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EFFECT OF INTRAUTERINE CYTOMEGALOVIRUS INFECTION ON PLACENTAL FORMATION AND THE MECHANISM OF PREGNANCY FAILURE[4]

Abstract:
Intrauterine infection occurs as a result of transplacental, amniotic, ascending or descending infection. The spectrum of pathogens is diverse: bacteria, viruses, fungi, protozoa, mycoplasma, chlamydia, and combinations of pathogens. When an infection enters the body of a pregnant woman, pathological changes in the fetus and amniotic fluid structures can have varying degrees of severity, ranging from local to generalised. Cytomegalovirus infection is a widespread infection in the human population, affecting 50 to 100% of the adult population. The infection leads to miscarriage, severe complications during pregnancy, birth of severely premature babies, birth of children with congenital malformations and internal organ pathologies, autism, further lagging in physical and mental development, and disability of children. Timely prevention of CMV infection before pregnancy and during pregnancy, compliance with hygiene standards, knowledge of leading a healthy lifestyle, culture of sexual relations, methods of contraception and methods of preventing infection with sexually transmitted

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infections, rules for caring for disabled children and the elderly , identification and formation of risk groups among pregnant women regarding primary infection or recurrence of a chronic process, timely laboratory diagnosis of the activity of the infectious process and carrying out specific treatment - make it possible to bear a healthy child, give birth to a healthy generation, and, accordingly, for the country - to have a healthy nation.

Keywords:
pregnancy, infection, miscarriage, placenta, cytomegalovirus.

Prenatal infections are diseases of the fetus or newborn resulting from haematogenous (transplacental), amniotic, ascending or descending infection that develops in the late fetal period (after 22 weeks of pregnancy) with clinical manifestations of the disease during the early neonatal period.

Intrauterine infection is a disease of the fetus with pronounced clinical manifestations, the diagnosis of which is based on the detection of a particular pathogen in the blood, cerebrospinal fluid, or urine. The spectrum of pathogens of intrauterine infection is diverse: bacteria, viruses, fungi, protozoa, mycoplasma, chlamydia, and combinations of pathogens [1, 19,21,22]. Any infectious disease that occurs during pregnancy deserves special attention because it poses a threat not only to the pregnant woman but also to the fetus. Immunodeficiency in a pregnant woman contributes to the activation of infection and the entry of the pathogen into the amniotic fluid, placenta, and fetus. Infection of a pregnant woman has a negative impact on the development of pregnancy and the fetus: the formation of placental dysfunction, miscarriage, non-developing pregnancy, fetal delay, fetal anomalies, antenatal fetal death, stillbirth, severe newborn diseases, and disability of children [2]. However, the presence of an infection in a pregnant woman is a risk factor for adverse pregnancy outcome and termination, but does not always indicate fetal infection (2% to 12% of fetal infections occur) [4, 20, 21,22].

Intrauterine infection is the fact that a microorganism invades the fetus, which does not always lead to pathology and therefore cannot be used as a diagnosis.

The risk factors for intrauterine infection include: chronic foci of infection; primary infection during pregnancy, activation of infection; reduced general and local immunity; slightly increased permeability of the placental barrier in the second and third trimester of pregnancy; complicated obstetric and gynaecological history; bad habits; low social and domestic status; occupational hazards. The ways of infection are: haematogenous, ascending, descending, transmural (spread from the uterine wall to the decidual membrane), contact (during passage through the birth canal).

When the infection first enters the body of a pregnant woman, pathological changes in the fetus and perinatal structures can be of varying severity, local or generalised. The degree of fetal damage depends on the intensity of virus replication, gestational age, and virus aggressiveness. In case of secondary infection, a seropositive woman has antiviral antibodies in her body, so the intensity of viral replication and the degree of viremia decreases, and the risk of transmission to the fetus decreases. The peculiarities of pregnancy in case of intrauterine infection of the fetus, depending on the gestational age, are:

