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Cytomegalovirus Infection in Obstetrics and Gynecology

Rakhimova Madina Mannonovna
Teacher of Samarkand State Medical University

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ABSTRACT

Cytomegalovirus infection is an urgent problem of modern obstetrics and gynecology, which is characterized by a wide distribution, a long latent course, the possibility of participation in the event of infertility and unsuccessful pregnancy outcomes, and a negative impact on the health of the newborn.

Viral infection plays an important role in the development of pathology of pregnancy, diseases of the fetus and newborn. The urgency of the problem of viral infections in obstetrics and perinatology is increasing due to unfavorable socio-economic changes in society, which are manifested in an increased risk of infection in women during pregnancy [1].

It is known that at least 10% of pregnancy pathologies are of an infectious nature. A special role in modern clinical medicine belongs to one of the most common viral infections - cytomegalovirus (CMVI). In 1955, Margaret Smith isolated and cultivated in the laboratory, which gave rise to its active study [2]. CVM (Cytomegalovirus bominis) belongs to the family of herpes viruses. subfamily Betaherpesviridae. It has the specific name Herpeshuman Virus 5 (HHV5) (official name) or Cytomegalovirus (common name) [3]. The genome of the virus contains a double-stranded DNA consisting of 240 thousand base pairs. There are more than 40 strains of wild -Cytomegalovirus, as well as strains isolated in the laboratory (Davis, AD-169, Towne, Kerr) [4]. There are three strains registered in the world. According to the latest epidemiological data, 70% of people are infected with CMV, while the incidence of infection varies from 40 to 80%. Among pregnant women, this figure reaches 89-99%. Primary clinical CMVI occurs in 0.7–4% of all pregnant women.

Age-related infection (reactivation) may occur in 13.5% of infected pregnant women. The source of infection is an infected person. The virus can be found in urine, blood, nasopharyngeal secretions, tears, saliva, cervical and vaginal secretions, semen, milk, amniotic fluid, which serve as a factor in the transmission of CMV.

The virus can enter the human body in various ways:

- ✓ hematogenous (during transplantation of organs and tissues, blood transfusion, intrauterine infection);

- ✓ intranatally (during the passage of the fetus through the infected birth canal of the mother);
- ✓ orally;
- ✓ aerogenic;
- ✓ contact-household way (contact with secrets and excretions on household items, toys);
- ✓ sexually.

Specific modes of transmission are not always clear [5]. Once in the body, the cytomegalovirus penetrates into the cells, where it actively replicates, forming daughter viral particles. Virions leave the infected cell, being covered with an outer shell, in the formation of which the cell membrane of the cell affected by cytomegalovirus participates. Cytomegalyvirus can replicate in any cell of the body. Virus DNA is found in leukocytes, fibroblasts, endothelial, neuroglial, and muscle cells. But cytomegalovirus has the most pronounced tropism for the cells of the epithelium of the ducts of the salivary glands, where it is able to slowly multiply without damaging the cells [6,7]. The most pronounced changes in CMV infection occur in the subpopulation of T-lymphocytes, the level of which falls, at the same time the level of CD4/CD8 suppressors/killers. The subpopulation of lymphocytes increases, the activity of NK cells decreases. At the same time, the regulation of the immune response is disrupted due to damage to the interleukin system [6]. After infection, cytomegalovirus, as a rule, is present in the body in a latent form, mainly in peripheral blood mononuclear cells, periodically reactivating. When a seropositive person is infected with another strain of CMV, the formation of specific immunity against this strain of the pathogen will occur as in the case of primary contact. Previously developed antibodies to other CMV strains inhibit the active replication of the virus, however, effective immune protection will be formed only 2–4 weeks after infection with this strain of the virus [7]. The greatest risk to the fetus is the primary infection in early pregnancy [8,9]. On average, 2% (0.7–4%) of women experience primary CMV infection during pregnancy, with a transmission rate of the virus to the fetus of 35–40% (24–75%) [10,11]. A study of 250 cases of primary maternal CMVI and infection of the fetus showed that the risk of antenatal transmission of the virus from mother to child was 17%, in the case of acute CMVI from 1 to 10 weeks before pregnancy, 35% in case of infection of the mother at 1-5 weeks of pregnancy and 30, 38 and 72% of cases with the development of acute CMVI in the I, II and III trimesters, respectively [12].

