Zika virus disease in pregnancy and associated fetal neurological complications – a descriptive review

Roxana Georgiana Bors¹, Maria Anghelache¹, Maria Ciocarlan¹, Vlad Dima², Mihaela Plotogea³, Valentin Varlas¹,⁴

¹Department of Obstetrics and Gynecology, Filantropia Clinical Hospital, Bucharest, Romania
²Department of Neonatology, Filantropia Clinical Hospital, Bucharest, Romania
³“Nicolae Malaxa” Clinical Hospital, Bucharest, Romania
⁴“Carol Davila” University of Medicine and Pharmacy, Bucharest, Romania

ABSTRACT

Zika virus is a flavivirus transmitted mainly by Aedes mosquitoes, and pregnant women are usually asymptomatic or have non-specific symptoms. The virus can cross the placental barrier and is intensely neurotropic, with destructive and malformative consequences on the fetal central nervous system, causing a series of severe abnormalities in infected fetuses in the first trimester, more severe than in TORCH infections. Viral infection can be suspected during ultrasound screening by highlighting severe microcephaly and macroscopic calcifications in the fetal brain. In addition, auditory, ocular, or musculoskeletal abnormalities have been reported. Prophylaxis of infection in pregnant women is essential due to the increased risk of fetal damage currently, there is no vaccine or approved treatment.

Keywords: Zika virus, neurological complications, pregnancy outcomes, Guillain-Barré syndrome, microcephaly

INTRODUCTION

Zika virus is a Flavivirus RNA that was first identified in 1947 in Uganda in Rhesus monkeys [1], and a few years later, the first human infection was reported [2]. Due to globalization, the geographical spread of the virus has increased over time, with over breaks occurring in tropical and subtropical countries [3].

The virus is transmitted to humans through the bite of infected Aedes mosquitoes, with Aedes aegypti species being the main vector [4]. Sexual, intrauterine, perinatal, laboratory and transfusion-transmitted infections have also been reported. Zika RNA can be detected in the female genital tract up to 2 weeks after infection, and in the seminal fluid, it can persist for up to 6 months [3,5]. The virus has also been identified in breast milk, but its transmission through breastfeeding has not been identified [3].

Zika infection can easily go unnoticed among pregnant women, 74-81% of cases being asymptomatic, mild forms of the infection have flu-like symptoms (low-grade fever, arthralgia, conjunctivitis) accompanied by a diffuse rash, while severe forms are manifested by autoimmune Guillain-Barré syndrome, which affects peripheral nerves, leading to muscle weakness or paralysis [3,5,6,7]. Thus, all pregnant women suspected of having the infection should be tested, IgM Zika virus can be detected in the pregnant woman’s serum starting on the 4th day from the onset of symptoms up to 12 weeks [8].

Prophylaxis of Zika infection transmission among pregnant women is done by avoiding travel to endemic areas and avoiding mosquito bites in these areas, the use of insect repellent, as well as protection against sexual transmission from infected partners [5,9,10]. These measures are crucial because identifying a fetal malformation caused by the infection has consequences on the quality of life of the pregnant woman, with medical, psychological, and social implications [9]. There is currently no specific vaccine or antiviral treatment approved for Zika virus infection. The therapeutic approach in pregnancy is to control symptoms and consists of the administration of analgesics and antipyretics [11,12].

MATERNAL-FETAL TRANSMISSION

The virus crosses the placental barrier, and potentially exposed pregnant women should have an ultrasound examination at 4 weeks for fetal growth,
microcephaly, and possible intracranial fetal abnormalities secondary to viral infection [13,14,15]. When Zika infection is contracted in the first trimester, the neurotoxic effects are the most severe, compared to the second and third-trimester infections, which produce undetectable ultrasound changes, which can only be seen after birth [15]. In addition to transplacental transmission, the fetus may be infected with the Zika virus during labor or delivery [16].

Intrauterine transmission has been reported during the outbreak in Brazil, with Zika viral RNA being identified in the amniotic fluid of infected pregnant women, placenta tissue, brain, and serum in newborns and fetuses [3,5,13,17].

Vertical transmission is not systematic, the risk of congenital Zika virus syndrome varies between 5-8% [18] and 40% [19].

**FETAL AND NEWBORN NEUROLOGICAL AND ASSOCIATED ANOMALIES**

The target of the Zika virus is the human cortical neuronal progenitor cell of the developing brain. Following infection, the virus affects the neurodevelopmental stages of neural and glial proliferation, neuronal migration, organization, and myelination, causing even the death of these cells [5,20]. In the fetal brain, the virus causes severe damage in 5-10% of cases, severe congenital malformations of the central nervous system, and effects on neurodevelopment being reported [3,5].

Microcephaly is the major fetal structural defect caused by perinatal infection, with the highest risk if the infection occurs in the first trimester of pregnancy [3,5]. In Brazil, the country most affected by Zika virus infection, there has been a 20% increase in microcephaly in newborns [21]. Following reports of cases of microcephaly and Guillain-Barré syndrome in the outbreak in Brazil, on February 1, 2016, the World Health Organization declared Zika virus infection a global public health emergency [5]. Microcephaly is defined as the circumference of the head (HC) with 2 standard deviations (SD) or more below the mean gestational age or less than the 3rd percentile. In severe microcephaly cases, the standard deviation is 3 or more below the mean gestational age [22].

