Human Cytomegalovirus and Related with Abortion among Iraqi Woman

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Abstract

Background: Human cytomegalovirus is endemic in many areas of the world and the seroprevalence is high in lower socioeconomic of the tested women and responsible for congenital infection, it can lead to significant morbidity, mortality, or long-term sequelae, including sensorineural hearing loss. Although the increase of awareness and international guidelines on the management of HCMV is observed across the developed country but still high infection rate is reported in many countries.

Objective: To determine the infection rate of human cytomegalovirus among pregnant women in our population.

Results: High reported pooled prevalence of HCMV IgG among pregnant women (70%-100%) as well as high pooled reported IgM among pregnant women (0%-43.9%) in different Iraqi cities using blood samples for immunological techniques such as immune chromatography (Rapid test) and enzyme linked immunosorbent assay (ELISA) or molecular methods such as polymerase chain reaction (PCR) and real time-polymerase chain reaction (RT-PCR) the variation related with many factors such as sociodemographic and clinical characteristics.

Conclusions: Most studies performed reflect very necessary epidemiological assessments rather than on-going routine diagnostic practices and there are currently no internationally or nationally adopted guidelines in the region regarding HCMV management.

Keywords: Maternal, congenital human cytomegalovirus, abortion.

Introduction

Spontaneous abortion (SA), also known as miscarriage, is considered as one of the most frequent problems a woman may face during early pregnancy, is not only related to morbidity or mortality, but also has an obvious social and psychological impact on women. It was estimated that 6-15% of all clinically detected pregnancies end with spontaneous abortion [1]. There are several factors related to spontaneous abortion, such as genetic abnormalities and infections [2]. Many studies showed virus such as human cytomegalovirus (HCMV), human herpes simplex virus (HHSV1/2), human parvovirus B19 (B19V), enterovirus, adenovirus, and varicella-zoster virus are causative agents of spontaneous abortion [3-5].

Human cytomegalovirus is endemic in most areas of the world. The seroprevalence of HCMV varies in different geographical areas ranging from 30-100% [6]. Human cytomegalovirus infection passes undetected in healthy children and adults. However, several high-risk groups, including immunocompromised organ transplant recipients, hematopoietic stem cell transplant recipients, and individuals infected with human immunodeficiency virus (HIV), are at risk of developing life-threatening and sight-threatening HCMV disease [7].

Human cytomegalovirus also known as human herpesvirus 5 (HHV-5), belongs to the herpesviridae family subgroupbeta herpes virus [8], which is an enveloped double-stranded linear DNA virus that like other members of the herpes virus family [9]. Establishes lifelong latency following primary infection results in a persistent or latent infection that can be found within various tissues, peripheral blood mononuclear cells (PBMCs), and endothelial cells [10].

Vertical maternal viral transmission to her fetus or newborn is usually combined with significant visceral damage [11]. Human cytomegalovirus is secreted in saliva, urine and breast milk [12]. Sexual activity is the primary means of HCMV transmission among pregnant women and adolescents [13].

It is capable of infecting most of the body cells and acting in the cytoplasm and the nucleus of the infected cells, forming inclusions, HCMV presents the capacity to evade the immune system [8]. Human cytomegalovirus causes significant infection in immunocompromised patients with recognized syndromes of fever, hepatitis, pneumonitis, encephalitis and retinitis. Long term consequences of HCMV infection such as allograft rejection, accelerated atherosclerosis, reduced effectiveness of anticancer drugs, secondary fungal and bacterial infections are less well recognized clinically [14]. Through that mechanism, it remains latent in the body. When the host faces a situation of immunosuppression (such as pregnancy, chemotherapy,

acquired immunodeficiency syndrome [Aids], amongst others) [15].

The infection in pregnant women can be asymptomatic or cause severe symptoms at birth (10-15%) including intrauterine growth retardation, microcephaly, retinitis, jaundice, hepatosplenomegaly and 20% to 30% of them will die, permanent damage 50-80% are mental retardation, deafness and blindness [16, 17, 18].

There are many confounding studies describing the association between HCMV infection and pregnancy loss, which show that HCMV can result in abortion or stillbirth [19, 20]. The rate of susceptibility to HCMV during pregnancy is well established and among women of child-bearing age nearly ranging from 40% to 80% will be susceptible to HCMV at the beginning of pregnancy. The rate of susceptibility to HCMV infection varies by many factors including age, ethnic or racial, and socioeconomic factors [21].

Approach

This review summarizes congenital human cytomegalovirus and seroprevalence of human cytomegalovirus infection among Iraqi pregnant women done using several articles perform in different Iraqi cites about a specific population (pregnant women and newborns) through applied validated HCMV tests to patients.

