

Zika virus and the impact on pregnancy

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ABSTRACT

Since it was first associated with microcephaly and other central nervous system abnormalities, Zika virus infection emerged as a global health issue and discouraged pregnant women from traveling to areas affected by the Zika virus. Zika virus can be transmitted from mother to fetus during pregnancy, and can cause microcephaly, and other congenital malformations, known as congenital Zika syndrome. Microcephaly is determined by loss of brain tissue and abnormal brain development, and the outcome in children may vary, depending on the extent of the damage. Congenital Zika syndrome includes a broad spectrum of malformations, like limb contractions, increased muscle tone, eye abnormalities and hearing impairment. The purpose of this study is to synthesize available information about Zika virus and its impact on pregnancy and fetal development.

Keywords: Zika virus, pregnancy, transmission, diagnosis, treatment, prevention

INTRODUCTION

Zika virus was first described in 1947 in Uganda, in the Zika forest, during a yellow fever study on Rhesus monkeys [1,2]. It is a single-stranded RNA virus belonging to the Flaviviridae family, which includes other pathogens such as dengue, West Nile, Japanese encephalitis viruses and yellow fever virus [3,4]. Flaviviruses' spread is mainly influenced by the interaction between vector and host [5]. Like dengue, chikungunya and yellow fever, Zika disease is also transmitted through bites of infected *Aedes* mosquito [1,6]. These mosquitos generally bite during the day, with a peak in the early morning and late afternoon, unlike *Anopheles* mosquitos which cause malaria, and are active at nighttime, from dusk to dawn.

The first human infection with Zika virus was described in Nigeria in 1954, and by 2007 no more than 50 people had been affected by the virus [1,7]. The first major epidemic was reported in 2007 on Yap, an island in the western Pacific Ocean [7], and was followed by a second major outbreak in French

Polynesia in 2013 [8] and in other countries and areas in the Pacific between 2014 and 2016 [3]. At that time, none of these outbreaks were initially associated with pregnancy complications, but a sudden increase in cases of Guillain-Barré syndrome was observed in French Polynesia [3].

In most cases, Zika virus infection presents as an asymptomatic or mild, self-limited illness that usually lasts 4-6 days. The most common signs and symptoms include mild fever, itchy rashes, conjunctivitis, and arthralgia [9]. It resembles dengue or chikungunya fever and is even referred to as a dengue-like illness [2]. That is why it did not draw significant attention until 2015, when during the outbreak in Brazil, a concerning increase in the incidence of microcephaly, central nervous system malformations and neurological disorders, including Guillain-Barré syndrome [3], neuropathy and myelitis was observed, particularly in adults and older children [8].

On February 1, 2016, the World Health Organization (WHO) declared Zika virus outbreak a Public

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Health Emergency of International Concern (PHEIC), because of its association with clusters of Guillain-Barré syndrome and microcephaly [9].

METHODS

The purpose of this study is to review the literature and to synthesize available information about Zika virus and its impact on pregnancy and fetal development. We have used keywords such as ‘Zika’ an ‘pregnancy’, and we have searched articles through PubMed, the World Health Organization (WHO), the Center for Disease Control and Prevention (CDC) and European Center for Disease Prevention. We identified over 40 articles describing Zika virus pathogenicity and consequences in pregnancy and we summarised these information we found.

TRANSMISSION OF ZIKA VIRUS INFECTION

In humans, apart from vector-borne transmission, Zika virus can also be spread through sexual contact (heterosexual or homosexual transmission), blood transfusion, bone marrow or organ transplantation and, most concerning from an obstetrician’s point of view, mother-to-fetus [2,8,10,11]. Although Zika virus was also identified in breastmilk, there are still not enough evidence to support that the virus can be transmitted by breastfeeding [10,12].

Zika virus is primarily transmitted to humans through the bite of infected mosquitos, *Aedes aegypti* being considered the major vector [8,13]. Although *Ae. aegypti* is present in all tropical regions of the world, its’ distribution may expand because of climate change, population growth and migration [8,14].

According to the Center for Disease Control and Prevention (CDC), the prime reservoir of the virus are primate mammals, while vector-borne transmission occurs mainly during viral outbreaks. When a mosquito bites an infected human, its’ saliva becomes infected after an incubation period of approximate 10 days. Subsequently, an infected mosquito can infect a second mosquito, both directly and through the blood of a human [6,15].