- 1-3 weeks of gestation - blastopathy - contact with an infectious agent results in impaired development of the fetal egg (spontaneous miscarriage), death of the embryo (unviable pregnancy);
- 4-12 weeks of gestation - blastopathy - an infectious pathogen penetrates the chorion, causing impaired organ and system formation, which leads to teratogenic and embryotoxic effects - the formation of systemic fetal pathology, developmental defects at the organ and cellular level, and spontaneous miscarriage;
- from 16 to 26 weeks of gestation - early fetopathy - development of a generalised inflammatory reaction with a predominance of alternative and exudative components with the transition to fibro-sclerotic deformation of organs (endocardial fibroelastosis, polycystic lung disease, micro- and hydrocephalus), spontaneous late miscarriage, premature birth;
- from 26 weeks of gestation - late fetopathy - the development of a manifest inflammatory reaction with damage to various organs and systems (hepatitis, encephalitis, pneumonia, interstitial neuritis, thrombocytopenia).

The following echographic signs may indicate the presence of intrauterine infection in the first trimester of pregnancy: increased local uterine tone, chorionic detachment, deformation of the ovum, progression of isthmic-cervical insufficiency, chorionic hypoplasia, enlargement and persistence of the yolk sac, and discrepancy between the size of the embryo and the size of the ovum cavity. Echographic findings in the second and third trimesters of pregnancy indicating the development of fetal infection are as follows placental dysfunction; fetal retardation, fetal distress; high or low water; increase or decrease in placental thickness, presence of pathological inclusions; contrasting of the basal membrane; calcifications in the fetal liver, spleen, brain; polycystic kidney disease, fetal lungs; fibrous inclusions on the papillary muscles and valves of the fetal heart; dilated intestinal loops; presence of inclusions in the amniotic fluid [2,3,21]. Signs of an infectious process are also confirmed by the results of a morphological examination of the afterbirth, which is characterised by specific changes according to the pathogen.

Cytomegalovirus infection is a widespread infection in the human population. Depending on the geographical characteristics of the region, socio-economic, ethnic and age factors, 50 to 100% of the adult population is infected with cytomegalovirus. The causative agent of cytomegalovirus infection is *Cytomegalovirus hominis*, a DNA-containing virus that belongs to the family *Herpesviridae* (human herpesvirus 5), subfamily *Betaherpesvirinae* [5,18,20,22]. All strains of the virus are etiologically significant for humans. Several strains of cytomegalovirus can be isolated from one person. The virus has the ability to form characteristic large cells in infected tissues that look like an owl's eye. Cytomegalovirus is prone to long-term latent persistence in the human body, being released into the environment for a long time. With the development of immunosuppressive conditions (pregnancy, AIDS, corticosteroid therapy, cytostatics), the latent form of cytomegalovirus infection can become clinically evident. When the virus reactivates, it replicates and is massively shed through saliva, urine, breast milk, semen, and cervical mucus, posing a threat of infection to others.

Cytomegalovirus infection is characterised by the haematogenous (transplacental) route of fetal infection. In this case, the virus penetrates the placental barrier and enters the fetal bloodstream through the interventricular space with subsequent dissemination in its organs and systems. It is also possible to develop the syndrome of "infected amniotic fluid", when the virus reaches the amniotic membranes with the bloodstream, adsorbs to them and infects the amniotic fluid. When the placenta is infected with cytomegalovirus, morphological findings include: focal or diffuse villitis; necrosis of villi and their polymorphic infiltration and/or sclerosis; damage to the villus stroma; hemosiderin grains; blood clots in the vessels; lymphocytic and plasma cell infiltration, especially near the vessels. Inclusions characteristic of cytomegaly are less common, usually found in endothelial cells, sometimes in the trophoblast of villi. The damaging effects of the virus result in placental circulatory disorders with thrombosis and vasculitis, cell necrosis, and immunological reactions with the formation of circulating immune complexes. Changes in the morphological and functional state of cell membranes due to activation of lipid peroxidation processes play a major role in the genesis of placental dysfunction. A high risk of developing chronic placental dysfunction in cytomegalovirus infection is a pronounced suppression of energy metabolism enzymes with the development of histotoxic hypoxia. At the same time, under conditions of hypoxia, the reproductive activity of almost all viruses increases in the fetal tissues, so not only viruses that enter the mother's body during acute viral diseases, but also those that persist in it pose a danger. Long-term persistence of cytomegalovirus or frequent reactivation of this infection adversely affects the condition of the placenta, fetal growth and development, leading to placental dysfunction and fetal delay.