Maternal HCMV seroprevalences in Iraq

The current review design to determine the infection rate of human cytomegalovirus among pregnant women in our population. So basically, several Iraqi researchers showed low infection rate while other showed high infection rate among pregnant women based on immunological methods such as immunological techniques as latex agglutination test, immune chromatography (Rapid test) and enzyme linked immunosorbent assay (ELISA) or molecular methods such as polymerase chain reaction (PCR) and real time-polymerase chain reaction (RT-PCR) and the rates of IgM varying between 0**-43.9%** depend on sociodemographic and clinical characteristics.

A study from Diyala province conducted using a serological test did not report any positive case for anti-CMV IgM among 92 pregnant women attending the primary health care centers in Baqubah [22].

A study conducted at General Kirkuk Hospital, Azadi Teaching Hospital and Al-Nasr Hospital in Kirkuk city, reported a 37% for IgG higher than IgM that had 1% using ELISA test among 100 women with pregnant loss [23]. In Kurdistan region of Iraq, seroprevalence is reported 2.27% (29 out of 1275) for anti-CMV IgM antibodies among 1275 women with early pregnancy loss from five major cities, including

Duhok (575 samples), Summail (189 samples), Zakho (201 samples), Akre (150 samples), and Amedi (160 samples) using ELISA test [24]. Yasir *et al* (2020) who reported 60.63% (97 out of 160) had chronic HCMV infection characterized by presence of positive IgG while only 2 (1.25%) were had acute HCMV infection characterized by the presence of positive IgM using Enzyme immunoassay and PCR amplification test in Al-Najaf Public Health Laboratory [25].

Another study done by Al-Mishhadani and Abbas (2008) showed that 6.1% (14 out of 230) samples from aborted women attended Al-Gailani Medical Laboratory (private laboratory) in Al-Anbar Govennorate [26]. Khudhair *et al.*, (2017) who showed that the anti-CMV IgM antibodies seroprevalence was 6.92% among 180 aborted women attended to Al-Battol Teaching Hospital for Maternity and Children in Baqubah-Diyala, and outpatient clinic in Baqubah Teaching Hospital [27]. Ali (2020) reported 8% sero-prevalence of HCMV- IgM among women with abnormal pregnancy, attended to emergency unit of maternity teaching in Erbil city [28]. Aljumaili *et al.*, (2014) who reported HCMV IgM (8.3%) among women with bad obstetric history (BOH) in Kirkuk General Hospital, Primary Health Care Centers in Kirkuk Governorate [29]. Al-Azzawi (2012) reported IgG antibodies were detected in 58 (36%), while the IgM antibodies were detected in 16 (9.9%) and the number of both IgG and IgM seropositivity was 50 (31.1%) among 161 pre-marital women without any clinical evidence of HCMV infection using ELISA test [30]. Al-Baiati *et al.,* (2014) who reported studied anti-HCMV antibodies in 152 aborted women attended Infertility Clinic of Kamal Al-Sammaraee Hospital and Al-Yarmouk Teaching Hospital and represent 100% IgG for and 11% for IgM, among patients with oldest age classes 41-45 years old, while the youngest age classes (16-20) years old showed the low rate of anti-HCMV IgG antibodies 75% and high for IgM 17% without significant differences [31].

Al-Dorri (2018) who reported 16.40% (21 out of 128) were positive (either IgM or IgG) against HCMV among aborted women attended Tikrit Teaching Hospital in Salah Al-Deen province [32]. Al-Saeed *et al.*, (2008) who reported 18.8% (8 Out of 120 samples) were positive for IgM antibodies among women who have consulted the-Children and Maternity Hospital and General Teaching Hospital in Al-Hilla city, during the period from November 2006 to April 2007 [33]. Jihad and Rehab (2015) showed that highest percentage of seropositive to HCMV which were 40% of IgG and 25% of IgM in miscarriage women compared with infertile women that showed 20% of IgG and 15% of IgM with a significant difference $P \leq 0.05$ using ELISA test in Baghdad [34]. Raisan and Saad (2020) showed that level anti-HCMV IgM antibody a high in (26-30) age group at a rate of 26.7% with a significant difference compared to the other age group, while level anti-HCMV IgG a high in the 31-35 years old and the 36-40 years old at rate of 100 % using ELISA test in 160 blood samples obtained from

women suffering from repeated embryo projections from private laboratories in Basrah province [35].

