Novelties regarding perinatal infections

Adrian Ioan Toma[1,2], Raluca Daniela Bogdan[3], Consuela-Mădălina Gheorghe[4], Teodor Salmen[5,6], Corina Grigoriu[7,8], Bianca Margareta Mihai[9], Vlad Dima[9], Roxana Elena Bohîlțea[7,9], Simona Vlădăreanu[7,10]

1. Department of Neonatology, Life Memorial Hospital, Bucharest, Romania

2. "Titu Maiorescu" University of Medicine and Pharmacy, Bucharest, Romania

3. Department of Pediatrics, Medicover Hospital, Bucharest, Romania

4. Department of Marketing and Medical Technology, "Carol Davila" University of Medicine and Pharmacy, Bucharest, Romania

5. "Carol Davila" University of Medicine and Pharmacy, Bucharest, Romania

6. "Nicolae Paulescu" National Institute for Diabetes Mellitus, Nutrition and Metabolic Disorders, Bucharest, Romania

7. Department of Obstetrics and Gynecology, "Carol Davila" University of Medicine and Pharmacy, Bucharest, Romania

8. Department of Obstetrics and Gynecology, Bucharest University Emergency Hospital, Romania

9. Department of Obstetrics, Gynecology and Neonatology, "Filantropia" Clinical Hospital of Obstetrics and Gynecology, Bucharest, Romania

10. Department of Obstetrics and Gynecology, "Elias" University Emergency Hospital, Bucharest, Romania

Corresponding author:
Consuela-Mădălina Gheorghe
E-mail: consuela.gheorghe@umfcd.ro

Abstract

The increase in the number of microorganisms that cause maternal-fetal infections has led to the need to update the acronym TORCH (Toxoplasma, Others, Rubella, Cytomegalovirus, Herpes) to SCRATVHEZ (Syphilis, Cytomegalovirus, Rubella, AIDS, Tuberculosis, Varicella, Herpes, Enterovirus, Zika). The multiple routes of transmission (transplacental, intrapartum, breast milk or posttransfusion), the multitude of microorganisms generating various and complex complications – from quasi-asymptomatic diseases to intrauterine growth restriction, neurological sequelae and to fetal death, the treatment that varies from case to case, between symptomatic and etiological and the possibility of preventing infections, outline their complexity and importance. A complete and correct early diagnosis involves clinical, biological and serological evaluation from the prenatal period, in order to prevent the evolution of infections, especially in the case of those in which there is an etiological treatment. The importance of knowing these infections and the effort to prevent their transmission, in order to limit the development of the consequences they can cause, are key elements in the optimal management of a pregnancy.

Keywords: *intrauterine infections, TORCH, SCRATVHEZ, congenital syphilis, cytomegalovirus infection, congenital rubella, HIV, tuberculosis, congenital toxoplasmosis, perinatal varicella, herpes simplex virus, enterovirus, parechovirus, Zika virus*

Rezumat

Creșterea numărului de microorganisme care provoacă infecții materno-fetale a dus la necesitatea actualizării acronimului TORCH (Toxoplasma, Altele, Rubeola, Citomegalovirus, Herpes) la SCRATVHEZ (Sifilis, Citomegalovirus, Rubeola, SIDA, Tuberculoză, Varicelă, Herpes, Enterovirus, Zika). Căile multiple de transmitere (transplacentară, intrapartum, laptele matern sau posttransfuzie), multitudinea de microorganisme generatoare de complicații diverse și complexe – de la boli cvasiasimptomatice la restricționarea creșterii intrauterine, sechele neurologice, până la moartea fetală, tratamentul care variază de la caz la caz, între simptomatic și etiologic și posibilitatea prevenirii infecțiilor, conturează complexitatea și importanța acestora. Un diagnostic precoce complet și corect presupune evaluare clinică, biologică și serologică încă din perioada prenatală, pentru a preveni evoluția infecțiilor, mai ales în cazul celor în care există tratament etiologic. Importanța cunoașterii acestor infecții și efortul de a preveni transmiterea lor, pentru a limita dezvoltarea consecințelor pe care le pot provoca, sunt elemente-cheie în managementul optim al unei sarcini.

Cuvinte-cheie: *infecții intrauterine, TORCH, SCRATVHEZ, sifilis congenital, infecție cu citomegalovirus, rubeolă congenitală, HIV, tuberculoză, toxoplasmoză congenitală, varicela perinatală, virus herpes simplex, enterovirus, parechovirus, virusul Zika*

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Introduction

The number of microorganisms involved in maternal-fetal infections is increasing, so the old acronym TORCH (Toxoplasma, Others, Rubella, Cytomegalovirus, Herpes) becomes insufficient and is replaced by the acronym SCRATVHEZ (Syphilis, Cytomegalovirus, Rubella, AIDS, Tuberculosis, Varicella, Herpes, Enterovirus, Zika). The transmission of the pathogen can occur in three ways: transplacental, intrapartum or through breast milk or, rarely, by transfusion, leading to inflammatory or teratogenic maternal-fetal effects, clinically reflected by various degrees of impairment, respectively asymptomatic, acute symptomatic or chronic progressive infection, or sequelae after intrauterine infection. Each pathogen has particularities of evolution, diagnosis, prognosis and treatment[1,2].

Congenital syphilis

Congenital syphilis is caused by *Treponema pallidum*, an extracellular, spiral microorganism that causes a sexually transmitted infection in adults, that develops in four stages (primary, secondary, latent and tertiary), and in a neonate a transplacental infection that develops in two stages (early congenital syphilis, if the signs appear in the first two years of life, a stage corresponding to adult secondary syphilis; and late congenital syphilis, signs that appear after two years – a sequelae stage corresponding to adult tertiary syphilis)[3].

The risk of vertical transmission depends on the stage of maternal infection (Kassowitz's law): it is high in mothers with primary or secondary syphilis, and low in mothers with latent syphilis (however, there is a significant risk in early latent syphilis) and tertiary syphilis[4].

