REVIEW ARTICLE

PERINATAL ASPECTS OF INTRAUTERINE INFECTIONS

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ABSTRACT

The aim: To analyze Ukrainian and foreign literature data on the consequences of perinatal infection and the peculiarities of their manifestation.

Materials and methods: Literature sources on the peculiarities of the course of infection that occur in the perinatal period and are a threat of congenital malformations or diseases in the newborn are collected.

Conclusions: The analyzed data of the clinical picture and management of the early neonatal period fully reflect the coherence and timeliness of medical care for infants born with signs of perinatal infection. It should be noted that the tactics of such a newborn depend on the clinical manifestations, the general condition of the baby, and the duration of infection of the mother with a particular infection.

KEY WORDS: fetus, newborn, congenital infections

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INTRODUCTION

To date, one of the biggest problems is an intrauterine infection of the fetus due to its involvement in maternal morbidity and mortality, as well as the fetus. Infections cause the termination of every fifth pregnancy. The causes of infection are different. These include sexually transmitted infections, vaginal dysbiosis, and infections that are part of *TORCH infections*. The list of pathogens that cause perinatal lesions of the fetus is being updated. [1]

Perinatal infection is an infection that is transmitted from mother to child during its fetal development (intrauterine infections), during childbirth (intranatal), or immediately after birth (postnatal). [1] In other words, infection with the pathogen can occur at any time: during pregnancy, during childbirth, or immediately after birth. Intrauterine infections are transmitted to the fetus from the mother transplacentally, intranatal infections – through the infected anogenital area, postnatal – through direct contact of the mother during breastfeeding.

Fetal damage occurs mainly during the early fetal period (9-22nd week of gestation) with the formation of congenital malformations or specific symptom complex (ZVUR, hydrocephalus, brain calcifications, hepatosplenomegaly, severe jaundice).

Possible adverse effects of perinatal infections during pregnancy:
– delay of fetal development;
– premature birth;
– congenital malformations;
– perinatal losses;
– acute infections in the newborn;
– persistent infections in the newborn;
– asymptomatic infections with late clinical manifestations;
– disability from childhood. [2-5]

Among the causes of infant mortality in recent years, fetal VUI occupies one of the first places, causing from 11% to 45% of perinatal losses. VUI is the cause of the whole spectrum of antenatal pathology: infectious diseases of the fetus, malformations, stillbirths, prematurity, development of fetoplacental insufficiency, and fetal growth retardation. [6]

The period of pregnancy at which the pregnant woman becomes infected is the most important pathogenetic factor in the development of VUI. There is an inverse relationship between the stage of pregnancy and the risk of infection: in the first trimester, the risk of infection is 15%, in the second – 45%, and in the third – 70%. [7]

Urogenital infection, which occurred in the mother's body in the first (embryonic) period of pregnancy, is a serious threat because during this period the formation of the placental barrier is not yet complete and can be realized by ascending or hematogenous infection of the ovum. In the second (fetal) three months of pregnancy, the main manifestations of intrauterine infection of the fetus include signs of inflammatory pathology in the amniotic membranes and tissues of the placenta from the placenta, and from the fetus, there is a generalization of the infectious process, various fetopathies, fetal growth retardation. Increased permeability of the fetoplacental barrier causes a high risk of transplacental infection during the trimester. There are four stages of fetal infection. At the first stage, there is excessive growth of opportunistic pathogens or

the presence of pathogenic microorganisms in the mother's body. After the pathogenic flora enters the uterine cavity, the decidual membrane becomes infected (second stage). The resulting local inflammatory process passes to the chorionic membrane – chorionitis. Subsequently, fetal vessels – choriovasculitis and/or amniotic membrane – amnionitis are involved in the infectious process, with subsequent infection of amniotic fluid (third stage). Rupture of the membranes is not a necessary prerequisite for water infection, as the ability of microorganisms to penetrate intact membranes has been established. After bacterial contamination of amniotic fluid, infection of the fetus (fourth stage) can occur in several different ways.