In some cases, secondary infection with other CMV strains is observed [13,14]. The frequency of transmission of the virus from mother to fetus is 0.15-0.36%. With a secondary infection or its exacerbation, 0.2-1% of newborns are born infected. The incidence of CMVI is endemic and is not subject to seasonal fluctuations [13, 15, 14]. The presence of CMV in the genital tract in pregnant women is the cause of infection of the child during childbirth. The frequency of detection of CMV in the cervical canal, vaginal secretion of healthy pregnant women ranges from 2–8 to 18–20% [16, 11, 12, 17]. With increasing gestational age, the likelihood of detecting the virus in the vaginal contents increases. Our examination of HIV-infected pregnant women revealed CMV DNA in scrapings from the cervical canal in 33.3% of cases [18]. The risk of intranatal infection of a child in the presence of a virus in the genital tract of the mother is, according to S. Stagno (1995), 50–57% [19]. The main route of infection for a child under the age of one year is the transmission of the virus through breast milk. CMV DNA is found in the milk of up to 60% of seropositive mothers [20]. CMV is excreted in breast milk during the first 2–12 weeks of lactation. Children of seropositive mothers who are breastfed for more than 1 month become infected in 40–76% of cases [20]. It is extremely dangerous to infect a newborn with CMV during a blood transfusion from a seropositive donor that has not undergone appropriate processing. The blood of about 1% of donors contains CMV DNA. Consequently, up to 2-3% of all newborns become infected with CMV during fetal development, 4-5% -

intranatally; by the first year of life, the number of infected children is from 10 to 60%. Among newborns, the frequency of cytomegaly is 0.5–2% based on the detection of the virus in the first month of life. In the presence of CMVI, it is possible to develop an asymptomatic infection without consequences for the health of the child, or the birth of a child with low body weight. The development of infection can lead to the death of the fetus. The congenital form of CMVI can be manifested by fetal malformations; in addition, at the 2–5th year of life, it can manifest itself as blindness, deafness, speech inhibition, and retardation in psychomotor and mental development. The risk group for the development of congenital CMVI is the children of patients who do not have basic immunity to CMV (lack of immunoglobulins - Ig - to CMV in serum).

In the first year of life, CMV antibodies are found in 20% of children, in children attending kindergartens, the prevalence of infection is 25-80%, in the adult population, antibodies to CMV are found in 85-90% of the population [22, 21, 25, 23, 24]. Diagnosis of cytomegalovirus infection Difficulties in diagnosing CMVI are associated with the absence of seasonal cyclical incidence, characteristic clinical manifestations, and the presence of latent forms of the course of the infectious process. The main methods for diagnosing CMV are the serological method with the detection of specific antibodies to the antigens of the virus. To identify the features of the course of infection, it is recommended to determine the avidity of IgM and IgG antibodies to the supraearly protein. Molecular biological methods (DNA hybridization, ligase chain reaction, polymerase chain reaction - PCR) make it possible to detect early stages, latent and persistent infection, quantitative parameters of viremia. The cytological method is used for express diagnosis of CMVI on the surface of the chorion, fetal membranes [26]. respectively [20,27,28].