The clinical manifestations can be caused by damage to any of the body's apparatus and systems. One-third of neonates with congenital syphilis are symptomatic at birth and two-thirds are asymptomatic; thus, in the absence of treatment, they will develop signs and symptoms years later[5].

Congenital syphilis has been arbitrarily divided into two categories: early or late. In the early stages, clinical signs may appear intrauterine: fetal hydrops, hepatosplenomegaly, intrauterine growth restriction or placental abnormalities; or in the first two years of life: skin, mucosal, visceral, hematological, osteoarticular, central nervous system and, rarely, pulmonary or renal (Table 1)[3,6-9]. In the case of the late congenital syphilis, the clinical signs appear after two years and are represented by dental abnormalities (incisors with central notch), interstitial keratitis, deafness by affecting the cranial nerve eight (Hutchinson's triad), to which facial abnormalities (protrusion of the mandible, hypoplasia of the middle layer of the face, rhagades at the site of skin lesions), coryza, bone signs, signs of central nervous system damage (mental retardation, seizures, optic nerve atrophy, cranial nerve palsies) are added, which can be prevented by treating the child at risk, with the exception of chorioretinitis[3,6].

The definitive serological diagnosis is made by the isolation of *Treponema* from lesions (usually cutaneous) or culture by inoculation in rabbits and includes two types of tests: *Treponema pallidum* hemagglutination (TPHA), which identifies antitreponemal antibodies and are specific, but remain positive throughout life, unable to identify progression and the stage of the infection and which, because antibodies pass passively through the placenta, cannot be used to identify the infection in the neonate; and nontreponemal (VDRL), which identify anti-cardiolipin antibodies, are positive in syphilis but also in other diseases, especially autoimmune; the quantitative ones can help diagnose congenital syphilis and assess the evolution of the disease, and those from cerebrospinal fluid (CSF) can determine the presence of neurosyphilis[3,10].

The management of the neonate at risk of congenital syphilis is achieved by prevention and early diagnosis of the pregnant woman, respectively mandatory VDRL testing twice during pregnancy, at the beginning and at 28 weeks. Afterwards, in the case of pregnant women at risk, the test will be repeated at birth, and the neonate will not be discharged from the maternity without at least a VDRL test performed in the mother during pregnancy or postnatal. Postpartum, a quantitative VDRL test is performed in the mother and the neonate, but not from the umbilical cord blood, due to the significant risk of false-positive reactions, and the neonate with a positive VDRL test or risk of syphilis based on maternal history will be clinically examined for signs of congenital syphilis[10].

The diagnostic and therapeutic management should consider the following factors: identification of maternal syphilis, treatment received by the mother (appropriate or inappropriate), presence of clinical signs, laboratory or radiological signs of syphilis in the neonate and comparison of VDRL titer in the mother and neonate. The following situations may occur: **confirmed congenital syphilis** (evidence of *Treponema pallidum* in placental, umbilical cord or neonate lesions), **presumptive congenital syphilis** (quantitative VDRL test with a titer fourfold higher in the neonate than in the mother and signs of congenital syphilis), **possible congenital syphilis** (asymptomatic neonate with a VDRL titer equal to or less than fourfold that of the mother, and any of the following: mother treated improperly or no treatment record,

Table 1 Postnatal signs of early congenital syphilis infection

Skin	*Mucosal lesions*, mostly buccal, replaced at 2-3 months by wide warts; syphilitic coryza, which occurs in the first week of life and indicates damage to the respiratory tract; *syphilitic rash*, with copper-colored oval maculopapules, which then turn brown, similar to those of secondary syphilis, appearing 1-2 weeks after the onset of rhinitis; sometimes *syphilitic pemphigus* in the palms and soles, with severe infectious lesions and scaling of the palms and soles.
Visceral	*Hepatomegaly* associated or not with splenomegaly is the most common, sometimes detected antenatal. It occurs due to extramedullary hematopoiesis and direct infection. *Jaundice* may be the only manifestation of the disease.
Hematological	Anemia (Coombs-negative hemolytic), thrombocytopenia (consumption) and leukopenia or leukocytosis.
Bones and joints	These are symmetrical lesions that most commonly affect the long bones; *periostitis* (radiologically visible from birth); *bone demineralization* and osteochondritis mostly affecting the knees, elbows, ankles and fists. The *Wimberger's sign* is radiologically characteristic and consists of demineralization and bone destruction in the medial metaphysis of the tibia. Parrot pseudoparalysis; pathological bone fractures are the only symptomatic bone change.
Central nervous system	Acute syphilitic leptomeningitis, between 3 and 6 months, with a clinical presentation of acute meningitis: stiff neck, vomiting, bulging fontanelle, altered general state. Chronic meningovascular syphilis appears at the end of the first year of life and develops slowly, progressively, with progressive hydrocephalus, paralysis of the cranial nerves (III, IV, VI), strokes and impaired intellectual function.
Other signs	Syphilitic pneumonia – white, fibrous pneumonia, with radiological appearance of opacification of both lung fields. Nephrotic syndrome, at 2-3 months, caused by circulating immune complexes.

mother treated with an antibiotic other than penicillin, mother who received the treatment less than four weeks before the birth, mother treated correctly, but there was no decrease in the titer of the treponemal tests four times during pregnancy, mother treated correctly, but there is no data showing an adequate therapeutic response), **probable congenital syphilis** (asymptomatic neonate with a mother's VDRL equal to or less than fourfold in which both the following are true: the mother was treated during pregnancy, the treatment was adequate and ended more than four weeks before the birth and the mother has no clinical or laboratory signs of reinfection or relapse), **congenital syphilis less likely** (asymptomatic neonate with a VDRL titer equal to or less than fourfold that of the mother and both of the following: adequate treatment of the mother performed before pregnancy and the titer of the mother's treponemal tests remained low and stable – VDRL less than ½)[19,20].