The most common infections that cause perinatal infection are the following:

- *Herpes simplex virus (HSV) type 1 or type 2.*
- *Cytomegalovirus (CMV)*
- *Chlamydial infection*
- *Toxoplasmosis*
- *Rubella*
- *Syphilis*

THE AIM

To analyze Ukrainian and foreign literature data on the consequences of perinatal infection and the peculiarities of their manifestation.

MATERIALS AND METHODS

Literature sources on the peculiarities of the course of infection that occur in the perinatal period and are a threat of congenital malformations or diseases in the newborn are collected.

REVIEW AND DISCUSSION

HERPES SIMPLEX VIRUS TYPES 1 OR *TYPE 2*

Herpes infection is a common cause of minor symptoms in the mother and a rare cause of extremely severe neonatal infection. Congenital intrauterine infection is very rare. However, neonatal infection is associated with high mortality and occurs in approximately 1 case per 3000-5000 births. [8]

Neonatal herpes is a very rare but serious viral infection with a high incidence and mortality. It is classified into three subgroups depending on the locus of infection of the baby:

- skin, eyes, and/or oral mucosa;
- the localized disease of the central nervous system (CNS) (encephalitis);
- disseminated infection with damage to several organs.

Herpetic lesions of the skin, eyes, and/or oral mucosa: Children with symptoms of lesions of the skin, eyes, or oral mucosa have a better prognosis, accounting for about 30% of all cases of neonatal herpes infection. With appropriate antiviral therapy, the rate of neurological and/or ophthalmic morbidity does not exceed 2%. Localized CNS disease and disseminated infection 70% of infants with neonatal herpes have disseminated and/or CNS infection, and in approximately 60% of cases, the disease is characterized by no infection of the skin, eyes, and/or mouth. Localized CNS damage in newborns is usually detected quite late – usually at the age of 10 days to 4 weeks. Against the background of antiviral treatment, mortality from this form of infection is about 6%, and neurological morbidity (the disease can last a lifetime) – 70%. At the disseminated infection, the worst forecast is defined. With the use of appropriate antiviral drugs, the mortality rate reaches 30%, 17% of patients have long-term neurological complications. The bad consequences of disseminated infection and localized CNS damage are explained by the delay between the onset of symptoms and the appointment of treatment. Neonatal infection occurs as a result of infection of the newborn during childbirth, in contrast to congenital herpes, which is extremely rare and is associated with the transmission of infection to the fetus in uterus. [9]

The incidence of neonatal herpes in the UK is about 50% of the number of reports from other European countries. In the United States, the average incidence reaches 1 in 15 thousand live births per year, but there are significant differences between populations, in particular in some disadvantaged groups of the urban population (1: 7500).

The tactics of managing newborns born to mothers with HSV infection, which arose in the third trimester, is to monitor the baby during the first 24 hours after birth, informing parents about the hygiene of child care. It is established that the risk of transmission of the infection from the mother in the case of infection with the herpes simplex virus in the third trimester is very low and does not pose a threat to the baby.

Intranatal herpes virus infection has a high risk of infecting the baby, so swabs from the mouth and nasopharynx, skin, rectum, and conjunctiva are needed to test for the presence of the herpes simplex virus by PCR. Also, prescribe therapy with acyclovir at a dose of 20 / kg every 8 hours until the exclusion of the presence of active infection in the infant. However, cohabitation with the mother and breastfeeding is not prohibited if the woman does not have herpetic rashes around the nipples. If the condition of the newborn is unsatisfactory, in addition to the above smears for PCR testing and active therapy with acyclovir, a spinal tap is taken for examination, even in the absence of CNS damage.

If a woman has a recurrent herpes infection, the risk of infecting the baby is very low. In this case, swab collection and treatment of newborns are not performed.

