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A REVIEW ABOUT HUMAN CYTOMEGALOVIRUS (HCMV) SERO-PREVALENCE IN PREGNANT AND ABORTED WOMEN IN IRAQ (ARTICLE REVIEW)

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Abstract:

The cytomegalovirus is the most prevalent member of the herpes virus family (CMV). Human cytomegalovirus (HCMV) is the most common cause of congenital malformation resulting from viral intrauterine infection in wealthy countries. In the majority of the world, CMV is endemic. The range of the HCMV sero-prevalence, which varies geographically, is between 30 and 100 percent**.** The presented review summarizes some studies conducted in Iraq to find out the Human cytomegalovirus (HCMV) seroprevalence in women who have had abortions and those who are pregnant.

Conclusion: In both pregnant and aborted women, the HCMV seropositive rate is rising in different parts of Iraq, There is high rate of anti-HCMV- IgG antibodies among pregnant and aborted women, The majority of the women infected aged (20-45), Most of the abortion cases happened during the first trimester of pregnancy, ELISA technique used at most, and the socioeconomic status effect the prevalence of HCMV.

Keywords:

1-INTRODUCTION:

Cytomegalovirus, a member of the herpes virus family, is the most prevalent type (CMV). The most common cause of congenital malformation resulting from viral intrauterine infection in wealthy countries is human cytomegalovirus (HCMV) [1]. In the majority of the world, CMV is endemic. The range of the HCMV sero-prevalence, which varies geographically, is between 30 and 100 percent [2]. Is a DNA virus that can infect hosts with healthy immune systems with a variety of illnesses. The most commonly impacted organs are the lung (severe community-acquired viral pneumonia), liver (transaminitis), spleen (splenomegaly), GI tract (colitis), CNS (encephalitis), hematologic system (cytopenias), and multisystem. In immune-competent adults, CMV infections are uncommonly found in the esophagus, pancreas, kidneys, adrenals, salivary glands, and adrenal glands [3]. It is debatable whether CMV must be viewed as a dormant whether an infection is a persistent, slow-replicating one that can reactivate, as in immune-compromised individuals [4,5]. Primary infections are often mild in immune-competent people and frequently happen in the early years of childhood involves the transfer of an infected body fluid, such as salvia, through breast milk. However, estimates place its contribution to 8% of all instances of infectious mononucleosis [6]. Contrary to other infections, Because the virus frequently reactivates throughout the reproductive age and can transfer to the fetus despite maternal immunity, cytomegalovirus (CMV) infection during pregnancy is particularly challenging [7]. CMV infection was a complicated phenomenon because the virus develops a range of immune evasion techniques to escape being eliminated from the host, acting as an immunological modulator. Additionally, Its viral proteins are involved in the control of cellular gene expression, the induction of inflammatory cytokines, or the induction of autoimmune state [8]. The severity of CMV as a health issue was also exacerbated by a number of other issues, including the lack of an approved vaccination and a particular antiviral treatment for HCMV infection [9]. Pregnancy can result in original infection or reactivation of previously acquired congenital CMV, the most frequent cause of congenital viral infections [10]. Cytomegalovirus infection, which is more common in developing countries and in populations with lower socioeconomic status, is the most prevalent viral cause of birth defects in industrialized countries [11]. Furthermore, given the high birth rate and high seroprevalence of congenital CMV, poor nations may in fact bear the brunt of this disease [9]. Since the majority of patients with acute CMV infections have vague symptoms, laboratory techniques are necessary for diagnosis [12]. The discovery of an immunoglobulin G (IgG) or immunoglobulin M (IgM) antibody specific to the virus and associated with low IgG avidity For the diagnosis of primary maternal CMV infection in a pregnant