The management in presumptive and possible congenital syphilis involves evaluation: CSF (VDRL, cellularity, protein), blood count and, as needed, long bones radiography, thoracic, liver function tests, neuroimaging, eye examination, audiological evaluation – auditory evoked potentials and treatment with crystalline penicillin G 100,000-150,000 IU/kg/day or 50,000 IU/kg at 12 hours, 7 days, followed by 50,000 IU at 8 hours, or procaine penicillin G 50000 IU/ kg in a single dose for 10-14 days, with a total treatment duration of 10-14 days, and if one day is interrupted, it is resumed from the beginning, stating that, if possible, a single dose of benzathine penicillin 50,000 IU/ kg can be administered if there are no manifestations or laboratory data suggestive of neurosyphilis[10]. In probable congenital syphilis, with an asymptomatic neonate, with a VDRL titer equal to or less than fourfold that of the mother and in which both of the following are true: the mother was treated during pregnancy, the treatment was adequate and ended with more than four weeks before birth and the mother has no clinical or laboratory signs of reinfection or relapse; or congenital syphilis less likely, with an asymptomatic neonate, with a VDRL titer equal to or less than fourfold that of the mother and when appropriate pre-pregnancy treatment and the mother's treponemal test titer remained low and stable (VDRL less than ½), no evaluation is required and no treatment is usually given, but the doctor may decide to administer a single dose of benzathine penicillin[10].

Monitoring of patients with congenital syphilis requires that all neonates with reactive VDRL are monitored by determining VDRL every 2-3 months until the test is negative[10].

Cytomegalovirus (CMV) infection

Intrauterine infection with CMV, a DNA virus that affects only humans, has an increased incidence (0.2-2% of the total number of pregnancies), with short-term and long-term consequences. Maternal-fetal transmission occurs transplacental, intrapartum and postpartum, as a primary infection, by reactivation of the virus, or with another strain. Acute maternal infection is most often asymptomatic or with symptoms such as a mild respiratory virus or a mononucleosis-like syndrome[1,2,11].

Clinical signs manifest antepartum, they relate to the affecting of the general condition of the fetus (restriction of intrauterine growth) or damage to the central nervous system (microcephaly, ultrasound abnormalities – germinolytic cysts, periventricular calcifications, or MRI – micropolygyria, lissencephaly, pachygyria, schizencephaly); or postnatal, related to the acute infection syndrome (infection in the last trimester of pregnancy), infection of the central nervous system (inflammation and direct infection of progenitor stem cells in the germinal area and glial cells) and hearing impairment (progressive deafness)[1]. Acute infection syndrome affects the reticuloendothelial system: hepatosplenomegaly, rash, thrombocytopenia, increased liver enzymes, rarely pneumonia or inguinal hernia in boys[2]. The neurological sequelae syndrome is manifested by: microcephaly, convulsions, usually periventricular intracranial calcifications, association of calcifications with cerebral vasculitis, abnormalities of gyration (polymicrogyria, pachygyria), lissencephaly, schizencephaly, predominant damage of the anterior and parietal temporal lobes, cerebellar hypoplasia; the neurological lesions are not progressive, and chorioretinitis may be encountered[1]. Deafness occurs as a result of damage to the inner ear and the auditory nerve, due to direct inflammatory or teratogenic causes and may be present at birth or may occur along the way and is progressive[1,2,11].

The diagnosis of CMV infection in the neonate is made by determining the presence of the virus in the urine or saliva (PCR), and in order to establish an antepartum infection, the sample must be collected in the first three weeks after birth[1,2,11].

The prognosis is influenced by the risk of death of 12% in the first year of life in symptomatic patients, who also have a risk of long-term sequelae of 80% compared to 15% in asymptomatic patients[2]. The risk of harm to the fetus is high in the first trimester of pregnancy, the appearance of brain abnormalities on fetal ultrasound and the association of MRI abnormalities[1]. The risk of long-term damage is high in the case of signs of central nervous system damage present in the neonatal period (clinical, ultrasound or MRI), and the risk of deafness is high in the case of symptomatic infection[1].

The prevention of CMV infection is impossible once the maternal infection exists. It is indicated to prevent the primary infection or reinfection of CMV-negative mothers through educational programs[1,11]. Pregnant women, nursery and kindergarten workers, along with medical staff should be instructed regarding the risk of CMV infection and the following prophylactic measures should be applied to pregnant women: they should not share food, drink or other hygiene items with children, they should not put the baby's pacifier in the mother's

mouth, they should avoid contact with the baby's saliva and wash their hands carefully after the contact with the baby's urine, stool or saliva[1].

The treatment of CMV infection in the neonate should be symptomatic in acute syndrome (treatment of liver failure, shock, anticonvulsants) and in case of sequelae (physical therapy, treatment of deafness). The etiological treatment is indicated only in case of moderate and severe symptomatic infection and consists in the oral administration of valganciclovir 16 mg/kg/dose, two times a day. The therapy should be started in the first month of life and will last for six months. The following will be monitored: hemogram (risk of neutropenia) weekly for six weeks, then in the eighth week, then monthly; transaminases – monthly. Studies have shown that the treatment can improve or stop the progression of neurological signs and deafness[3]. In addition, as both neurological impairment and deafness may progress over time or occur later in an initially asymptomatic child, in case of a CMV infection (asymptomatic or symptomatic), audiological examination at six-month intervals in the first three years of life is indicated and subsequently annually, until the age of 19 years old, an ophthalmological consultation and neurological follow-up are also indicated in a program for at-risk neonates[11]. The treatment of pregnant women with anti-CMV or antiviral hyperimmune immunoglobulins (teratogenic effects and toxicity) is not indicated[11].

Congenital rubella

The first infection (rarely the reinfection) of the pregnant woman can cause fetal infection and a severe malformative syndrome, although in most countries rubella is eradicated by vaccination, because there is no etiological treatment[1].