CYTOMEGALOVIRUS (CMV)

In the world, cytomegalovirus infects up to 2% of newborns and 45-60: in the first year of life. In addition, according to the WHO, the detection of antibodies to *CMV* in different segments of the population is tweed 40 to 100%.

The virus belongs to the family of parvoviruses and is transmitted only from person to person. The most danger-

ous moment of infection of the child is the passage of her birth canal. The virus also enters breast milk. [10]

Intrauterine infection can occur at any time. In newborns, the most common manifestations of infection were respiratory distress syndrome (RDS), anemia. Intrauterine *CMVI* can occur in the form of generalized and local forms, there are acute, subacute, and chronic stages.

In the early stages of ontogenesis, the fetus is most sensitive to the action of *CMV*, because the virus has tropism to cells with a high level of metabolic processes. The fetus may die, or a malformation of the internal organs and brain. For such newborns, acute and subacute stages of infection occur in utero, they are born with manifestations of chronic *CMVI*. They are dominated by the following defects: holoprosencephaly, microcephaly, spinal hernia, hydrocephalus, coloboma, cataracts, underdevelopment of the eyeball, syndactyly, cyst fibrosis of the pancreas, heiloschis, palatoschis, and others. After birth, signs of generalization of the infection develop in the form of interstitial pneumonia, hepatitis, and other diseases. Among the neurological signs prevails and long-lasting syndrome of CNS depression, develops, if not formed in utero, hydrocephalus.

When infected in the late fetal period or during childbirth, children are born with signs of acute *CMVI*, which is most characterized by a generalized form of infection.

The generalized form often simulates the course of hemolytic disease of newborns, especially its prenatal form. The main symptom is jaundice. Hepatosplenomegaly, which is characteristic of 95% of newborns with intrauterine *CMVI*, appears early.[11]

In the blood serum, there are high levels of indirect and direct bilirubin, increased activity of transaminases, and alkaline phosphatase. The general signs of intoxication are expressed. *Cytomegalovirus* hepatitis is characterized by damage to the bile capillaries. Clinically, this is manifested by cholestasis and subsequent development of liver failure and portal hypertension.

Changes in the liver are often accompanied by CNS damage in the form of meningoencephalitis, dominated by CNS depression. The process is associated with the direct action of the virus on neurons, as well as with toxic effects on small vessels of the brain with disruption of their nutrition and oxygen transport and the development of autoimmune mechanisms of CNS damage.

Characteristic and such local manifestations of *CMVI* as respiratory distress syndrome, anemia. Polychromic anemia is accompanied by reticulocytosis, normoblastosis, thrombocytopenia. Hemorrhagic syndrome develops in the form of petechiae, ecchymoses, nasal, umbilical hemorrhages, melena.

Jaundice on the background of hepatosplenomegaly, anemia, hemorrhagic syndrome, and meningoencephalitis – the most typical manifestations of generalized intrauterine *CMVI*.

Localized forms, in addition to those listed above, are also characterized by interstitial chronic pneumonia, obstructive bronchitis. At involvement in process of small bronchial tubes and bronchioles, peribronchitis develops, at the transition to a chronic stage – fibrosis, and pneumosclerosis.

The prognosis in such newborns is unfavorable, mortality reaches 60-80%. More than 90% of surviving children have psychoneurological disorders, delayed psychomotor reactions, intellectual and speech development, deafness, chorioretinitis with optic nerve atrophy, dental development disorders, diabetes mellitus. [12]

Chlamydial infection (XI). In the structure of STIs, chlamydial infection (XI) occupies a leading position. The results of studies by European scientists have shown that 80% of acute PID develop due to STIs, with 60% due to XI and only 20% due to other infections [8]. XI leads to a variety of reproductive health disorders in women, including the development of chronic salpigophoritis, tubal-peritoneal infertility, and ectopic pregnancy. 70% of patients with chlamydial cervicitis often have an erased clinic, in some cases – asymptomatic course of the disease.