In addition, the fetal head has an abnormal shape, with overlapping sutures and occipital bone extending above the parietal bones, with redundant folds of skin and facial disproportionalty [23,24]. In the case of ultrasound objectification of microcephaly, prenatal or postnatal genetic evaluation is recommended to differentiate primary microcephaly from microcephaly caused by infection [20]. The presence of the ZIKA virus in the brain tissue of fetuses with microcephaly has been demonstrated by RT-PCR testing and electron microscopy [3,5,21].

Another characteristic ultrasound aspect in the case of congenital Zika virus infection in addition to microcephaly is the coarse calcifications located predominantly at the junction of the gray matter with the white matter [15,17,23]. Calcifications in the placenta can also be seen, which worsens the neonatal prognosis by the onset of intrauterine growth restriction, oligohydramnios/anhydramnios, and placental insufficiency [20,21].

Other central nervous system abnormalities highlighted on ultrasound in fetuses exposed in utero to Zika virus are cerebral atrophy, corpus callosum, vermian dysgenesis, cerebral hemisphere asymmetry, midline displacement, severe unilateral ventriculomegaly, mega cisterna magna, thalimus developmental failure [17,20,25].

Congenital neurosensory hearing loss, usually bilateral and severe, is another problem among fetuses exposed to congenital viral infections such as cytomegalovirus, toxoplasmosis, syphilis or herpes simplex. Leal et al. found sensorineural hearing loss in 5.8% of infants with severe microcephaly and congenital Zika virus infection. Thus, the hearing test should be performed on all newborns of mothers infected with Zika virus during pregnancy, even if no neurological organic lesions are evident on ultrasound. This screening can be repeated later because hearing loss due to a congenital viral infectious disease is progressive or fluctuating and can be undetectable at birth [26].

Although most congenital Zika virus syndrome cases have a neurological impairment, there are also ophthalmic or orthopedic lesions. These abnormalities may be present synchronously with or in the absence of microcephaly.

Several studies have shown their presence in infants with microcephaly and congenital Zika virus infection regarding eye lesions. Diagnosing them in utero is often difficult, but it is important to recognize them in the newborn [15]. The more severe the microcephaly, the more severe the eye damage [27]. Eye damage varies between 11.4% [25] and 67.7% [27], bilateral damage being more common. Vision-imparing injuries most commonly reported are focal retinal pigment spots and chorioretinal atrophy especially in the macular area (64.7%) followed by optic nerve abnormalities (47.1%) [28]. Other lesions that may occur are chorioretinal scars [27,29], bilateral iris coloboma, lens subluxation [28,29], pathological strabismus, nystagmus, and congenital cataracts [27] or intraocular calcifications with asymmetry of the eyes [17].

Associated lesions also affect the musculoskeletal system. Arthrogryposis, rarely found in congenital infections, is associated with congenital Zika virus syndrome in 9.6% - 15.8% of cases and can be caused by damage to the brainstem or cerebellum leading
to fetal akinesia [25,30], spinal cord atrophy, and impaired peripheral nerve root [15]. Arthrogryposis can be proximal or distal and unilateral or bilateral [15]. These fetuses may also associate abnormalities such as talipes, radial club hands, polydactyly, leg length discrepancy [25].

Congenital infection with Zika virus can affect neurodevelopment in normal phenotypic children at birth, with preserved arcaic reflexes, but can lead to manifestations such as convulsions, tremors, hyperreflexia, irritability, joint contractions, tone abnormalities (hypertension or spasticity), hearing loss, visual disturbances, difficulty swallowing and developmental delay [24,31]. Arthrogryposis, intrauterine akinesia, and neurogenic muscle atrophy are due to the loss of motor cells in the spine [15,32]. At birth, the newborn does not have hepatosplenomegaly or skin lesions such as petechiae or purpura [24].

Although with an ultrasound pattern similar to cytomegalovirus infection, damage to the central nervous system is more severe and destructive in the case of the Zika virus, with coarse calcifications predominantly located at the junction of the gray and white matter. Differentiation from Toxoplasma infection is due to the lack of multiple characteristic calcification nodules [15,17,23].

Pathological examination in dead fetuses revealed abnormalities such as ventriculomegaly, small transcerebellar diameter, microencephaly, hydrocephalus, almost complete agirism, and multifocal dystrophic calcifications in the subcortical white matter and cortex [21]. In addition to the serum and brain tissue fetal serum were identified large loads of Zika RNA and viral particles [33].

CONCLUSIONS

Zika virus can cross the placental barrier, with prenatal infection causing more severe fetal malformations than TORCH infections and, although rare, should be suspected in potentially infected women, often asymptomatic. Thus, it causes serious fetal neurological complications, of which microcephaly is among the most common. Other severe congenital anomalies of the central, ocular, or skeletal nervous system may be associated. Neurological impairment is a predictor of subsequent postnatal disabilities. In the absence of antiviral treatment or a specific vaccine, prophylaxis of infection in pregnant women is the only way to reduce perinatal transmission and thus protect the health of the fetus of apparently healthy newborns in terms of sight, hearing, neurodevelopment and neurobehavior.

Conflict of interest: none declared
Financial support: none declared

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