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woman who was previously seronegative, blood samples must be used [13, 14]. Immunoglobulin M (IgM) specific for CMV is formed during original infection and is also present during reactivation and reinfection [15]. 4 to 8 weeks after the first infection, IgM antibodies are present, and they can last for years. However, false positive results might happen as a result of cross-reactivity with different diseases, such as autoimmune conditions or other viral infections [14]. The presence of CMV IgM has been used as a marker for recent or current CMV infection. As a result, the simultaneous finding of CMV-IgG and IgM in a pregnant woman who has never had a screening test could indicate a primary infection [16]. So, several researchers have backed the need for a CMV specific IgM serological evaluation during pregnancy [17]. IgG antibodies, the only type of antibodies that can cross the placenta, provide passive immunization to the fetus during pregnancy. IgG2 responses are triggered by the combination of capsular and polysaccharide antigens, however IgG2 subclass antibodies are unable to penetrate the placenta. Because of this, some infections linked to these antigens might persist and cause serious intrauterine disease [13]. Cytomegalovirus- IgG antibodies is a marker for past or present infection; it lasts for a long time in the body and provides protection for the remainder of a person's life. IgG seronegativity is a marker of both past and present absence of CMV infection. The detection of CMV-IgG has a low diagnostic value due to the large prevalence of the antibody, but it can be very helpful for identifying seronegative individuals [18]. The presented review summarizes some studies performed in Iraq to find out the Human cytomegalovirus (HCMV) seroprevalence in expectant and post abortive women.

2-Historical facts about Cytomegalovirus:

Ribber [19], observed big cells in slices of a stillborn baby's kidney and in children's parotid glands, mistaking them for protozoa when he first observed intranuclear inclusions of CMV infections in 1881 [19]. Lwenstein [20], In 1907, researchers found these cells in the parotid glands of 4 out of 30 newborns. These intranuclear inclusion-containing cytomegalic cells seem to be described for the first time [20]. Although its viral etiology was unknown in 1950, Wyatt et al. [21], proposed the moniker "generalized cytomegalic inclusion disease (CID)" [21]. Minder [22], Using electron microscopy, researchers in 1953 [22] identified the virus in the clear halo surrounding the intranuclear inclusion of pancreatic cells in a case of CID. The virus was given the name "cytomegalovirus" by Weller [23] in 1970 [23].

3- Cytomegalovirus life cycle and structure:

The shape of the CMV virion is similar to that of the herpes virus, and the replication cycle includes a completely controlled gene expression cascade. The double-stranded DNA is housed in an icosahedral protein capsid on the virion. An exterior lipid coat and a proteinaceous tegument surround the capsid [24]. They enter a cell by a membrane fusion process involving the cell's outer membrane and glycoproteins on the virions' lipid envelope. After the fusion of these two membranes, the DNA-containing protein capsid and the tegument proteins are released into the cell [25]. Other herpes viruses employ a similar cascade in their gene expression patterns [26]. The expression of viral immediate-early genes occurs during the lytic infection [27]. As a result of the expression of these genes, immediate-early viral proteins are created, which change the environment of the host cell and encourage the production of viral early genes [24]. The viral genomic double-stranded DNA is replicated by proteins made by the viral-immediate early genes. Upon DNA replication, these immediately early genes trigger the expression of viral late genes. The virion's structural elements known as viral late proteins play a major role in the assembly and expulsion of recently generated viral units [24]. When specific cell types become infected with HCMV, It is possible to mute early-onset genes, it causes latent infection [28]. Reduced viral gene expression and inhibited assembly and discharge of new viral progeny are characteristics of latent infections [25]. Latent infections, however, can become lytic infections in response to particular environmental cues, which causes illness and promotes viral multiplication [24, 26].

4- Pathogenicity of HCMV:

research to support the association between HCMV infection and age showed that there had been three times where the prevalence of infections are most common in early childhood, adolescence, and during pregnancy. Different secretions of an infected person may contain the virus. such as milk, urine, vaginal discharge, semen, or oropharyngeal discharge and blood substances. When a person comes into contact with a parenterally administered, vertically transmitted, infected person, such as bone marrow or organ transplants, blood transfusions, etc [29]. An important risk factor for the emergence of a serious primary infection is immunosuppression. The previous risk of HCMV pneumonia in this group of individuals was 10–30%, roughly resulting in 80% of fatality. As a result of the prophylactic and/or therapeutic use of antiviral drugs to reduce the frequency of reactivation, some statistics suggest a drop in these numbers [30].

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A remarkable variety of host cells are susceptible to HCMV infection. The virus can also infect several types of hematopoietic cells, as well as parenchymal and connective tissue cells from any organ. Epithelial, endothelial, fibroblastic, and smooth muscle cells are the principal targets for viral propagation [31]. The respiratory system or sexual contact are the two main entry points for infection.

