

REVIEW ARTICLE

Maternal Infections Associated with Bad Obstetric Outcome: Cytomegalovirus and Herpes Simplex Virus.

Mohamed Almoustafa Alsamarai, Laboratory Investigation Department, Samara University College of Applied Sciences (SUCOAS), Samara, Iraq.

Email: mohamedalmoustafaa@gmail.com Mobile: +9647718814092

ORCID: <http://orcid.org/0000-0002-3051-725X>

Hala Majeed Hassan, Tikrit University College of Veterinary Medicine, Tikrit, Iraq, Email: m.hala.17@yahoo.com, Mobile: +9647701227150

ORCID: <http://orcid.org/0000-0003-3772-1218>

Correspondence author: Mohamed Almoustafa Alsamarai, Laboratory Investigation Department, Samara University College of Applied Sciences (SUCOAS), Samara, Iraq. Email: mohamedalmoustafaa@gmail.com Mobile: +9647718814092

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Cytomegalovirus:

1. Introduction.

Cytomegalovirus (CMV) infection is with global distribution and range of 30-100% [1, 2]. CMV infection is the most common congenital viral infection worldwide [3]. The sign of congenital CMV infection encountered most frequently is hearing loss, which wills 12.6% of congenitally infected newborns and congenital CMV infection form 10-20% as a cause of total hearing loss in children [4]. About 10% of the live-born infants with congenital CMV infection are symptomatic at birth. Where as an additional 10% of the infected newborns will develop permanent sequelae in the following years. [5] Among children with bilateral profound hearing loss, the hearing incapacity is attributable to congenital CMV infection in one out of five patients. This makes CMV the leading cause of non genetic congenital hearing impairment [6]. Asymptomatic CMV infection at birth may develop hearing loss in adolescent age [4]. In spite of the detailed knowledge about the epidemiology and pathogenesis of CMV infections in pregnant women, this infection stays largely unknown to the majority of women in the United States .Few, if any pregnant women are routinely screened for CMV infections during pregnancy. Questions surrounding the suitability of serologic screening for CMV during pregnancy are important because over 90% of primary maternal CMV infections during pregnancy are asymptomatic and may remain asymptomatic in the fetus. Israel and eight European countries (France, Belgium, Spain, Italy, Germany, Austria, Portugal, and the Netherlands) routinely screen the majority of pregnant women serologically for CMV This routine serologic screening occurs without the recommendations or guidelines of any governmental agency, authority, or a professional medical society [7].

2. Pathogenesis of Congenital CMV Infections.

Forty percent to 60% pregnant women are susceptible to CMV at conception. However, only 1-4% infected during pregnancy and neonatal infection acquired in 40%-50% of them. The neonatal CMV infection is more when the mother acquired the infection in the 3rd trimester (73%) as compared to 1st trimester (35%).[8] There is considerable uncertainty about the role of maternal immunity to CMV earlier to conception. Infant infection may occur even in the presence of mother preconception immunity and may occasionally present with symptoms at birth and possibility of hearing defect development. Nevertheless, there is no insecurity concerning the fact that the rate of congenital infection among women with preconception immunity is only between 0.5% and 2% while the corresponding value is 40-50% in those with seroconversion during pregnancy. In one study, 3% of prepregnant women are sero-negative at or before conception had congenitally infected infants compared with 1% for women seropositive before conception [9].

3. High-Risk Women

The major risk factor for maternal acquisition of CMV during pregnancy is numerous and prolonged contact with a child less than three years of age as in home or nursery centers. CMV sero-negative health care workers, even those caring for hospitalized young children and infants, are not at an increased risk. In the USA, 60% of the mothers of children in daycare are CMV sero-negative, and at least 25% of all young children attending large group child care centers are shedding CMV. Sero-negative mothers with infected children acquire CMV at rates, 10 to 25 times larger than other women in the population. The annual infection rate for sero-negative women without exposure to children is 2% [10]. In Western countries, the primary CMV infection during pregnancy is 2-4% of pregnant women and subsequent foetal infections in 40% of them [11, 12]. In a systematic review in developing countries, the maternal CMV infection is with range of 84-100%, while the neonatal infection ranged from 0.6% to 6.1% [13].