The share of chlamydia infection in pregnant women is 5-40%, and with a burdensome obstetric and gynecological history (salpingo-oophoritis, infertility, miscarriage) – up to 63%, while in 4-11% urogenital XI occurs without clinical manifestations in pregnant women XI can lead to asymptomatic bacteriuria, inflammatory diseases of the urinary and genital tract, the development of cervicitis, obstetric complications with possible antenatal infection of the fetus. The main pathogenetic factor contributing to the development of intrauterine infection is an infection of amniotic fluid, at the same time with chlamydial cervicitis infection of the fetus can occur during childbirth. When involved in the process of the fallopian tubes, endometrium *Ch. trachomatis* penetrates the decidual membrane, the chorion, which contributes to the pathogen entering the amniotic fluid, in the future the infection can affect the conjunctiva, urethra, vagina, causing various clinical forms of perinatal infections. During the passage of infected birth canals in newborns may develop a chlamydial infection in the form of neonatal conjunctivitis (22-44% of cases). Also, 2-12 weeks after birth, the respiratory system may be damaged up to pneumonia, which can give complications in older age (11-20%). When infecting women *Ch. trachomatis* in the early stages, when the embryo develops, there are infectious embryopathies, which are manifested by congenital malformations of the fetus. In the early stages of pregnancy, primary placental insufficiency begins to form, which can lead to miscarriage or miscarriage.

At the infection of the woman in later terms of gestation threatening miscarriage, formation of secondary placental insufficiency, polyhydramnios, premature childbirth are more often observed. XI also causes complications during childbirth, most often premature rupture of the amniotic sac. Ingestion of infected amniotic fluid often leads to the defeat of *Ch. trachomatis* of the lungs and digestive tract of the fetus, as evidenced by infection of the entire amniotic sac in the case of removal of the fetus by cesarean section.

Intrauterine infection of the fetus is verified by morphological examination of dead newborns, reveals the defeat of

Ch. trachomatis meninges, vascular plexuses of the brain, and lungs. With the hematogenous route of infection in the fetus, there are various pathological changes in the form of the edema-hemorrhagic syndrome, hemorrhage into the ventricles of the brain, pneumopathy, hepato-renal and adrenal insufficiency, which is the direct cause of antenatal fetal death or early neonatal death. [13]

TOXOPLASMOSIS

Toxoplasmosis is a parasitic disease caused by protozoa, which is characterized by damage to the nervous and lymphatic systems, eyes, skeletal muscles, myocardium, and other organs. The causative agent of this disease is an intracellular parasite – *Toxoplasma gondii* (belongs to the type of protozoa and has a crescent shape, size 4-7x1.5 μm). The final host is cats and other animals of the same family,intermediate – man and several other mammals and birds. Human infection occurs through food when eating insufficiently cooked meat.

The pathogenesis of toxoplasmosis remains poorly understood. getting into the human body in different ways, toxoplasmas are captured by macrophages, transported to the lymph nodes, where they multiply and enter the bloodstream. On lymphatic and blood vessels parasites can extend on bodies and fabrics, be fixed there, and cause inflammatory changes of alternative-productive character. Exudative, especially purulent inflammation is uncharacteristic of toxoplasmosis. [14-16]

Within 3 weeks in an organism, antibodies are made and accumulate, serological reactions become positive. Further toxoplasmas form real cysts in the tissues, the inflammatory reaction disappears, the foci of necrosis are organized or calcareous.