HCMV can persist for a very long time, similar to other herpesviruses, following an initial infection that lasts for years and shows up in the pharynx and urine. The virus is stored in monocytes and polymorphonuclear leukocytes from whence it is discharged. Larger cells are more likely to show the consequences of infection, and "Owl-eyes" are created by the presence of distinctive intracellular inclusions that are encircled by a halo of poor reflection. Among the organs that the virus can infiltrate include the salivary gland, breast epithelium, prostate, endometrial, and kidney tubules. Additionally, the lungs and bone marrow may become infected. This allows it to be distinguished from saliva, tears, breast milk, semen, cervical secretions, blood products, and urine [29]. An infection with HCMV can be latent (not causing any symptoms), lytic (causing symptoms), asymptomatic, or symptomatic. Clinical symptoms of CMV infection in immunosuppressed individuals include protracted fever over 38°C with (or without) leukopenia, hepatitis, pancreatitis, gastrointestinal problems, pain with fever, oesophageal inflammation, dysphagia, disorders that may be linked to Candida infection, interstitial pneumonia, inflammation of the heart muscle, bladder inflammation, and inflammation of the retina - frequently seen in AIDS patients [32].

5- Identification & management:

The diagnosis of HCMV infection may be supported by one of the following: viral isolation, detection of HCMV antigen in blood and tissues, detection of HCMV genome in tissues, DNA amplification, or serology. an electron microscope's ability to detect a typical HCMV virion [33]. The systemic drugs foscarnet, cidofovir, and ganciclovir, or its prodrug valganciclovir have been licensed for the treatment of CMV [34].

6- HCMV research on expectant and post-abortive women

There were numerous research conducted in several locations across Iraq about HCMV seroprevalence in pregnant and aborted women. In a study [35], conducted in Tikirt city, Iraq, from October 2015 to April 2016, the medical records of 173 women who had abortions between the ages of 20 and 50 who had visited the Samaraa General Hospital were examined. *T. Gondii* antibodies were found in 54 (31.2%) of the women who had abortions, whereas 23 (13.3%) had cytomegalovirus infections, and 7 (4.1%) had both toxoplasmosis and cytomegalovirus. This information was obtained by the use of the VIDAS technology. The study also revealed that 77 (44.5%) of aborted women were in the 21- to 30-year-old age range, and that only 30 (17.34%) of these women had anti-cytomegalovirus IgM and IgG antibodies, while 66 (38.2%) of them had antibodies against Toxoplasmosis. In 2017 another study [36], taken place at the Al-Elwiya hospital between May and August 2017, a study involving 122 Iraqi pregnant women with persistent HCMV infection (They were IgG antibody positive) and ten healthy females (whom IgM and IgG antibodies were negative) functioned as a benchmark. Blood samples from the study women's veins were drawn to determine the concentrations of serum anti-HCMV IgG and IgM antibodies. The results of the study showed that HCMV infection rates and antibody titers were both highest in women under the age of 25 (both at 55%), but there was no obvious difference between IgG and IgM levels in the categories of number of pregnancies. In a further study from 2018 [37], (1500) samples from each woman who had an abortion at hospitals in Mosul and Baghdad collected for the study. Al-Salam Teaching Hospital, Al Khansaa Teaching Hospital for Maternity and Children, and Al-Batool Hospital for Gynecology and Obstetrics, respectively, are chosen as the three hospitals in Mosul City, along with Al-Alwaiya Maternity Teaching Hospital, Al-Kademia Hospital for Children, and Al-Yarmuk Teaching Hospital. For each case, information case reports are employed to obtain the information. Each woman who has had an abortion has venous blood collected and placed in three tubes: EDTA blood tubes for molecular tests, serum in a plain tube for serological tests. Viral Transport Media (VTM) was utilized to conduct molecular assays on cervical swabs. Using the ELISA test, 300 positive samples showed the existence of IgM and IgG antibodies. IgG antibodies were positive for CMV in 189 cases (63%) while IgM antibodies were positive for CMV in 146 cases (48.7%). From the 300 positive samples in the ELISA testing, DNA was extracted, and only four samples (1.3 percent) tested positive for CMV using Real-Time PCR. Between January 2015 and October 2018, samples were taken for a cross-sectional study [38] in the Kurdistan region of Iraq, where 1275 women in total were recruited, in order to demonstrate the seroprevalence of Toxoplasma, Cytomegalovirus, and Rubella Infections in women with abortion. 2.82 percent of these patients—36 out

