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Cytomegalovirus Infection and Reproductive Health of Women

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Abstract: Cytomegalovirus infection is an important problem in obstetrics and perinatology, because of its high prevalence, long latent duration, as well as potential negative effect on pregnancy outcomes and infant's health. High rates of infertility, adverse pregnancy outcomes, including pregnancy with the use of reproductive technologies, necessitate the search for the causes of complications, including those of infectious genesis, also with the involvement of cytomegalovirus. In the paper, current literature data on the influence of cytomegalovirus infection on reproductive function of women are reviewed.

Key words: cytomegalovirus infection; pregnancy; infertility

Relevance. Cytomegalovirus is the causative agent of cytomegalovirus infection.

Viral infection plays a key role in the development of pregnancy pathology, fetal and neonatal diseases. The relevance of the problem of viral infections in obstetrics and perinatology is increasing due to unfavorable socio-economic changes in the life of society, which are manifested in an increased risk of infection of women during pregnancy [1]. One of the most common viral infections, cytomegalovirus (CMV), plays a special role in clinical medicine today.

German pathologist H. Ribbert was the first to describe cytomegalovirus-altered kidney and parotid salivary gland cells in deceased newborns in 1881, mistakenly assuming that they were affected by protozoa. In 1955, Margaret Smith isolated and cultured it in laboratory conditions, which gave rise to its active study [2].

Cytomegalovirus belongs to the Herpesviridae family, Betaherpesviridae subfamily and has the species name Herpes human virus 5 (HHV5) (official name) or Cytomegalovirus (common name) [3]. The viral genome contains double-stranded DNA consisting of 240 thousand nucleotide pairs. There are more than 40 strains of wild cytomegalovirus, as well as strains isolated in laboratory conditions (Davis, AD-169, Towne, Kerr) [4].

Specific methods of transmission of infection are not always obvious [8].

Once in the body, the cytomegalovirus penetrates into the cells, where it actively replicates, forming daughter viral particles. Virions leave the infected cell, covered with an outer membrane, the formation of which involves the cellular membrane of the cell affected by the cytomegalovirus. The cytomegalovirus can replicate in any cells of the body. Viral DNA is found in leukocytes, fibroblasts, endothelial, neuroglial, and muscle cells. However, cytomegalovirus has the most pronounced tropism for the epithelial cells of the salivary gland ducts, where it is able to slowly multiply without damaging the cells [8, 9]. The most pronounced changes in CMV infection occur in the subpopulation of T-lymphocytes, the level of which decreases, while the level of suppressors/killers of the CD4/CD8 lymphocyte subpopulation increases, and 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 [8].

After infection, cytomegalovirus is usually present in the body in a latent form, mainly in the mononuclear cells of the peripheral blood, periodically reactivating.

When a seropositive person is infected with another CMV strain, the formation of specific immunity against this strain of the pathogen will occur as with primary contact. Previously developed antibodies to other CMV strains inhibit active replication of the virus, but effective immune protection will only form 2–4 weeks after infection with this strain of the virus [9.10].

Cytomegalovirus infection and pregnancy.

As is known, the pathogenesis of CMV is determined by the interaction between viral replication and the host immune response [8]. A feature of the physiological course of pregnancy is the suppressor changes in the immune system of the mother's body, which ensures immunological tolerance to fetal alloantigens [11].

Cytomegalovirus infection is one of the infections that make up the TORCH syndrome in newborns. Women who register with a antenatal clinic undergo screening tests for the presence of CMV antibodies. In seronegative women with symptoms of primary infection, repeated tests are carried out after 3-4 weeks to confirm seroconversion. Cytomegalovirus infection in pregnant women is usually asymptomatic and in most cases latent. Under certain conditions, cytomegalovirus can reactivate. Such reactivation, without clinical manifestations, can lead to vertical transmission of the virus and, as a result, to spontaneous abortions, premature births [12], developmental anomalies, fetopathy and neonatal disease. Therefore, women from the risk group need virological monitoring of CMV markers and immunocorrective therapy when its active forms are detected [13].

In pregnant women, three forms of CMV infection can be distinguished:

• primary;
• recurrent;
• persistent.