The gestational age is an important factor in the prognosis. Pregnancy with cytomegalovirus infection is usually associated with complications. It has been established that the earlier the embryo or fetus is infected, the more severe the consequences are: non-developing pregnancy; spontaneous miscarriage; miscarriage; intrauterine infection; primary and secondary placental dysfunction; fetal abnormalities; fetal growth retardation syndrome; fetal distress; stillbirth; preterm labour; threat of premature birth; premature detachment of a normally located placenta. The degree of fetal damage does not always correspond to the severity of the mother's disease. Severe fetal damage can be observed in cases of mild or inapparent maternal disease, and even in cases of latent virus carriage. Women with latent infection can give birth to a child with no visible lesions, or with the development of mononucleosis-like syndrome, as well as with latent cytomegalovirus syndrome.

In recent years, not only has the incidence of cytomegalovirus infection increased worldwide, but also the clinical course has become more severe and mortality rates have increased. Cytomegaly (or cytomegalovirus (CMV) infection) is a widespread infection on the Earth, which belongs to infectious processes with unique features of interaction at the level of "virus-infected cell" and "virus-immune system". In different countries, the incidence of cytomegalovirus infection ranges from 45 to 98% (economically developed countries - about 60% of the Caucasian population are seropositive since childhood, countries with low economic development - about 90-98%). Congenital cytomegaly, which is formed as a result of intrauterine transmission of the virus (up to 1-1.5% of fetal infection), is particularly dangerous.

The greatest risk of intrauterine infection and development of severe clinical forms of CMV is primary infection in a pregnant woman (40-50% chance of fetal infection). The risk of infection is high in seronegative women (lacking IgG to CMV) involved in caring for sick children, the elderly and immunocompromised. The incidence of clinically evident congenital CMV infection is 0.2% among children born to socially and economically advantaged mothers, and up to 2.2% among children born to mothers with low socioeconomic status. The risk of infection of a child during breastfeeding by a mother with primary CMV infection is 30-70%. After primary infection, the virus persists for years [7,9,13,14]. Decreased immunity during pregnancy can lead to activation of latent infection. In case of reactivation of latent CMV infection, the risk of fetal infection is much lower (from 0.15% to 1%). The epithelial cells of the mucous membranes are the entry gate of infection. The primary reproduction of the virus occurs in leukocytes and mononuclear phagocytes. The virus has the ability to remain latently in the human body for a long time [3,11,19]. With the development of conditions that lead to a decrease in immunity (HIV infection, administration of corticosteroids and cytostatics), CMV infection can progress from latent to clinically manifested forms. The

virus is transmitted from person to person with all secretions (saliva, urine, blood, tears, cervical mucus); the ways of infection are airborne, contact, sexual, and mother-to-child. In the case of prenatal infection, the virus is transmitted from mother to fetus via transplacental transmission (the risk increases at the end of pregnancy), in intrapartum infection - by contact with the fetal mucous membranes, and after birth - through breastfeeding. The source of infection for a pregnant woman is younger children with whom she comes into contact in the family; her sexual partners; during the performance of professional duties, visits to healthcare facilities; and during haemotransfusion. Among congenital infections, CMV is the most common cause of developmental disabilities and one of the main reasons for mental retardation in the context of sensorineural deafness. Factors that increase the incidence of intrauterine cytomegalovirus infection include: significant genetic variability of virus strains; high prevalence of CMV infection in a certain category; predominance of subclinical forms; variety of mechanisms and routes of infection; immaturity of the fetal and newborn immune systems; reduced functional activity of cellular immunity mechanisms, which can reactivate latent and persistent CMV infection. Placental dysfunction and pathological conditions of the placenta lead to a breach of the placental barrier and fetal infection. In intrapartum infection, the virus enters the fetus through aspiration or ingestion of amniotic fluid, contact with infected maternal birth canal secretions. Antenatal infection can lead to miscarriage, severe fetal damage, and asymptomatic latent carriage of the infection.