In the case of pregnant women, it is recommended to determine the status of anti-rubella antibodies, in which case the following situations can be encountered: positive IgG and negative IgM (chronic infection or effective vaccination, without risk of infection in pregnancy), negative IgG and IgM (seronegative patient, risk of infection during pregnancy, to be monitored), negative IgG and positive IgM (nonspecific result, monthly determinations are performed until the fifth month, and in positive IgG, the infection occurred, meaning seroconversion) and positive IgG and IgM (possible infection). The avidity test is indicated, a low avidity showing an infection during pregnancy[12].

In case of infection of the pregnant woman, the possible infection of the fetus will be investigated by RT-PCR from the amniotic fluid, preferably after 20 weeks, and fetal ultrasounds will be performed to determine the possible malformations. A positive diagnosis of fetal infection is followed by parental advice on the risk of malformations.

The risk of infection is present if the rash occurs at least 12 days after the last menstrual cycle[13]. The risk and severity of infection are highest in the first trimester and decrease sharply in the second and third trimesters of pregnancy[1]. The risk of malformations can be accurately assessed according to the time of infection: maximum risk of cataracts (days 27-56), risk of heart malformation (days 25-93), risk of deafness (days 16-131), risk of severe mental retardation (days 26-45)[14].

Malformations and eye lesions no longer occur if the infection occurs after the first trimester of pregnancy (period of organogenesis), but deafness and growth retardation also occur in the case of infection after this period[1]. The risk of malformations is estimated at 90% for weeks 2-10, 34% for weeks 11-18 and 0% after 18 weeks[14].

Congenital rubella syndrome includes general signs (hepatosplenomegaly, thrombocytopenia, dental and bone lesions – transient)), cardiovascular malformations (persistent arterial duct, pulmonary stenosis – usually peripheral, ischemic myocardial necrosis – usually septal), eye damage (progressive unilateral or bilateral cataract – the crystalline is a reservoir of postnatal virus, chorioretinitis with a characteristic appearance of "salt and pepper", microphthalmia, glaucoma, strabismus), hearing impairment (progressive deafness), damage to the central nervous system (meningoencephalitis, calcifications of the *corpus callosum* or of cerebral vasculitis type, microcephaly or risk of cerebral palsy, seizures and developmental delay, which occur over time) and long-term consequences (insulin-dependent diabetes, thyroid dysfunction, panencephalitis, affective disorder and increased incidence of autism spectrum disorders)[1,12,14].

The serological diagnosis of neonate affecting is made by demonstrating the presence of IgM antibodies in the blood of the newborn[1,12].

Neonates of mother with HIV infection

Human immunodeficiency viruses (HIV 1 and HIV 2) are RNA viruses that target cells that have CD4 receptors (lymphocytes and cells of the reticuloendothelial system).

HIV causes a human immunodeficiency syndrome in humans. Mother-to-child transmission (MTCT) of HIV can occur *in utero*, during labor and birth, and postpartum[15]. In the absence of prophylaxis, it is considered that the risk of transmission of HIV from mother to child is 10% during pregnancy, 15% during labor and birth, and 10-15% postpartum through breast milk[15,16].

Risk factors for mother-to-child transmission of HIV include: increased maternal viremia in the absence of therapy, acute infection (seroconversion) during pregnancy and lactation, advanced stage of the disease, low CD4 lymphocyte count, vaginal birth, premature rupture of membranes, and breastfeeding – the strongest risk factor[16-18].

Interventions that have proven to reduce the risk of mother-to-child transmission of HIV are: highly active antiretroviral therapy (HAART) and monotherapy,

which reduce the risk of MTCT through two mechanisms – decreased viremia and antiretroviral effect in the fetus through transplacental passage[17-19]; caesarean section performed before labor with intact membranes at 38-39 weeks; antiretroviral prophylaxis in neonates and artificial feeding[20].

The strategy for the prevention of mother-to-child transmission of HIV includes monitoring the HIV status of all patients (up to two times per pregnancy to identify seroconversion), appropriate antiretroviral therapy of the mother (collaboration with the infectious disease doctor), caesarean section at 38-39 weeks of pregnancy with intact membranes, antiretroviral prophylaxis in the neonate (in the first 4 hours postpartum), artificial feeding of the neonate and monitoring of the his status (proviral DNA PCR – gold standard, or HIV RNA PCR – in the first 48 hours of life, but not from the umbilical cord at 2, 6, 12 weeks and 6 months, ELISA/Western Blot at birth and every 6 to 18 months, tests to monitor the effects of antiretroviral therapy: complete blood count, ionogram, urea, creatinine, blood gas test, glucose[17,20-22].

Depending on the diagnostic tests, the time of infection may be: *in utero* if the specific diagnostic test for virus identification (DNA or RNA PCR) is positive within the first 48 hours, necessarily confirmed by a second positive test or intrapartum if the test performed in the first 48 hours is negative, and subsequent tests are positive and the mother is not breastfeeding[22].

Because the diagnosis of HIV infection in neonates and infants is based on two positive virus identification tests, the absence of infection can be stated in the presence of two negative virus identification tests (DNA or RNA PCR), at the interval of at least two weeks after stopping antiretroviral prophylaxis, with concomitant verification that tests may identify the viral subtype that caused the mother's infection, and one of the tests must be performed at the age of 1 month old and at least one test result performed at the age of 4 months old is negative[17,22].

Hepatitis B vaccination in HIV-positive neonates is not contraindicated, but BCG vaccination will be delayed until the status of the neonate is established – infected or uninfected, and the decision is made after consultation with the infectious disease doctor[21,22].

Neonates of mother with tuberculosis

The pregnant woman may be infected with *M. tuberculosis* in pregnancy (primary infection), at risk of transplacental transmission and high congenital tuberculosis, or the infection may be reactivated in the immunological context of pregnancy or may have a form of genital tuberculosis, which also has a risk infecting the fetus[23].