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of 1275—tested positively for anti-toxoplasma IgM antibodies. Additionally, anti-CMV IgM antibodies were found in 29 of 1275 samples (2.27%) and anti-Rubella IgM antibodies in 22 of 1275 samples (both 2.27 percent) (1.73 percent). A case-control study was conducted between October 2018 and April 2019 [39] the control group in Erbil city was made up of 75 pregnant women without a history of abortion or intrauterine mortality and 75 healthy women with normal pregnancies (Kurdistan area, Iraq). The ladies had been referred to the Maternity Teaching Hospital's central laboratory department for the purpose of determining and evaluating the sero-prevalence of CMV-specific IgM and IgG markers. The study found that the sero-prevalence of HCMV-specific IgG was 100% in each study group. None of the women in the control group had a positive IgM, whereas 8 percent of the women who had abnormal pregnancies had a sero-prevalence of HCMV-specific IgM. None of the sociodemographic parameters or risk factors, including abortion, intrauterine mortality, or hypertension, significantly correlated with HCMV-specific IgM sero-prevalence ($p>0.05$). In a study [40], investigates the prevalence of Cytomegalovirus (CMV) in Babylon city, Iraq. To do this, Each woman referred to Babylon Teaching Hospital for Maternity and Children who was pregnant or had an abortion had (90) samples taken from her. Twenty expectant women without a history of abortion were used as the control group out of these. In this investigation, the enzyme immunoassay test kit and enzyme-linked immunosorbent assay were used to measure the IgG, IgM, and anti-HCMV IgG, IgM levels in patients and controls (ELISA). Polymerase chain reaction (PCR) DNA detection for CMV also relies on the amplification of pathogen genomes in a specific region utilizing a variety of primers. Using the Chi-square test, the data were examined. The results show that among 90 samples of women who had CMV infection testing, the seroprevalence titer was significantly higher in seropositive cases at P 0.05, ranging from 62 (89%) toward positive CMV IgG to 65 (93%) of patients from (70) women who had abortions. When compared to the controls, 9 (or 45% of the subjects) had IgG seropositivity while no one had IgM seropositivity. The anti-HCMV IgG result demonstrated a considerable degree of positivity, which represents the majority of CMV infections in females between the ages of 20 and 29. Moreover, the outcomes of molecular detection showed that fewer samples (13, or 19%) had HCMV DNA detectable in them than in pregnant women (3). (15 %). In another study [41], additionally carried out in Babylon, Iraq, Research was done on (145) pregnant women who were sent to the Babylon Teaching Hospital for Maternity and Children in order to ascertain the prevalence of CMV in the province of Babylon. The minividas test was used in this investigation to identify CMV-specific IgM and IgG antibodies in a total of (145) pregnant participants. Blood hemoglobin (Hb) concentration and neutrophil and lymphocyte counts were measured. The C3 and C41 levels in infected women were assessed using a single radial immunological diffusion plate. 95 percent of the 145 pregnant women who underwent CMV testing had positive IgG and 4% had positive IgM results. Women between the ages of 20 and 29 make up the majority of CMV infection cases. While haemoglobin and neutrophil levels were normal, it was discovered that CMV patients had higher lymphocyte counts, lower C4 levels, and higher C3 levels than the control group. A descriptive case control study was conducted to determine the sociodemographic factors associated with the local seroprevalence of CMV in women of reproductive age. [42] took place in Babylon, Iraq. Seropositivity increased between the ages of 26 and 35 and decreased between the ages of 36 and 45, according to this study. But among people aged 26 to 35 and women aged 36 to 45, the evidence of current infection remained constant at 25%. Seropositive status made 77.32 percent of persons vulnerable overall. With a prevalence of 22.68 percent, seropositivity for IgG was most common in educated individuals and those who lived in crowded areas. individuals from poor obstetric backgrounds and situations. The use of various techniques, such as ELISA and ELIFA techniques, technicians' error, the sensitivity and specificity of the used kits to determine anti-HCMV IgG and IgM, the kinetic of HCMV response in the community, the socioeconomic status of the patients, and the patients' educational level could all be contributing factors to the variations in the results of the studies that have been presented.

7- CONCLUSION:

In both pregnant and aborted women, the HCMV seropositive rate is rising in different parts of Iraq, There is high rate of anti-HCMV- IgG antibodies among pregnant and aborted women, The majority of the women infected aged (20-45), Most of the abortion cases happened during the first trimester of pregnancy, ELISA technique used at most, and the socioeconomic status effect the prevalence of HCMV.

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