In each of them, 2 variants are distinguished. For primary infection, these variants are the manifest form, which is rare, occurs as a mononucleosis-like syndrome, hepatitis, etc., and the asymptomatic form (often).

The recurrent form of infection can be caused by reactivation or reinfection.

The persistent form includes two stages: productive replication and latency of cytomegalovirus infection.

Primary infection in 24–40% of cases leads to vertical transmission of the virus to the newborn [14–16], and there is a certain relationship between the frequency of antenatal infection of the fetus and the gestational age. Thus, the frequency of vertical transmission of cytomegalovirus in the first trimester of pregnancy is about 30%, and in the third trimester – 40–70% [17]. Intrauterine cytomegalovirus infection in newborns is asymptomatic in 80–90% of cases, and only 10–22% of children have clinical forms of infection and congenital anomalies (in the form of early and late manifestations) [1, 10, 15–19]. It has been noted that although vertical transmission of cytomegalovirus infection in seropositive pregnant women occurs significantly less frequently, the percentage of children with clinical manifestations of this infection is the same in both seropositive mothers and women with primary infection that developed during a given pregnancy [16]. The most dangerous cause of adverse effects on the fetus is primary infection in a pregnant woman in the first trimester of pregnancy. With confirmed vertical transmission of the virus to the fetus, the frequency of birth of children with sensorineural hearing loss was 24% in women infected with CMV for the first time in the first trimester of pregnancy, and only 2.5% in women infected with CMV for the first time in the second and third trimesters. Other complications in children (mental retardation, cerebral palsy, seizures, chorioretinitis) were also 2 times more common in primary CMV in early pregnancy than in the second and third trimesters (32 and 15%, respectively) [13, 20].

Materials and Methods

In case of CMV reactivation or reinfection with another strain of the virus, the infection is asymptomatic for both the mother and the newborn. Children born to such mothers may also have complications of congenital CMV, but this occurs much less frequently (approximately 0.2 to 2%) [15, 20]. The frequency of detection of antibodies to CMV among women of childbearing age in different countries varies from 40 to 100%. The discrepancy between researchers in the frequency of CMV may be a consequence of the heterogeneity of the distribution of herpes viruses in different parts of the globe, as well as, possibly, differences in the sensitivity and specificity of the detection methods used (culture method, PCR or indirect immunofluorescence) [21].

According to domestic authors, the prevalence of the cytomegalovirus in women of reproductive age in Russia ranges from 87.6 to 91.6% [18]. In the USA, seropositive women of reproductive age account for 50 to 80% [20]. From 1 to 4% of seronegative women are infected with the cytomegalovirus during pregnancy [15].

CMV markers are detected in 97.4% of women with a burdened obstetric history and in 97.9% of pregnant women. Cytomegalovirus infection was latent in 61.5% of women with a burdened obstetric history and in 72.9% of pregnant women; recurrent form in 12.5 and 11.3%, respectively, and persistent form in 25.7 and 15.8%, respectively. Observations have shown that persistent form of infection is significantly more often diagnosed in women with habitual miscarriage. A certain correlation has been established between non-developing pregnancy and recurrent form of CMV infection. A high correlation has been shown between the recurrent form of CMV and the threat of termination of pregnancy in the first trimester [8].

The main risk factor for intrauterine infection of the fetus is the recurrent form of CMV in the mother during pregnancy, the immunodeficiency state of the pregnant woman, and a violation of the fetoplacental barrier. The presence of a latent form of CMV in women in labor cannot serve as a prognostic sign of intrauterine transmission of CMV, since

CMV reactivation can occur at earlier stages of pregnancy [18].

In the case of antenatal infection of the fetus, in the overwhelming majority of cases, the transplacental route of transmission of CMV occurs.

In the case of intrapartum infection, the virus enters the body through aspiration, ingestion of infected amniotic fluid or secretions of the mother's birth canal.

A newborn can also be infected through breast milk, which is of particular importance for children with extremely low body weight [9, 22].

Given the high frequency of adverse effects on pregnancy outcome and fetal health, it is very important to correctly assess the risk to the fetus and provide appropriate recommendations to parents to prevent possible consequences if there is a suspicion of possible cytomegalovirus infection in the mother [14].