Tuberculosis infection in neonates can take two forms:

a) congenital (transplacental intrauterine infection or by inhalation or ingestion of infected amniotic fluid); clinically, it presents nonspecific signs: hepatosplenomegaly, respiratory distress, feeding difficulties, fever, chest radiographic changes, and the diagnostic criteria are lesions in the first week of life, the presence of a primary hepatic complex or caseous hepatic granuloma, tuberculous infection of the placenta or maternal genital tract and exclusion of postnatal transmission by investigating contacts;

b) neonatal (secondary to postnatal infection from the mother or other person infected, in the following ways: inhalation of infectious drops, ingestion of infectious drops or infected milk, contamination of the skin or mucous membranes by contact with infectious secretions)[23,24].

In the diagnosis of congenital tuberculosis, the most important is the clinical suspicion, based on the signs or medical history of the mother. In case of clinical suspicion in a patient with suggestive symptoms, the following are indicated: tuberculin test (IDR-PPD) and, regardless of the result, chest X-ray, lumbar puncture, and gastric aspiration – in the morning, on waking, because it may be the only way to isolate the germ in the neonate and the baby, who do not cough but swallow secretions. The treatment is started immediately with four antibiotics[23].

The conduct in the case of an infected neonate depends on the case: for a neonate with a diagnosis of congenital tuberculosis – therapy with four antituberculosis drugs (isoniazid, rifampicin, pyrazinamide, ethambutol) and periodic evaluation; for the neonate of the mother with active tuberculosis or the neonate from an outbreak of tuberculosis – one of the following attitudes may be adopted, either BCG vaccination in the maternity followed by isolation for at least two months (preferably three months) until immunity is established, if the mother/source of the contagion has been in treatment for at least six weeks, the neonate may be introduced into the family without specific treatment or prophylaxis with isoniazid 10 mg/kg/day for three months, with family reintegration, pyridoxine 15 mg/kg/day will be administered to prevent neuritis secondary to isoniazid treatment, and IDR is performed at three months – if the IDR is negative (scar below 10 mm), the baby is vaccinated for BCG, otherwise the baby is assessed for the risk of TB (radiologically), and he it is asymptomatic and the radiography is within normal limits, isoniazid prophylaxis is continued; however, if the radiography or clinic shows signs of disease, a treatment scheme is followed[24].

The mother on antituberculosis treatment can breastfeed, the treatment of the pregnant woman with antituberculosis aminoglycosides being avoided due to the risk of deafness and kidney damage of the child, and if the mother's tuberculostatic regimen contains isoniazid, the breastfed neonate should receive pyridoxine, even if it does not receive isoniazid chemoprophylaxis[23,24].

Adverse effects of tuberculostatic drugs in the fetus and neonate for isoniazid are liver failure and peripheral neuropathy, the prevention of which require

prophylaxis with pyridoxine in both pregnant and parturient women and the neonate; for rifampicin, orange staining of urine and stools and the appearance of hepatitis, leukopenia and thrombocytopenia in the neonate, monitoring of the blood count and the administration of an additional dose of vitamin K are required; for pyrazinamide, hepatic dysfunction, and for ethambutol, in high doses, optic neuritis or impaired color vision[23,24].

In the case of a mother with multidrug-resistant tuberculosis, the neonate is isolated, the mother will not breastfeed, and the treatment is done under the coordination of a specialized team, considering the mother's *M. tuberculosis* strain[24].

Congenital toxoplasmosis

Toxoplasma gondii is an intracellular parasite, and about one-third of the human population is infected with this germ[1]. Pregnant women can be infected with *Toxoplasma* by contact with contaminated soil from feline feces, contact with contaminated uncooked meat (pork, lamb, beef), and others: unpasteurized milk, water, transplantation of infected organs, and, in 50% of primary infections with *Toxoplasma*, no risk factor can be identified[4,26].

The infection is asymptomatic or oligosymptomatic in immunocompetent individuals, but the infection of the pregnant woman can cause severe damage to the fetus and lifelong neurological and visual sequelae[1,2,4]. Parasitemia occurs approximately three weeks after the infection[25]. The treatment of the pregnant woman and the child allows the consequences of the disease to decrease until they disappear[1,4].

Congenital toxoplasmosis occurs following transplacental transmission of the parasite that may occur during parasitemia in the following circumstances: first infection in the mother – the most common, with an incidence of 0.5-2/1000 births, reactivation of toxoplasmosis in case of immunodepression of the pregnant woman, reinfection with another strain of higher virulence[4]. The risk of infection is low in the preconception period and the first weeks of intrauterine life and increases progressively during pregnancy: 17% in the first trimester, 25% in the second trimester, 65% in the third trimester, and the severity of the damage is maximum in the first trimester (60%) and gradually decreases in the second and third trimesters (30% and 0%, respectively)[4,26].

The diagnosis of maternal infection is serological, IgG and IgM being recommended for *Toxoplasma*, with repetition in case of abnormal results[1,4,25]. The diagnosis of seroconversion is established when IgG is positive (negative on a previous examination) and the following situations can be encountered: negative IgG and IgM – there is no infection, but it is recommended to repeat the test monthly until birth; IgG positive and IgM negative – if the test is performed within the first 20 weeks, it is very likely to be a chronic infection, otherwise additional tests (avidity test, agglutination test) are needed to rule out seroconversion in the first part of pregnancy; IgG negative and Ig M positive – it may be an acute infection, but the test is repeated after three weeks, and in case of IgG positive, the diagnosis of seroconversion is made; if IgM remains positive and IgG is negative, it is probably a false-positive reaction and a sample is sent to a reference laboratory; and IgM and IgG positive represent an acute infection with seroconversion in pregnancy[4].