To increase the specificity of the test (reduce the probability of a false positive result), the immunochemiluminescence method, which has a higher analytical sensitivity and specificity compared to ELISA, is currently recommended for use. The immunoblot method, which allows the detection of anti-IgM and anti-IgG to individual structural and non-structural CMV proteins, is the “gold standard” for detecting IgM class antibodies (analytical sensitivity and specificity 100%), but it is expensive and rarely used in practical healthcare. Antibodies of the IgM class in most cases disappear 1-2 months after the initial infection with the virus. If anti-CMV IgM is detected in the blood, but in the absence of anti-CMV IgG, it is necessary to repeat the blood test after 2 weeks to establish the fact of the appearance of IgG (seroconversion), and in the presence of IgG antibodies, it is necessary to determine their degree of avidity. Antibody avidity characterizes the rate and strength of antigen-antibody binding. Low avidity of anti-CMV IgG with or without specific IgM antibodies in the blood confirms recent (within 3 months) infection. Primary infection with the virus in the case of pregnancy also serves as a marker of a high risk of transplacental transmission of the pathogen to the fetus. The sensitivity of a low maternal antibody avidity index as a risk factor for fetal infection is 100% in a blood test at 6–18 weeks of gestation and 63% in a blood test at 20–23 weeks of gestation (combination with detection of anti-CMV IgM increases this indicator up to 80%). If low avidity is detected at 12–16 weeks, then recent infection before conception cannot be completely ruled out. A test for the avidity of IgG antibodies is mandatory when they are detected together with IgM in a pregnant woman or a newborn. In latent infection, only highly avid IgG antibodies are present in the blood. Reactivation of the virus and especially reinfection (possibly with a new strain of CMV) during pregnancy can also lead to infection of the fetus and the development of congenital CMV infection. Studies show that about 20% of newborns can be infected with CMV when the mother is re-infected during pregnancy, in 30–50% of children with congenital CMVI, mothers were seropositive [29, 28]. Only 17% of women with high titers of antiCMV IgG had children infected in utero [18,27]. Of decisive importance for establishing the presence of an active infectious process (active virus replication) and confirming the nature of CMV organ damage belongs to direct methods for detecting the virus, its antigens and DNA. The clinical and

prognostic significance of the determination of CMV DNA in various biological fluids is not the same. In 20–30% of healthy pregnant women, CMV is present in saliva [16, 20]. The presence of CMV DNA in saliva is only a marker of infection (important only when examining newborns), does not indicate significant viral activity in a pregnant woman and the risk of infection of the fetus. This study to detect active CMVI, in particular in a pregnant woman, is not indicated. The presence of CMV DNA in the urine, detected in 3–10% of healthy pregnant women, proves the fact of infection and a certain viral activity, but due to the long-term detection of the virus in the urine, it cannot be the only laboratory criterion for active CMV infection, especially CMV disease, and requires additional research. Only in 29% of pregnant women with the presence of CMV DNA in the urine (in the vast majority of cases in combination with the presence of CMV DNA in the blood), babies were infected transplacentally [18,27]. The predictive value of the isolated detection of the virus in the urine of a pregnant woman for antenatal CMVI is no more than 20-30%. The likelihood of antenatal infection of the fetus increases with the combination of the presence of CMV DNA in the urine and anti-CMV IgM in the blood of a pregnant woman. The most important diagnostic value is the detection of CMV DNA in the blood. The presence of CMV DNA in the blood leukocytes of a pregnant woman is a reliable sign of active CMV replication and serves as an important marker of a high risk of antenatal infection of the fetus [30]. Direct evidence of infection of the fetus is the detection of CMV DNA in the amniotic fluid and cord blood. If laboratory markers of acute CMVI are detected in a pregnant woman (antibodies of the IgM class, low-avid IgG antibodies, CMV DNA in the blood), it is possible to perform amniocentesis and study the amniotic fluid for CMV DNA 5–7 weeks after the diagnosis of acute CMVI in the mother, but not earlier than 16 th and no later than the 21st week of gestation.

The positive predictive value (probability of detecting the fact of infection of the fetus) is 90–100%, the negative predictive value (specificity) is 92–98% [12, 31]. The absence of CMV DNA in the amniotic fluid means that the fetus is not infected. The risk of CMV infection and the development of clinically significant congenital CMVI in a child is associated with the concentration of CMV DNA in the amniotic fluid. If the amount of CMV DNA is <103 copies/ml, in 83% of cases the child will remain uninfected, if the amount of CMV DNA is 103 copies/ml or more, the child is infected in 100% of cases. The level of CMV DNA <105 copies/ml with a probability of 92% indicates the absence of manifestation of infection in the fetus and newborn. The concentration of CMV DNA in the amniotic fluid, equal to 105 copies/ml or more, indicates the development of a clinically pronounced CMV disease in a child [12, 30, 32]. Algorithm for laboratory examination of a pregnant woman for CMVI markers A planned examination of pregnant women for serological markers of CMVI (antibodies of the IgG, IgM classes in the blood) should be carried out when registering for a dispensary. The feasibility of a routine examination of pregnant women for the presence of CMV DNA in blood cells and urine upon registration at the dispensary and at 22–24 or 32–34 weeks of gestation requires further discussion. Cytomegalovirus infection and infertility The incidence of infertile marriages currently ranges from 10 to 20%. The female factor is the cause of infertility in marriage in about 45% of cases, the male factor in 40%, and the combined factor in 15% [33].

