THE IMPACT OF INTRAUTERINE INFECTION WITH CYTOMEGALOVIRUS ON THE FORMATION OF PLACENTAL PATHOLOGY AND PREMATURE TERMINATION OF PREGNANCY

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Summary

Intrauterine infection occurs as a result of transplacental, amniotic, ascending or descending infection. The spectrum of pathogens is diverse: bacteria, viruses, fungi, protozoa, mycoplasmas, 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, from local to generalized. Cytomegalovirus infection is a widespread infection in the human population and affects 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 pathology of internal organs, autism, further lag in physical and mental development, and disability of children. Timely prevention of CMV infection before and during pregnancy, compliance with hygiene standards, knowledge of a healthy lifestyle, culture of sexual relations, contraceptive methods and methods of prevention of sexually transmitted infections, rules of care for children with disabilities and the elderly, identification and formation of risk groups among pregnant women for primary infection or relapse of a chronic process, timely laboratory diagnosis of the activity of the infectious process and specific treatment

Key words: pregnancy, cytomegalovirus, miscarriage, placenta, infection.

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1. Introduction

Intrauterine infection is a fetal disease with pronounced clinical manifestations, the diagnosis of which is based on the detection of a particular pathogen in the blood, cerebrospinal fluid, and urine. The spectrum of pathogens of intrauterine infection is diverse: bacteria, viruses, fungi, protozoa, mycoplasma, chlamydia, and combinations of pathogens *(Tkachenko Yu.H., 2012).* 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 retardation, fetal anomalies, antenatal fetal death, stillbirth, severe newborn diseases, and disability of children. However, the presence of an infection in a pregnant woman is a risk factor for unfavorable pregnancy and its termination, but does not always indicate fetal infection (2% to 12% of fetal infections occur) *(Shcherbyna, M.O., 2016).*

2. Risk factors and primary changes

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

When the infection first enters a pregnant woman's body, pathological changes in the fetus and amniotic fluid may be of varying severity, localized or generalized. 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, spontaneous miscarriage;

– from 16 to 26 weeks of gestation – early fetopathy – the development of a generalized 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).

Cytomegalovirus infection is a widespread infection in the human population. Depending on the geographical characteristics of the region, socioeconomic, 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 *(Znamenska T.K., 2012).* 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 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 excreted through saliva, urine, breast milk, semen, and cervical mucus, posing a threat of infection to others.

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. Echography 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 liver, spleen, fetal 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 *(Tian, C., 2010; Pylypchuk, I.S., 2021).* Signs of an infectious process are also confirmed by the results of a morphological examination of the afterbirth, which is characterized by specific changes according to the pathogen.

Cytomegalovirus infection is characterized by the hematogenous (transplacental) route of fetal infection. In this case, the virus, penetrating the placental barrier, enters the fetal bloodstream through the interstitial 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, morphologically, the following is observed: focal or diffuse villitis; necrosis of villi and their polymorphic infiltration and/or sclerosis; damage to the stroma of villi; 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 result of the damaging effect of the virus is a violation of the placental circulation against the background of thrombosis and vasculitis, cell necrosis and immunological reactions with the formation of circulating immune complexes. In the genesis of placental dysfunction, one of the main roles is played by changes in the morphological and functional state of cell membranes due to activation of lipid peroxidation processes. 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 negatively 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 complicated. It has been established that the earlier the infection of the embryo or fetus occurs, 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 labor; 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 is observed in cases of mild or non-infectious maternal disease, and even in cases of latent 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, the world has seen not only an increase in the incidence of cytomegalovirus infection, but also a more severe clinical course and an increase in mortality rates. 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 (the probability of fetal infection is 40–50%). The risk of infection is high in seronegative women (who lack IgG to CMV) involved in the care of sick children, the elderly and immunocompromised. The incidence of clinically manifested 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. 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 *(Trubina L.M., 1999; Pylypchuk, I.S., 2021; Rudenko A.O., 2002).* With the development of conditions that lead to a decrease in immunity (HIV infection, 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 the case of intrapartum infection – by contact with the fetal mucous membranes, and after birth – during 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 health care facilities; and during hemotransfusion. Among congenital infections, CMV is the most common cause of developmental defects and one of the main causes of mental retardation in the context of sensorineural deafness. Factors that increase the frequency of intrauterine infection with cytomegalovirus 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 system; decreased 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.

3. Clinical manifestations and prognosis

Clinical manifestations in the mother during pregnancy with primary infection are non-specific. Most 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 asymptomatic. In the setting of immunodeficiency of various etiologies (HIV infection, drug immunosuppression), disseminated forms of CMV can develop in combination with interstitial pneumonia, 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 during the newborn period (developmental defects, mental retardation, neonatal disease) and several years later (delayed neuropsychological development, progressive deafness, optic nerve 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, congenital malformations such as microcephaly (53% of children with CMV symptoms), microphthalmia, hydrocephalus can occur *(Tian, C., 2010).* The most typical clinical manifestations of CMV infection are low birth weight (LBW – 50%, prematurity – 34%), jaundice (67%), hepatosplenomegaly (60%), hepatitis, neurological disorders (encephalitis, seizures, CNS depression – 7–19%), chorioretinitis (14%), hemorrhagic rash (13%), petechiae or purpura (in the form of "blueberry pie"). Laboratory tests reveal thrombocytopenia and anemia. Computed tomography shows calcifications in the brain of 70% of children with CMV symptoms. 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 hemorrhagic syndrome. Lymphadenopathy, interstitial pneumonia (respiratory distress, tachypnea, cough, apnea), CNS lesions (encephalitis), chorioretinitis, and sometimes kidney and gastrointestinal tract lesions are often observed *(Hospodarskyi I.Ia., 2006).* A complete blood count reveals anemia, leukocytosis or leukopenia, neutropenia, eosinophilia, thrombocytopenia; biochemical tests reveal elevated transaminases, hyperbilirubinemia, and coagulation abnormalities. The course of CMV infection in preterm infants is particularly severe *(Pylypchuk, I.S., 2021).* One of the ways of infection of preterm infants born to seronegative mothers can be nosocomial – as a result of hemotransfusion 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, the form and course of the disease. Mortality in severe manifestations of 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) *(Rudenko A.O., 2021; Pylypchuk, I.S., 2021).*

4. Conclusions

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 of children. Timely prevention of CMV infection before and during pregnancy: adherence to hygiene standards, knowledge about healthy lifestyles, sexual relations culture, contraceptive methods and methods of preventing sexually transmitted infections, rules for caring for disabled children and the elderly, identification and formation of risk groups among pregnant women for primary infection or relapse of a chronic process, timely laboratory diagnosis of the activity of the infectious process and specific treatment of.

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