Detection of TORCH infections is part of the mandatory examination of women with infertility, as well as before entering the IVF program.

Cytomegalovirus infection and infertility. The frequency of infertile marriages currently ranges from 10 to 20%. The female factor is the cause of infertility in marriage in approximately 45% of cases, the male factor - in 40%, and the combined factor - in 15% [25].

The question of the etiological role of the cytomegalovirus in the development of male infertility is considered controversial. Cytomegalovirus can be contained in whole ejaculate and motile spermatozoa, seminal vesicles, and prostate tissue [7, 26, 27]. In men without clinical manifestations of urogenital tract infections, CMV markers are detected in 8.8% of sperm samples. The frequency of detection of the virus increases in the winter months [7]. The frequency of detection of cytomegalovirus DNA in the ejaculate of patients with infertility is 2–3% in France [5], 2.7% in Denmark [28], 3.6–8.7% in Germany [29, 30], 7.1–56.5% in Greece [30]; 9.6% in China [32], 25% in the USA [33].

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 [27]. However, most researchers indicate the absence of an effect of the virus on spermogram parameters [34, 35]. Thus, in a prospective study of subfertile couples conducted by W. Eggert Kruse, no clinically significant changes in spermogram parameters were noted, and no deterioration in the quality of endocervical mucus in women was detected. CMV can be present in semen and cause infection of endometrial cells, but sexual transmission is extremely rare [34]. An earlier study conducted 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 CMV DNA in the urogenital tract [35].

And yet, interest in testing donor ejaculate for the presence of CMV is high, given the risks of adverse effects of the virus on the outcome of future pregnancy.

There are recommendations to include testing ejaculate for herpesvirus markers using PCR in the diagnostic algorithm for male infertility, as well as when using ART and natural pregnancy planning to prevent the risk of vertical transmission of herpesvirus by male gametes [21, 31, 35]. Unfortunately, this leads to an increase in the cost of the process, since it is necessary to test all samples, and not a random selection, taking into account that donor sperm with a positive CMV test at one time will not necessarily be so at another time [28].

According to the recommendations of the American Society for Reproductive Medicine and Assisted Reproductive Technologies for donors of gametes and embryos, testing for cytomegalovirus is necessary for both men and women entering the IVF program. The presence of an active infection in potential sperm donors (detection of CMV by PCR in urine or nasopharyngeal secretions and/or a reliable (fourfold or more) increase in IgG in the study of paired blood sera, detection of IgM at least 30% of the IgG level) is a criterion for exclusion from the assisted reproductive technology program. Insemination from a seropositive partner without signs of active cytomegalovirus infection in a concordant couple is possible, given its high prevalence in the population; however, the risk of superinfection with another strain of the virus and, as a result, damage to the fetus remains (1%). Women with active cytomegalovirus infection are also not included in the program [37].

Discussion

Diagnosis of cytomegalovirus infection.

Difficulties in diagnosing CMV are associated with the absence of characteristic clinical manifestations, the frequency of latent forms of the process, and the absence of seasonal cyclicity [6].

To diagnose CMV, virological methods are used, which involve isolating the virus or detecting its protein antigens in a cell culture infected with materials from patients. Virological methods are combined with immunological methods, which include the determination of specific antibodies of various classes. In addition, molecular biological methods

aimed at determining the genome of the virus are used to diagnose CMV. For this, the polymerase chain reaction is used as a highly specific and sensitive method. But even when using this method, false positive results are possible. It should be borne in mind that PCR, as a highly sensitive method, detects not only the DNA of an actively replicating virus, but also the DNA of a virus in a latent form. Therefore, the PCR method is used in addition to other methods of laboratory diagnosis of CMV [19].

Laboratory markers indicating viral replication are as follows:

- isolation of CMV from clinical samples (blood, cervical mucosa, urethra, vagina, urine, saliva, sperm, etc.) using sensitive cell cultures (the "gold standard");
- detection of virus-specific antigen in patient cells, in cell cultures infected with patient material, and viral extracellular antigen in biological fluids;
- detection of CMV genomic DNA and virus-specific mRNA;
- detection of antiviral M antibodies (during primary infection and reactivation),
- low-avidity G antibodies (during primary infection), and G antibodies to early CMV proteins;
- detection of cytomegalic cells;
- reliable increase (fourfold or more) in G antibodies in a study of paired sera (during primary infection).