The damage to the fetus in case of congenital toxoplasmosis is inflammatory, with signs of damage to the following: reticuloendothelial system – hepatosplenomegaly, hyperbilirubinemia, anemia, petechiae; central nervous system – meningoencephalitis with convulsions, hydrocephalus caused by aqueductal stenosis due to irritation given by the penetration of parasites into the cerebrospinal fluid (CSF), intracranial calcifications throughout the brain mass, porencephalic cysts due to inflammatory phenomena of vasculitis and consequent necrosis, microcephaly caused by destruction of the brain; unilateral or bilateral chorioretinitis with characteristic damage to the macula, with cotton colored yellowish plaques and optic nerve atrophy; or other rare manifestations – pneumonia, deafness[1,4].

The treatment includes, first and foremost, the prevention of the first infections in HIV-negative mothers, avoiding contact with cat feces and soil (gardening with gloves), consumption of water or food from a controlled source, proper thermal preparation, and preservation of meat in the refrigerator, handling of raw meat with gloves and thorough washing of vegetables and fruits[27]. In case the first infection is identified in pregnant women, if the pregnancy is less than 18 weeks, spiramycin treatment (1 g three times/day) is indicated, up to 18 weeks of pregnancy, when amniocentesis is performed and the presence of the parasite in the amniotic fluid is determined by PCR, and if it is present or there are ultrasound signs of fetal infection, the treatment is changed to pyrimethamine, sulfadiazine and folinic acid until birth; otherwise, spiramycin treatment is continued in the absence of signs of fetal impairment[4].

After birth, the diagnosis of congenital toxoplasmosis depends on the infectious status of the child and there are four situations: the persistence of anti-*Toxoplasma* IgG antibodies after the age of 12 months; anti-Toxoplasma IgG and IgM positive (taken at least five days after birth) and/or IgA (taken at least 10 days after birth); positive PCR of amniotic fluid, peripheral blood, CSF, urine or other body fluids; anti-*Toxoplasma* IgG positive in the neonate (with IgM and IgA negative) and serological evidence of an acute infection of the mother with *Toxoplasma* during pregnancy and suggestive clinical manifestations[4].

Children with suspected congenital toxoplasmosis will be treated for 12 months with: pyrimethamine 2 mg/kg/day, in two doses, for two days, then 1 mg/kg/day for up to six months, then 1 mg/kg/day, three times a week; sulfadiazine 100 mg/kg/day, in two doses, and

folinic acid (leucovorin) 10 mg three times a week, with blood count monitoring for the risk of neutropenia, and in case of severe chorioretinitis, corticosteroid treatment may be added[1,4]. Postnatal treatment seems to decrease the severity of cerebral manifestations and especially the ocular ones[4].

Monitoring the patient with congenital toxoplasmosis or at risk of congenital toxoplasmosis includes a complete clinical examination and neurological examination at 2-3 months in the first year of life and at 4-6 months after the first year; ophthalmological examination at 3-4 months in the first year of life and at 4-6 months after the first year, and in case of identification of chorioretinitis, the frequency of examinations may increase, as well as auditory evoked potentials at birth and annually in the first three years of life[4].

Congenital and perinatal varicella

The varicella-zoster virus (VZV) is a DNA virus, exclusively human, with airborne transmission to humans and has an infection characterized by rash, subsequently enters a latent state in the sensitive lymph nodes, from where it reactivates at certain moments of low immunity, causing a painful blistering rash on the path of a dermatome (shingles)[28].

The incidence of acute infection in pregnant women is very low (0.7/1000 births) and causes two distinct syndromes: congenital varicella syndrome and perinatal varicella[1,28].

Congenital varicella syndrome occurs in the case of maternal VZV infection in the first 20 weeks of pregnancy, in 1-2% of cases, and causes: meningoencephalitis, myelitis with damage to the neurons in the anterior horns, infection of the lymph nodes in the dorsal roots of spinal nerves, followed by denervation and the onset of segmental hypoplasia of muscles[29]. The clinical manifestations include low birth weight, prematurity, segmental, depressed, zig-zag skin scars; limb abnormalities – segmental hypoplasia, equinus deformity, hypotonia; signs of pharyngeal paralysis – swallowing or phonation difficulties, signs of phrenic nerve paralysis – difficulty breathing; brain damage – microcephaly, convulsions; ocular abnormalities – chorioretinitis, retinopathy, microphthalmia, cataract, Horner syndrome, and in 51-75% of cases there is a delay in neurological development. Death in infants occurs in 26-50% of cases[1,28].

Perinatal varicella occurs in 25% of neonates whose mothers had varicella in the last part of pregnancy, from 21 days before birth and up to 2-5 days postnatally, and is considered only if signs of the disease appear by day 10 of life of the neonate. The incubation period is 9-15 days after the onset of the rash in the mother, and the risk of developing perinatal varicella is maximum if the rash occurs in the mother between five days before and two days after birth[1,28]. Perinatal infection occurs transplacental, and antibodies passively transmitted by the mother play an important role in limiting the infection. So, if the disease occurs in the neonate in the first four days of life, the infection occurred a few days before birth and there was time for transplacental antibody passage, so the disease will be of medium severity, without risk of death. If the disease occurs after day 5, the transmission occurred shortly before birth, there was no time for transplacental passage of antibodies, and the patient will develop a severe form of the disease, with a 30% risk of death[1,15,28]. The clinical manifestations are similar to those of varicella in immunocompromised individuals, respectively vesicular rash, sometimes with hemorrhagic aspect, and systemic manifestations by affecting the reticuloendothelial system (hepatosplenomegaly with liver failure) and pulmonary (varicella pneumonia, with respiratory insufficiency – the main cause of death)[1,28].

Postnatal varicella occurs in neonates between 10 and 28 days of age, is generally mild and can be caused by infection from the mother, a sick sibling or exposure to a case in the neonatal intensive care unit (NICU)[28].