Clinical manifestations in the mother during pregnancy with primary infection are nonspecific. The majority of women infected with CMV during pregnancy have no clinical symptoms of the disease, and only a few manifest it as an influenza-like or mononucleosis-like syndrome (lymphadenopathy, hepatosplenomegaly). In the vast majority of cases, congenital CMV infection is asymptomatic or mild or asymptomatic. In the setting of immunodeficiency of various etiologies (HIV infection, drug immunosuppression), disseminated forms of CMV can develop in combination with interstitial pneumonia and vasculitis, lesions of the liver, gastrointestinal tract (specific esophagitis, duodenitis, enterocolitis with ulcerative necrotic damage), central nervous system (encephalopathy, encephalitis), and kidneys, varying in severity. Signs of intrauterine CMV infection can occur both in the newborn period (developmental defects, mental retardation, neonatal disease) and several years later (delayed neuropsychological development, progressive deafness, optic atrophy). Clinical manifestations depend on the gestational age at which the infection occurred: at the stage of blastogenesis (0-14 days), embryo death or the formation of systemic pathology similar to genetic diseases is possible; during embryogenesis (15-75 days), miscarriage and congenital malformations such as microcephaly (53% of children with CMV symptoms), microphthalmia,

hydrocephalus can occur [2, 8, 10]. The most typical clinical manifestations of CMV infection are low birth weight (50%, 34% prematurity), jaundice (67%), hepatosplenomegaly (60%), and hepatitis, neurological disorders (encephalitis, seizures, CNS depression - 7-19%), chorioretinitis (14%), haemorrhagic rash (13%), petechiae or purpura (in the form of "blueberry pie"). Laboratory tests reveal thrombocytopenia and anaemia. Computed tomography scans reveal calcifications in the brain in 70% of children with symptoms of CMV. Long-term consequences of intrauterine CMV infection (from 1 to 58%) develop in children with both clinically manifest and latent forms of infection: sensorineural deafness, epilepsy, cerebral palsy, chorioretinitis, optic atrophy, delayed motor and mental development, delayed speech development, and autism. Intra- or postnatal infection of full-term infants usually leads to latent infection. The incubation period of the disease is 2-4 weeks or more. The most common forms are jaundice, hepatomegaly and splenomegaly, thrombocytopenic purpura and haemorrhagic syndrome. Lymphadenopathy, interstitial pneumonia (respiratory distress, tachypnea, cough, apnoea), CNS lesions (encephalitis), chorioretinitis, and sometimes kidney and gastrointestinal tract lesions are often observed. The results of a complete blood count reveal anaemia, leukocytosis or leukopenia, neutropenia, eosinophilia, thrombocytopenia; biochemical tests show an increase in transaminase levels, hyperbilirubinaemia, and coagulation abnormalities. The course of CMV infection is particularly severe in preterm infants [6, 12, 17]. One of the ways of infection in preterm infants born to seronegative mothers may be nosocomial - as a result of haemotransfusion or (rarely) due to violation of sanitary and hygienic standards.

The prognosis depends on the duration of the infection, the gestational age of the child, and the form and course of the disease. The mortality rate for severe CMV infection is 30%. In the acute course of congenital CMV infection with severe organ damage, 90-95% of surviving children have severe consequences. In the latent course of the disease, disability is possible due to damage to the central nervous system, eyesight and hearing. Among the long-term consequences of CMV infection are the following: deafness - in 58% of children with symptomatic disease and in 7% - with asymptomatic disease; delayed neuropsychological development (40-50% - in symptomatic form, 4% - in asymptomatic form); seizures (23% and 1%, respectively); paresis or paralysis (12% vs. 0%); chorioretinitis (20% and 2%, respectively); dental damage (27% and 4%, respectively) [6, 7,11,16].

Conclusion

The number of infected women is steadily increasing every year, which leads to significant difficulties in carrying a pregnancy, severe complications

during pregnancy, the birth of severely premature babies, the birth of children with congenital malformations and pathologies of internal organs, physical and mental retardation, complications after birth, and even disability. Timely prevention of CMV infection before pregnancy and during pregnancy: adherence to hygienic norms, knowledge about healthy lifestyle, culture of sexual relations, methods of contraception and methods of preventing infection, sexually transmitted, rules for the care of children with disabilities and the elderly, the identification and formation of risk groups among pregnant women for primary infection or recurrence of the chronic process, timely laboratory diagnosis of infectious process activity and specific treatment make it possible to bear a healthy child, give birth to a healthy generation, and accordingly for the country - to have a healthy nation.

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