As the immune response develops, viral replication ceases [1].

The virological method is the most reliable, but its use requires a significant amount of time, which makes it impossible to carry out timely adequate therapy and prevention [8, 38].

The importance of diagnosing primary cytomegalovirus infection in pregnant women has led to the study of the properties of antibodies produced by the body in response to the infection [39]. Two main properties of antibodies:

- affinity - the degree of specific affinity of the antibody to the pathogen antigen;
- avidity - the degree of strength of binding of the antibody molecule to the antigen molecule.

A close relationship has been established between them: the higher the affinity, the more strongly the antibody binds to the antigen (higher the avidity). The degrees of affinity and avidity allow us to determine the age of class G antibodies and judge the duration of infection and the course of the infectious process (latent course, relapse). In primary infection, an increase in IgG levels occurs over several weeks. Initially, low-affinity antibodies are formed, which are formed during active reproduction of the virus in the body and persist for up to 1.5 months from the onset of the disease. Then the body produces high-affinity IgG antibodies, which persist for a long time, providing immunity from infection [3].

The avidity index is determined quantitatively. An avidity index of less than 30% indicates the presence of low-avidity antibodies and, accordingly, a primary infection, 30–40% - a late stage of primary infection or a recent infection, an index over 40% - a long-standing infection. Primary CMV infection in a pregnant woman is diagnosed based on the detection of seroconversion (the appearance and increase of specific IgG) using enzyme-linked immunosorbent assay (ELISA) and chemiluminescent assay (CLIA) over time, detection of specific IgM in 2 samples (in a pregnant woman, IgM persists for up to 5 weeks), and the appearance of low-avidity (less than 30%) IgG [9, 15].

Reactivation of latent CMV or superinfection with a new CMV strain is diagnosed in the case of a 4-fold increase in the value of specific IgG with an avidity of more than 60%, regardless of the presence or absence of specific IgM, using ELISA/CLIA methods in dynamic studies with an interval of 4–6 weeks, performed in the same laboratory [9].

Despite the fact that ultrasound diagnostics allows identifying signs of congenital CMV only in 30–37.7% of cases, this method is an important part of a comprehensive examination when making a diagnosis and planning further diagnostic measures [39, 40].

In the presence of laboratory and clinical and instrumental signs of primary, exacerbation of latent or superinfection of cytomegalovirus, an examination of amniotic fluid is recommended. Amniocentesis is performed no earlier than 7 weeks from the expected onset of the disease (exacerbation, superinfection) and no earlier than 21 weeks of gestation. The study is performed using the PCR method or the virological method [9, 15]. If amniocentesis is not possible for a pregnant woman, etiotropic therapy for CMV is recommended. In this case, as well as in the absence of signs of congenital CMV during the initial ultrasound examination of the fetus, repeated ultrasound examinations are performed

every 2–3 weeks [9].

Conclusion

More than sixty years of experience in studying the cytomegalovirus have enriched our knowledge of it and its impact on human health, including reproductive function. However, the heterogeneity of the virus, the complexity of the relationship with the host immune response, as well as the widespread prevalence of cytomegalovirus in the human population and, as a result, the combination with other infections that can affect fertility, significantly complicate the task of studying this issue. The negative consequences of CMV for the fetus and newborn have been indisputably proven. The impact of the cytomegalovirus on the reproductive health of both men and women remains controversial and sometimes even contradictory. In the modern world, along with the growth of instrumental and laboratory diagnostics, human living conditions are also changing. Globalization of society, migration of people to megacities, changes in sexual behavior create a favorable environment for the development of mixed infections affecting human health and complicate the task of scientists. The active development of assisted reproductive technologies poses the task of more thoroughly studying each aspect that may affect the outcome of a possible pregnancy. Therefore, the study of human cytomegalovirus infection will remain relevant for scientists of various medical specialties now and in the near future.

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