To estimate the regularity of pregnancy and exposure to CMV among mothers contemplating a possible additional pregnancy and with a child less than 2 years of age in group daycare, a prospective study we recently performed which included a demographic questionnaire and serologic and virologic monitoring of mothers and their children in daycare. Of 60 women, 62% were sero-negative and 20% of sero-negative women had a child shedding CMV. Silent viral infection during pregnancy which may lead to CMV shedding from 35% of children in daycare center is a major health problem. This data, when extrapolated to the US population, estimate that every two years between 31,000 and 168,000 susceptible pregnant women will be exposed to CMV by an infected child [14].

In general female population CMV IgG seroprevalence is 51.7- 95.7%, while the IgM seroprevalence is 4.1 to 6.3%, while in women with bad obstetric history (BOH) the CMV IgG seroprevalence is with a range of 91.2% - 96.6% and 3.8% to 9.46% for IgM seroprevalence [15-19]. The association between CMV infection and age is with conflicting results, however, some study suggest that CMV infection is increased in women with age [16]. Other studies reported that CMV IgG and IgM is significantly higher in women with age of less than 30 years as compared to those of >30 years [15]. Women education and residence show a significant association with acute and chronic CMV infections [15, 16]. The high seroprevalence of CMV

infection in women and a non-significant difference between women with history of bad obstetric outcomes and those with normal child delivery suggest that CMV infection during pregnancy may be not important as a direct cause for development of BOH. However, it may be suggested that the role of CMV infection in BOH development is their ability to induce immunosuppression which lead to enhance super-infection with other microbes and lead to development of BOH [20, 21]. The wide spread of CMV infection in developing and developed countries illustrate the social and medical impact of such health problem. The effectiveness of vaccine in prevention and control of viral infections attributed to production of vaccines for herpes viruses including CMV. Nelson et al [22], in a review concerning the effectiveness of CMV vaccine concluded that human cytomegalovirus vaccination is effective in influence of congenital and incidence of CMV infection. New vaccine design may end CMV infection in pediatric population and immunosuppressed individuals [22].

4. Laboratory Testing.

Cell culture for virus isolation, antigen detection, histopathology to detect inclusion bodies, electron microscope, ELISA, PCR and serological tests form the panel of investigations for the diagnosis of CMV infection. [23, 24]. However, their uses is influenced by their specificity and sensitivity and availability. Detection of CMV DNA in tested sample indicated that CMV infection is present and the person has an active infection. High levels of viral DNA tend to indicate a more aggressive infection accompanied by serious symptoms while low levels indicate a CMV infection, usually one with no signs or ones that are mild. Like culture, negative results on a DNA test do not rule out CMV infection – the virus may be present in very low amounts or may not be present in the body sample tested.

Herpes simplex virus:

1. Introduction

Herpes simplex virus (HSV) is an abundant, enveloped, and double stranded DNA virus, belonging to the family of Herpesviridae transmitted across mucosal membranes and non intact skin, with ability to induce chronic latent infection [25]. Susceptibility to HSV infection is associated with HLA antigens [26]. The virus type incidence is about the same for both HSV-1 and HSV-2 strains, while HSV-2 is the most predominant in recurrent infections [27]. HSV -1 is the common strain in labial herpetic infection, while HSV-2 is the predominant in genital infection. The site of latency is the trigeminal ganglia for labial herpetic infection and lumbosacral ganglia for genital herpetic infection [27]. Changes in sexual behaviors of young adults may partly explain its higher incidence [28].

