified in neonates born from mothers that acquired primary infection

during the third trimester, while 80% of the neonates diagnosed with sensorineural hearing loss occur from patients that were exposed to the virus during the first trimester of pregnancy [7].

**TABLE 2.** Classification of clinical aspects of cytomegalovirus infection

<b>Asymptomatic</b>
No clinical symptoms with normal auditory perception
No clinical symptoms but with isolated abnormal auditory perception (sensorineural hearing loss)
<b>Symptomatic</b>
Heterogenous clinical symptoms +/- cerebrospinal nervous system association
One or two clinical symptoms

A longitudinal study, conducted by Dahle et al. showed that out of 860 neonates diagnosed with congenital cytomegalovirus infection, 7.4% in the asymptomatic group and 40.7% in the symptomatic group developed sensorineural hearing loss (SNHL), while quiescent consequences were found in both categories such as late or gradual outset of auditory impairment [8]. Besides neurological manifestations, ophthalmologic anomalies are also a part of the general clinical picture of cytomegalovirus congenital disease. The main ophthalmologic consequences found in neonates diagnosed with cytomegalovirus congenital disease were optic atrophy, macular scars, cortical visual impairment and strabismus, among others (Table 3) [9]. In opposition to the asymptomatic group, visual impairment is prevalent in symptomatic neonates as it is shown in a study conducted on 125 CMV seropositive neonates and 21 control patients [9].

**TABLE 3.** Main ophthalmologic aspects of cytomegalovirus infection

Optic atrophy
Cataracts
Cortical visual impairment
Chorioretinitis
Macular scars
Strabismus
Retinal hemorrhage

## SCREENING, DIAGNOSIS AND PREVENTION

Being acknowledged as the most prevalent congenital viral infection, congenital cytomegalovirus infection remains the main non-genetic cause of sensorineural hearing loss (SNLH). An important topic for further debate raises: is a generalized serological screening in early pregnancy for CMV justifiable? Studies have shown that congenital neonatal infection with cytomegalovirus mostly originates from seropositive patients with non-primary infection, to such a degree that universal screening for pregnant women could be repla-

ced by an extensive neonatal screening [10]. In an article published in September 2020 by Messinger et al., in a population-based cohort study, the prevalence of microcephaly at birth ranged from 2.1 to 7.7 per 10,000 live births, congenital infection with cytomegalovirus increasing the risk by 7 times [11]. Furthermore, data about cytomegalovirus infection should be available to all patients. In 2015, in Italy, a web questionnaire assessed the general population awareness about cytomegalovirus infection. The results showed that 52.5 % of the respondents heard of cytomegalovirus and only 60.1% of them were aware of the possibility of developing a congenital disease [12]. For this reason, general population knowledge about transmission and prevention of the infection seems a better option than a generalized serological screening in early pregnancy.

Cytomegalovirus in pregnancy is diagnosed by serological determination of IgG and IgM antibodies. If IgM antibodies are positive, IgG avidity is further tested with low avidity denoting a recent infection, in the last 3 months [13]. Nonetheless, an intermediary avidity could not predict the exact moment of the infection, thus demanding further investigation. Additionally, during prenatal period, ultrasound surveillance is notably important, as in a third of cases, ultrasound anomalies could anticipate a congenital infection [14].

The leading prenatal test remains amniocentesis as urine is the main component of the amniotic fluid and cytomegalovirus is primarily excreted through fetal urine. Furthermore, the amniotic fluid probe can be assessed through polymerase chain reaction and quantitative polymerase chain reaction [15]. Guerra et al. concluded that the existence of  $\geq 1,000$  genome equivalents prognosticated future mother-neonate infection with 100% probability [15].

Prevention of cytomegalovirus infection remains an important issue, as reactivation of the virus or reinfection with a different virus strain are possible, while vaccine prevention of infection is aimed. Pass et al. evaluated the possibility of a vaccine in a double-blind trial with doses administered at 0, 1 and 6 months to seronegative patients [16]. The results were promising: the placebo group was more likely to acquire the infection, while vaccination could highly decline congenital disease rates [16]. Nonetheless, further research is needed in order to obtain a vaccine that could cover not only primary infection, but also reactivation or reinfection with a different strain.

## TREATMENT

The leading antiviral drugs used as therapy in cytomegalovirus infection are Ganciclovir and Valganciclovir, substances not approved in pregnancy, as they can cause neutropenia and have the potential to cross placental tissues and to exert high levels of toxicity [17]. Nigro et al. studied the effect of cytomegalovirus hyperimmune globulin (HIG) in two groups: a therapy group that was given 200 units of globulin per kilogram and that included women with cytomegalovirus detected in the amniotic fluid and a prevention group consisting of pregnant women with recent primary infection that were given 100 units of globulin per kilogram, but monthly [18]. The study concluded that hyperimmune globulin is safe in pregnancy and in both groups there was a significantly diminished risk of congenital cytomegalovirus disease: the therapy group (adjusted odds ratio, 0.02; 95 percent confidence interval, -infinity to 0.15;  $P < 0.001$ ) vs the prevention group (adjusted odds ratio, 0.32; 95 percent confidence interval, 0.10 to 0.94;  $P = 0.04$ ) [18].

As neonatal sequelae may be permanent, antiviral therapy could be averagely potent, preventing additional extent of the disease [19]. Therapy with Valaciclovir 8 g per day, divided in two doses per 24 h used in infected neonates decreased viral load and increased asymptomatic preponderance, but further studies are needed to be carried out [19].

## CONCLUSIONS

Congenital infection with cytomegalovirus is one of the leading causes of sensorineural hearing loss in neonates. There are two types of cytomegalovirus infection, primary, initially acquired during pregnancy period, and non-primary, the result of reactivation or reinfection with a different viral strain. Permanent sequelae are mostly found in neonates coming from pregnant women infected during the first trimester. As healthcare providers among the world struggle continuously to achieve a cost-efficient method of screening, as vaccination is not available and antiviral therapy is limited, prevention among general population could be implemented by educational programs. Moreover, the topic of a generalized serological screening in early pregnancy that could be successfully replaced by a general neonatal screening could be included in further research.

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