Other studies reported high rate of HCMV infections than others studies such as Khudhair and Raghad (2018) who found HCMV infection was 40(32.78%) among 122 pregnant women admitted to Al-Elwiya Maternity Hospital in Baghdad [36]. Al-Ouqaili *et al*., (2010) revealed 33.3% positive cases for CMV IgM (29 out of 87) as primary Hospital in Ramadi [37]. Saad *et al., (*2013) who demonstrated that seropositivity for human cytomegalovirus 35.38% in women with bad obstetric history (BOH) in Holy Kerbalaa [38]. Hussein *et al*., (2017) who showed that positivity frequency of human cytomegalovirus antigens was 36% (18 out of 50) in product of conceptus tissues of pregnant women with spontaneous abortion admitted to Al-Batool Teaching Hospital for Maternity and Children in Baqubah-Diyala [39]. A study conducted at Al-Karama Hospital and Al-Zahra Hospital of Wasit province, reported a 43.9% (345 out of 750) for HCMV IgM among aborted and pregnant women [40].

In general, the differences in the rates of HCMV infection in above studies could be attributed to the fact that, the virus varies from one region to another and from year to year due to diversity in the study which excelled it, and related with many factors

One of them, the age of women were included in each study had possible role in the distribution of infection so Jerman *et al*., (2016), in the United State of America, they study the characterize of abortion women from 2008-2014 and concluded the most spontaneous and firs abortions occur in women of ages ranged from 20-24 years, and the lowest cases of miscarriage occur in women of ages above 30 years [41]. Human cytomegalovirus acquisition in a population is characterized by an age-dependent rise in seroprevalence, and correlates most closely with socioeconomic level and race [42, 43].

Second factor, type of infection. It is commonly recognized that primary HCMV infections are transmitted more frequently to the fetus and are more likely to cause fetal damage than recurrent infections [44]. Due to latency following primary infection and periodic reactivation of HCMV replication causing recurrent infections, in utero transmission of HCMV [45]. As well as HCMV can produce maternal infection and exhibits a high tropism for cervical mucosa and is considered as the most implicated virus in recurrent spontaneous abortion (RSA) [46].

Living in developed countries had effective title role in the delivery of HCMV rates, Zhang *et al*., (2010) showed that seroprevalence of HCMV in adults ranges from 55% in developed countries to as high as over 90% in developing countries like China [47]. Also approved with other studies [48, 49, 50].

Financial strata, the recurrence human cytomegalovirus is the most common cause for an extreme disease which is higher in the developed countries among lower financial strata [48, 50].

The immune status of women, potential mechanisms identified included impairment of trophoblast progenitor stem cell differentiation and function, impairment of extravillous trophoblast invasiveness, dysregulation of Wnt signaling pathways in cytotrophoblasts, tumor necrosis factor-α mediated apoptosis of trophoblasts, CMV-induced cytokine changes in the placenta, inhibition of indoleamine 2,3-dioxygenase activity, and downregulation of trophoblast class I major histocompatibility complex molecules. can cause fetal injury through direct damage to the fetus and indirectly through placental dysfunction resulting from infection or immunity-mediated destruction, without evidence of transmission of the virus to the fetus [51, 52].

Type of test were use in detection, so serological tests are highly specific and sensitive, and although antibody can decline with age and severe immunosuppression but IgG seropositivity is usually lifelong. Techniques for detecting the virus itself are improving rapidly, and nucleic acid tests such as the polymerase chain reaction (PCR), branch DNA (bDNA) and nucleic acid sequenced based amplification (NASBA) are now available at larger centers. All the nucleic tests are useful and choice largely depends upon the laboratory preference and the tests being commercially developed at any given time [53].

Conclusion

Human cytomegalovirus infection during pregnancy is far more complex than other infections due to the ability of the virus to be frequently reactivated during the childbearing age and be transmitted to the fetus in spite of maternal immunity. Despite the high reported pooled prevalence of HCMV IgG among pregnant women (70%-100%) as well as high pooled reported IgM among pregnant women (0%-43.9%) in Iraq, there are barely efforts for diagnosis of maternal HCMV infections and HCMV in newborns.

Most studies performed reflect very necessary epidemiological assessments rather than on-going routine diagnostic practices and there are currently no internationally or nationally adopted guidelines in the region regarding HCMV management.

Many challenges found in our country like lack of management and diagnostic policies on HCMV intolerably results medical problem such as infected with other sexually transmitted disease, lack of optimal/structured ante and postnatal care, lack of adequate equipment and funding for laboratory facilities), as well as socioeconomic factors such as poverty, low awareness, and literacy and teenage pregnancies. So, the increase of awareness and international guidelines on the management of HCMV is required in many countries.

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