There are acquired and congenital toxoplasmosis. Acquired toxoplasmosis affects adults and older children, congenital occurs in fetuses and newborns in the first months of life. The gate of infection in acquired toxoplasmosis, as a rule, is the ileum. This is evidenced by a pronounced reaction of the mesenteric lymph nodes. In the latter, there is hyperplasia with the presence of giant multinucleated cells. Quite characteristic liver damage: there is hepatitis with cholestasis, small foci of necrosis, and billion granulomas. Typical lesions of the muscles of the lower leg and lower back, myocardium, rarely in the muscle tissue of other organs. They are areas of intermediate productive myositis, rarely focal muscle necrosis. Encephalitis sometimes develops against the background of immunodeficiency. [17]

The occurrence of congenital toxoplasmosis is due to the ability of toxoplasmosis to penetrate the placental barrier. The risk of transplacental transmission of the infection increases with increasing gestational age. Intrauterine infection of the fetus is possible only in cases of infection of women during pregnancy. The most dangerous for the fetus is the infection of women between the 10th and 24th weeks of pregnancy, as at this time the relatively high risk of transplacental infection of the fetus is combined with severe damage to the brain and other internal organs. [18]

There are three scenarios of toxoplasmosis infection for the baby: 1. Primary infection in a pre-seronegative mother. 2. Reactivation of the pathogen during pregnancy in a mother who had the fact of infection before pregnancy. 3. After re-infection of a previously immune pregnant mother with a new, more virulent strain (for example, after international travel or after eating undercooked meat from areas where more virulent atypical strains predominate). [19]

Clinical manifestations of congenital *toxoplasmosis* are characterized by significant polymorphism from subclinical variants to severe lethal forms of the disease. Clinically manifest forms of congenital toxoplasmosis (VT) develop in 12-25.5% of cases [9] and are prognostically unfavorable. Without adequate treatment, infected children develop hydrocephalus and microcephaly, movement disorders, mental retardation, episyndrome, and loss of vision and hearing after months or years. Subclinical forms of VT also do not go unnoticed, in 50-60% of cases the development of late manifestations of VT during puberty is possible. Exacerbations of chorioretinitis are common, with serious consequences in the form of decreased vision and intellectual deficits.

To date, the most effective treatment for toxoplasmosis infection is the administration of a combination of sulfadoxine/pyrimethamine, which acts synergistically and blocks the metabolism of folic acid in replicating tachyzoites. Additional administration of folinic acid prevents the toxic effects of pyrimethamine on the red bone marrow. Cells in the human body can use folinic acid to synthesize nucleic acids, but toxoplasma cannot. Sulfadoxine / pyrimethamine is prescribed to children in the first 2 days in a saturation dose – pyrimethamine 2 mg / kg per day (maximum 50 mg / day), and then – in a maintenance dose – 1 mg / kg per day (maximum – 25 mg / day) . The dose of drug saturation is 75 mg/kg per day, maintenance – 50 mg/kg every 12 hours. Of the antibiotics used to treat toxoplasmosis, including in pregnant women and infants, spiramycin is used; in case of intolerance, clindamycin and azithromycin are prescribed. [20]

RUBELLA

Congenital rubella occurs in the primary infection of the mother during pregnancy. It is known that the rubella virus can penetrate the placenta, causing hypoplasia, and the formation of conglomerates of fibrin-fused villi in the first half of pregnancy. There is also evidence that maternal and fetal macrophages are actively involved in the transmission of infection across the blood-brain barrier. Depending on the duration of infection, different types of fetal damage are caused. The most pronounced lesions are observed when infected in the first trimester. During this period, infant mortality is 10-25%. At later infection, congenital malformations of fruit are observed. [21]

In pregnant women, rubella may be asymptomatic or with catarrhal phenomena of the upper respiratory tract, a slight fever, swollen lymph nodes (especially occipital and auricular), and maculopapular rash. The disease may be accompanied by joint damage.