The question of the etiological role of cytomegalovirus in the development of male infertility is considered controversial. Cytomegalovirus can be contained both in whole ejaculate and motile spermatozoa, seminal vesicles, and in prostate tissues [34, 35,36]. In men without clinical manifestations of urogenital tract infections, CMV markers are detected in 8.8% of semen samples. The frequency of detection of the virus increases in the winter months [34]. The frequency of detection of cytomegalovirus DNA in the ejaculate of patients with infertility is 2–3% in France [37], 2.7% in Denmark [38], 3.6–8.7% — in Germany [39, 40], 7.1–56.5% — in Greece [40]; 9.6% - in China [41], 25% - in the USA [42]. There is evidence of a direct

gametotoxic effect of cytomegalovirus infection as a result of infection of immature germ cells and a decrease in their number, which can lead to the development of infertility [36]. However, most researchers point to the absence of the effect of the virus on spermogram parameters [43, 45].

Thus, in a prospective study of subfertile couples conducted by W. EggertKruse, no clinically significant changes in spermogram parameters were noted, and no deterioration in the quality of endocervical mucus in women was also detected. CMVI can be present in semen and cause infection of endometrial cells, but sexual transmission is extremely rare [43]. An earlier study in Taiwan showed similar data, in addition, it was shown that couples suffering from infertility are more often concordantly seropositive and have a positive result for the detection of cytomegalovirus DNA in the urogenital tract [45]. Possibility of transmission of CMV to a donor oocyte in a cycle IVF is incredible. In a study by Witzetal. (1999) examined both partners (women: n = 71; men: n = 60) participating in the IVF program for the presence of antibodies to CMV. Semen before and after preparation, cervical mucosal discharge during oocyte retrieval, embryos not suitable for cryopreservation were frozen in liquid nitrogen. The determination of virus DNA by PCR was carried out in all obtained samples. It was found that antibodies to CMV were found in 62% of women and 37% of men. Viral DNA was detected in 25% of ejaculate samples and 19% of cervical mucus samples. The virus was not detected in any of the oocyte or embryo samples. Based on the data obtained, it was concluded that the transmissible transmission of CMV to oocytes or the embryo is unlikely [41]. In a retrospective study conducted by C. Kling and D. Kabelitz in Germany in 2002 and 2012, it was found that IVF programs revealed IgG to CMV. Moreover, there were 45% women, 34% men in 2002 and 39.8% women and 28% men in 2012. Most couples were concordantly IgG seropositive (20.5%) or seronegative (41.8%). Discordant couples, where the woman is seropositive and the partner is seronegative, accounted for 24.6%, couples in which the man is seropositive and the partner is seronegative, amounted to 13.1% [46]. In couples with implantation failures in IVF programs in Germany, the authors found that among people of reproductive age, 45% of seropositive women, 34% of men, approximately the same ratio was determined in 2012 (39.8% of women and 28% of men). Similar data on the ratio of discordant couples who participated in IVF programs, in which the woman is seronegative and the partner is non-seropositive, were also obtained in the study by R. Levyetal. (1997) - 13.5% [44]. And based on the data, the authors concluded that in Germany more than 55% of women do not have specific anticytomegalovirus antibodies, that is, they are sero-negative. Conclusion: The negative effects of CMVI on the fetus and newborn have been proven. The impact of cytomegalovirus on the reproductive health of both men and women remains controversial and sometimes even controversial. In the modern world, along with the growth of the possibilities of instrumental and laboratory diagnostics, the conditions of human life are also changing. The active development of assistive technologies challenges us to study more carefully every aspect that can affect the reproductive health and pregnancy outcomes of women. Therefore, the study of human cytomegalovirus infection both now and in the near future will remain relevant for scientists of various medical specialties.

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