The positive diagnosis in case of perinatal or postnatal varicella is established based on the anamnesis, clinical appearance, and can be confirmed by laboratory data, respectively in vesicular lesions or PCR for viral DNA in the vesicle material and the presence of anti-VZV IgM antibodies in neonate or a fourfold increase in IgG titer in the neonate compared to the mother[1,28].

The management of the pregnant woman with varicella, with the onset of the rash between 7 and 20 days before birth, is done by keeping the neonate isolated from the mother until she is no longer at risk of transmitting the infection (crusted blisters), and no prophylaxis with intravenous immunoglobulins is necessary. If the onset of the mother's infection was less than seven days before birth or in the first two days after birth, the neonate is given 1.25 ml specific immunoglobulin (125 units) intramuscularly and is isolated from the mother until she no longer presents a risk of transmission. The treatment with acyclovir i.v. will be given to neonates with severe perinatal varicella, immunodeficiency, or to premature infants of less than 28 weeks of age[1,28].

In case of risk of postnatal varicella, respectively in case of a relative or a child with varicella at home, if the mother is immune (antibodies present), the neonate and mother are discharged because they will not have the disease. If the mother is seronegative, immunoglobulins will be administered to the mother and fetus, and they will be discharged. In case of perinatal varicella or mother with varicella, the neonate and the mother will be isolated in a separate room, the staff taking care of the neonate and the mother should ideally be immunized (anti-varicella antibodies present), and the mother will be encouraged to breastfeed the neonate (antibody transmission is facilitated)[28].

Herpes simplex virus infection

Herpes viruses (HSV1 and HSV2) are two distinct types of DNA viruses, transmitted to humans by direct contact with infectious secretions in the mucous

membranes or by infectious droplets. Adult infection may be symptomatic or asymptomatic. In the case of symptomatic infection, characteristic vesicular-macular lesions appear at the place of contact, followed by a state of latency, from which it is periodically reactivated. HSV1 is traditionally considered to cause labial infections and HSV2 genital infections, but currently HSV1 is also involved in the production of genital infections, with a higher incidence in the young population than HSV2[1,30].

Maternal-fetal infection is mostly caused by direct contact with infectious secretions from the birth canal or upwards in the case of labor with membranes of more than 4 hours (perinatal infection) – 85% of cases, transplacental (rare) or postnatal (10% of cases). Risk factors for infection are vaginal birth, absence of protective antibodies against HSV, duration of over 4 hours of labor with broken membranes and interventions during labor (monitoring *via* fetal scalp electrodes)[1,30].

Neonatal HSV infection is always symptomatic, and has three forms: localized at the skin level, eyes and mouth (skin-eyes-mouth disease – SEM; 45%), localized in the central nervous system (herpetic encephalitis; 30%) and disseminated (25%)[1,30,31].

The infection spreads affecting the reticuloendothelial system, occurs between 10 and 12 days of age, and is caused by the hematogenous spread of the virus. The onset is characterized by lethargy, loss of appetite, then a neurological syndrome (stupor, irritability, seizures with a coma or opisthotonos) and signs of damage to the reticuloendothelial system (hepatosplenomegaly, anemia, thrombocytopenia, bleeding, intravascular coagulation of other organs), gastrointestinal tract and lungs (pneumonia), the mortality being 29% and the risk of sequelae being 17%[1,30].

Herpetic encephalitis occurs at 16-19 days and is caused by infection of neurons, which explains the late onset, extensive areas of pancreatic parenchymal necrosis, the absence of skin signs (35% of cases) and late diagnosis by PCR in CSF. The signs are stupor and irritability, followed by convulsions, often focal and coma. CSF shows pleocytosis, high proteinuria and low glucose. PCR or viral cultures do not identify the presence of the virus from the beginning, sometimes two punctures being required to make a positive diagnosis. Characteristic imaging signs (cortical necrosis progressing to multicystic encephalomalacia, with a predilection for the frontal and more temporal area) can be identified by ultrasound, but require further MRI and EEG examination (presence of periodic, low-frequency, migratory complexes, with predilection for the temporal area). In the absence of adequate treatment, the risk of death is 50% and the risk of subsequent disability is 50% of the survivors[1,30].

Localized infection (SEM) shows the symptoms of the first 7-10 days of life, respectively: skin blisters with a characteristic appearance in the area they occurred or in the area where the fetal monitor was installed (injured area); ocular damage with keratoconjunctivitis which, in the absence of treatment, may progress to cataract, chorioretinitis and retinal detachment and damage to the oral cavity – blisters – without the appearance of gingivostomatitis. In 30% of cases, in the absence of treatment, the disease progresses to disseminated infection, and in 30-40% of cases, even in the absence of neurological symptoms, there are long-term neurological sequelae[1,30]. Very rarely, in transplacental HSV infection, it presents the following clinical triad: skin signs (active herpetic lesions, scars, hypo- or hyperpigmented *aplasia cutis congenita*); neurological signs (microcephaly, hydranencephaly, intracranial calcifications) and ocular signs (chorioretinitis, microphthalmia, optic nerve atrophy).

The positive diagnosis of HSV infection involves cytological techniques, isolation of the virus in cell culture or the detection of viral DNA: the isolation of the virus in cell culture from vesicular lesions, pharynx, stool, urine or CSF, the pharynx being the area with the highest detection rate and the culture duration is 1-3 days; the detection of viral antigen by PCR can be performed from CSF (requires repeated determinations), blood (positive only in case of disseminated infection), skin lesions, pharynx or urine. The serological diagnosis based on the detection of anti-HSV antibodies in the neonate has no value in detecting neonatal HSV infection[1,30].

The etiological treatment is with acyclovir: in case of localized SEM infection, with acyclovir i.v. 20 mg/kg/dose three times a day for 14 days. In the case of HSV encephalitis or generalized infection, the same doses are used and the duration of treatment is 21 days[1,30]. In case of ocular lesions, it is recommended to combine topical antiviral preparations and long-term acyclovir therapy – 300 mg/m^2, three times a day, six months, to avoid relapses and neurological sequelae in all forms of perinatal infection[1,30-32].