Congenital rubella syndrome (CRS) is a situation where the fetus develops death in the womb or multiple abnormalities, or there may be no consequences. The most common anomalies include:
- Delayed fetal development
- Microcephaly
- Meningoencephalitis
- Cataracts
- Retinopathy
- hearing loss
- heart defects (non-overgrowth of the ductus arteriosus and pulmonary artery stenosis);
- hepatosplenomegaly
- bone thinning

Less common manifestations include thrombocytopenia with purpura, cutaneous erythropoiesis, which causes bluish-red skin lesions, lymphadenopathy, hemolytic anemia, and interstitial pneumonia. Continuous monitoring is required to detect subsequent hearing loss, mental retardation, behavioral disorders, endocrinopathy (eg, diabetes mellitus), or, in some cases, progressive encephalitis. Infants with congenital rubella may develop immunodeficiencies such as hypogammaglobulinemia. [22]

Treatment of rubella, like other viral infections, is symptomatic. Since vaccination is the best way to prevent this disease, it is the only sure way to avoid infecting the fetus and causing it to be infected with the virus.

SYPHILIS

The causative agent of syphilis belongs to the order *Spirochaetales*, family *Spirochaetaeceae*, genus *Treponema*, species *Treponema pallidum*, subspecies pallidum (syn. *Spirochaeta pallidum*). Pale treponema is easily destroyed under the influence of external agents: drying, heating at 55 ° C for 15 minutes, exposure to 50-56% solution of ethyl alcohol. At the same time, low temperatures contribute to the survival of pale treponema. Pale treponema is a spiral-shaped microorganism; the number of revolutions of the spiral from 8 to 12, its curls are uniform, have an identical structure. Performs characteristic types of movement: rotational, translational, wavy, and bending. Propagated mainly by transverse division into two or more segments, each of which then grows into an adult. The microorganism can also exist in the form of cysts and L-forms. The cyst is a form of survival of pale treponema in adverse environmental conditions, is considered a dormant stage of T. pallidum, and has antigenic activity. L-form is a way of survival of pale treponema, which has weak antigenic activity.

According to official state statistical reports, the epidemiological situation regarding the incidence of syphilis in Ukraine is generally characterized by a gradual decline (in 2014 – 3674 cases (8.6 per 100,000 population) in 2015 – 3228 cases) (7.6 per 100 000 population).

There is early and late congenital syphilis. Early syphilis is any syphilitic condition that occurs before the age of 2 years. The main manifestations and types of syphilis include:
- skin lesions
- lesions of the mucous membranes
- visceral
- laryngitis
- oculopathy
- osteochondropathy
- pharyngitis
- pneumonia
- rhinitis.

Late congenital syphilis is attributed
- Late congenital syphilitic investment keratitis
- Late congenital oculopathy
- Neurosyphilis.

For the treatment of syphilis use the following treatment regimen:
- benzylpenicillin sodium crystalline salt (B): children under 1 month – 100 thousand IU per kg of body weight per day, divided into 4 injections (every 6:00). Given the anatomical and physiological features of the urinary system in newborns and children in the first month of life, it is permissible to reduce the frequency of administration of penicillin to 4 times a day.
- intramuscularly; children aged 1 to 6 months – 100 thousand IU per kg of body weight per day, divided into 6 injections (every 4 hours), intramuscularly; children older than 6 months – 75 thousand IU per kg of body weight per day intramuscularly; children older than 1 year – 50 thousand IU per kg of body weight per day intramuscularly for 20 days with monosymptomatic and latent forms of early congenital syphilis and for 28 days – with manifest syphilis and central nervous system damage (confirmed by positive serological reactions of cerebrospinal fluid)) [1,2,3]. If the mother refuses to perform a lumbar puncture on the child, the course of treatment should also be 28 days). These terms of treatment should also apply to alternative therapies (ampicillin, ceftriaxone) [23]

CONCLUSIONS

The analyzed data of the clinical picture and management of the early neonatal period fully reflect the coherence and timeliness of medical care for infants born with signs of perinatal infection. It should be noted that the tactics of such a newborn depend on the clinical manifestations, the general condition of the baby, and the duration of infection of the mother with a particular infection.

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