Sequential infection with different HSV strains are reported [29]. Recurrent infection occurs in a person with preexisting antibodies against the same HSV type 2. Infections during pregnancy may be transmitted to newborns: HSV-1 and HSV-2 may cause eye or skin lesions, meningoencephalitis, disseminated infections, or fetal malformations [30]. Two theories are proposed as explanation for induction of recurrent infections, the ganglion trigger theory and the skin trigger theory. These two theories may be responsible for recurrences in the same patient and same episode or one of them may be responsible for the episode pathogenesis [27]. Secondary bacterial infection play an important role in the natural history of HSV genital

infection and thus co-administration of cotrimazole with acyclovir is with better outcome in treating herpes genitalis [31].

2. Epidemiology

Globally, the prevalence of HSV-2 is 11.3%, while the incident infection is 0.5% in 2012 [32]. In general Iraqi population HSV-2 IgG seroprevalence is 24.2% to 29.9%, while the IgM seroprevalence is 2 to 3.2%. Additionally, the HSV IgG seroprevalence is significantly higher in women with BOH as compared to those with normal pregnancy [33]. The HSV-2 prevalence is significantly higher in women with age of < 30 years as compared to older, while in women with BOH the pattern is reversed [34,35].

Gender, age, residence, education level and sexual activity influenced the prevalence of HSV infection [33, 35]. In fact, the prevalence of HSV infection rises with age, reaching the maximum around 40 years. This infection appears related to the number of sexual partners, and regarding sex it is more occurrence regularity in women than in men. In addition, ethnicity, poverty, cocaine abuse, earlier onset of sexual activity, sexual behavior, and bacterial vaginosis can facilitate a woman's risk of infection before pregnancy [36]. Concerning pregnant women, the seroprevalence of HSV-2 is with a range of 7.6% to 35.2% [3, 34]. The acquisition of genital herpes during pregnancy has been associated with spontaneous abortion, intrauterine growth retardation, preterm labour, and congenital and neonatal herpes infections [33, 34, 37]. In a recent study the overall global neonatal HSV infection is 10 per 100 000 live births and mostly occurred in Africa [38]. Neonatal HSV infection occurs more when the mother gets infection close to term and this because of viral shedding through genital tract [38]. Some studies [39, 40] suggested that neonatal HSV infection occurs during labour in more than 85% of cases. Thus the incidence of neonatal HSV infection may be reduced through effective antenatal care and performance of elective cesarean section and/or antiviral therapy. When primary HSV infection occurs during late pregnancy, there is not suitable time to develop antibodies needed to destroy viral replication before labor [41] and this lead to increase the incidence of neonatal HSV infection. In addition, HSV infection immune responses are not completely understood and re-infection and/or recurrences occurred in the presence of IgG antibodies [42].

The treatment of HSV is influenced by the ability of the virus to induce latency and thus the treatment of the infection is palliative rather than curative [32]. This phenomenon is with psychological impact on the affected individuals and their families [43]. Additionally, the emergence of resistance to antiviral agents used for HSV infection hurdle the effectiveness of therapy [25, 44, 45, 46]. The global burden of disease can be alleviated by development of effective and safe HSV vaccine [47].

3. Laboratory Diagnosis:-

Virus culture, antigen detection, electron microscopy, and serological tests are used for the diagnosis of HSV infection. However, virus culture, direct antigen detection, and serological test are the most widely used laboratory test for diagnosis of HSV infection. Test selection depends on the availability of materials and equipments in each health settings. In developing countries serologic test is the most widely used approach. Serologic (blood) tests can recognize antibodies that are specific to the virus and its type, herpes virus simplex 1 (HSV-1) or herpes virus simplex 2 (HSV-2). When the herpes virus infects someone, immune system

produces specific antibodies to fight off the infection. If a blood test detects antibodies to herpes, evidence that you have been infected with the virus, even if the virus is in a non-active (dormant) state. The presence of antibodies to herpes also indicates that you are a carrier of the virus and might transmit it to others [48].

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