Antenatal prophylaxis recommends the identification of HSV1 and HSV2-negative pregnant women, who have a high risk of transmitting the virus in the case of primary infection and avoiding sexual contact in the last months of pregnancy with possible HSV-positive partners[1,30,31].

Peripartum prophylaxis, in case of identification of an active genital herpes lesion during the perinatal period, recommends sample collection and PCR to detect viral DNA from vaginal secretion, and the birth will be performed by caesarean section regardless of the local situation, if the membranes are intact or broken for less than 4 hours[1,30,31].

The prophylaxis of postnatal infection in neonates and mothers with active herpes lesions includes isolation; breastfeeding is allowed, unless there is an active lesion in the breast, and the mother with active herpes labialis lesion must wear a mask and wash her hands well before touching the neonate. Medical staff with active herpes lesions should wear a mask and wash their hands, and neonates from mothers with active HSV infection (positive cultures or PCR),

born vaginally, should be isolated from other neonates during hospitalization in the maternity ward – up to four weeks[30,31].

Enterovirus and parechovirus infection

Enteroviruses and parechoviruses are RNA viruses and comprise four families: polioviruses, Coxsackie A, B viruses and echoviruses, and are the leading cause of aseptic meningitis in children. They can be transmitted from the mother mainly by transplacental route, during birth, but also postnatal, by contact, from mother to child, and then from one child to another through the medical staff. In the case of enteroviruses, there is a seasonal incidence (summer and in autumn), and the risk of maternal-fetal infection is maximum if the infection and viremia occur in the immediate antenatal period, before the formation of maternal antibodies, the disease occurring most frequently in the first two weeks of life[1,33].

The most common clinical signs are fever, seizures, irritability, rash and eating problems (vomiting, diarrhea). Two particular situations, mainly caused by the Coxsackie B virus, are enteroviral myocarditis (which causes mitral regurgitation, left ventricular aneurysm and heart failure, and the complete recovery occurs in only 23% of cases) and enteroviral encephalitis, with altered general condition and hypotonia, but without seizures or focal motor deficit[1,34,35]. The neurological damage caused by these viruses is similar to the one of leukoencephalopathy, mimicking periventricular leukomalacia, and is due to the action of oligodendroglia, with the destruction of white matter and axons[1].

The diagnosis is to determine the virus by PCR from the pharyngeal exudate, stool, blood, urine or CSF, and CSF is recommended for neonates with neurological signs that suggest meningitis or encephalitis[1].

The treatment of the infection is symptomatic. There is no etiological treatment. Fetal disease can be prevented by delaying birth in case of a viral infection to allow the development of the immune response in the mother and the transmission of antibodies to the fetus and, except for severe forms of myocarditis and encephalitis, the prognosis is relatively good[1].

Zika virus infection

Zika virus is an RNA virus, transmitted to humans through vectors (mosquito), but also sexually, which produces an asymptomatic infection (80%) or with mild symptoms: fever, maculopapular rash, conjunctivitis and arthralgia. Viremia occurs in the first seven days after infection, and IgM antibodies are detected afterwards[1,36-38].

Fetal infection occurs transplacental or perinatal and a characteristic syndrome occurs with microcephaly, viscerocranium developed more than neurocranium, and occipital skin folds, hypertension, spasticity, hyperreflexia, convulsions, imaging abnormalities such as band-like intracranial calcifications, located at the cortico-subcortical junction, ventriculomegaly, lissencephaly/pachygyria, ocular abnormalities, congenital clubfoot and arthrogryposis[1,36-38].

It is recommended to test for the presence of Zika virus in pregnant women with epidemiological risk factors (travel or sexual contact with a person from a pandemic zone: Brazil, tropical area) and/or specific signs of clinical disease or in fetal ultrasound[1,36-38].

The serological diagnosis is based on the identification of the virus by PCR or by the identification of IgM antibodies. In pregnant women, the virus can be isolated in the first seven days after infection in the blood and urine. Then, IgM antibodies are detected in the blood, while in the fetus, the virus can be identified by amniotic fluid PCR, in the neonate, the virus can be identified in the blood and CSF or by IgG antibodies in the blood[1,36-38].

The positive diagnosis of Zika congenital disease is based on the concomitant existence of clinical signs and laboratory criteria: detection of virus in culture, presence of viral antigen or positive PCR in fetal tissues, umbilical cord blood, amniotic fluid, serum, CSF or urine, collected in the first two days after birth, or positive anti-Zika IgM from umbilical cord, serum or CSF sampled in the first two days of life, with positive anti-ZIKA neutralizing antibodies and negative titers of anti-dengue antibodies or other flaviviruses[36]. There is no etiological treatment.

Discussion

Congenital infections are a major public health problem and, although most are completely curable and the diagnosis and treatments are perfectly standardized, they still complicate pregnancies and lead to complications and increased maternal-fetal morbidity and mortality, such as perinatal death, prematurity, low birth weight etc.[1] Thus, the World Health Organization estimates that more than 1 million pregnancies are complicated annually by luetic infection, followed by perinatal death, low birth weight, or signs of congenital syphilis[39]. On the other hand, CMV infection is the leading cause of sensorineural hearing loss (SNHL) in children[1,11]. Rubella infection has no etiological treatment, but congenital rubella syndrome can be prevented by vaccinating the population[1,12] and, in HIV, the strategy to prevent maternal-fetal transmission is to completely eliminate the possibility of transmission of the virus[17]. In the case of congenital toxoplasmosis, symptoms appear in the first year of life in 19% of patients – more often, eye and neurological lesions and chorioretinitis may be absent at birth, but may occur at any time up to 19 years[1,25,40].

Conclusions

In conclusion, prevention is essential, so that maternal-fetal complications do not occur on the short or long term, considering the absence of etiological therapeutic resources in some cases, or even death. ■

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