Sexual transmission

Zika virus can also be spread through male-to-female, female-to-male or male-to-male sexual contact [4,8]. Viral RNA has been detected in semen 6 months following the onset of symptoms [4,16], and in female vaginal secretion [4,7]. First case of sexual transmission in Europe was described in a previously healthy 24-year-old woman from France, who was not receiving any treatment, had not received any blood transfusion and had not traveled lately to a region where Zika was epidemic. Nine days after

first sexual contact with a man recently returned from Brazil, she started developing acute fever, arthralgia, myalgia and pruritic rash. On the third day after the onset of the symptoms, samples of urine and saliva were obtained and tested positive for Zika virus RNA by reverse transcriptase polymerase chain reaction (RT-PCR) [18]. The CDC recommends that men should use condoms for three months after the last potential Zika virus exposure, and that women returning from endemic areas or who possibly had contact with the virus should wait for two months before trying to conceive [8,19].

Transmission through blood, bone marrow or organ transplant

Four cases of blood transfusion-associated transmission of Zika virus were reported and the prevalence of Zika virus RNA in blood donors was estimated to be around 1% [8,20,21]. The burden of blood transfusion transmission requires implementing strategies in order to prevent it. At present, in USA, all blood donations are tested for Zika virus RNA and the positive donations are excluded [8].

Although Zika virus transmission by bone marrow or solid organ transplantation has not been yet firmly confirmed, US guidelines recommends that is best to defer the donation, when a case of Zika virus-positive donor is suspected [8,22].

Vertical transmission

Vertical transmission during pregnancy raised new concerns, as infection at any point has been associated with fetal adverse outcomes [1,4]. Even if the moment of the infection and its impact on the fetus is difficult to assess, it appears that infections in the first trimester of pregnancy pose the highest risk of congenital Zika syndrome (CZS) [4,8]. In the first trimester, transmission of Zika virus across developing placenta into the amniotic or yolk sac may happen [23], and recent studies have found that the virus exhibits a broad tropism for cells in the human placenta [10], including placental trophoblasts, endothelial cells, fibroblasts and fetal macrophages located in the intervillous space, known as Hofbauer cells [4]. Materno-fetal transmission of Zika virus has been found in 20 to 30% of the infected pregnant women, whether the mother is symptomatic or asymptomatic [8,24,25]. Fetal loss was reported in 14% of the pregnancies affected by the virus, and severe neurological complications compatible with CZS occurred in 21% of the cases [25].

DIAGNOSIS

Diagnosis of Zika virus infection is mainly based on clinical symptoms. Laboratory diagnosis can be

accomplished by molecular testing, which consist of an RT-PCR that identifies the viral RNA in samples of serum and urine, and/or by serological IgM Elisa screening. Molecular testing is recommended in the first two weeks after the onset of symptoms, whilst serological testing may be used up to twelve weeks after the initial symptoms [10,25].

It is important to know that there is a high cross-reactivity with antibodies to other Flaviviruses, especially dengue virus, which is why, during the early stage of the Zika virus outbreak in Micronesia, serological tests mistakenly identified dengue virus, instead of Zika virus [2,10].

The CDC recommends that in non-pregnant individuals with possible exposure to Zika virus and without severe symptoms, serum and urine samples should be obtained and a RNA RT-PCR should be performed. Possible Zika virus exposure is defined as traveling to or living in an area with active Zika virus transmission or having sexual contact without condom with a partner who recently traveled or lived in an area with active transmission [10,19]. If Guillain-Barré syndrome is suspected, in addition to serum and urine RT-PCR testing, molecular testing of the cerebrospinal fluid is also recommended as soon as possible [10].

When molecular testing is negative, but the suspicion for Zika virus infection is high, seroconversion evaluation should be performed, by testing the serum samples for IgM within two to twelve weeks after symptoms onset [10].

For pregnant women with symptomatic Zika virus infection, serum, and urine molecular testing, as well as serological testing are recommended as soon as possible. If molecular testing is negative and the serologic test result is positive, a plaque reduction neutralization serologic test is recommended, in order to confirm the infection [10,26]. Prolonged viremia in pregnant woman may be explained by the ability of the virus to actively replicate in the fetal-placental unit, infect both compartments and move to maternal blood from any of them, where it can be measured for a longer time [9].

Women with symptoms and recurrent exposure to Zika virus should benefit from a detailed fetal anatomy ultrasound between 18 and 22 weeks of gestation, and every three or four weeks a scan should be performed, in order to overtake signs of congenital infection [27]. If microcephaly or other central nervous system abnormalities consistent with congenital Zika syndrome are found on a routine scan, and an amniocentesis should be performed for diagnostic purpose, amniotic fluid should be tested for Zika virus. In addition, molecular and serological testing should be performed. If congenital Zika infection is suspected, the newborn

and the placenta should be tested after delivery [10].

TREATMENT

There is no specific medicine that might treat or vaccine that might prevent Zika virus infection, and the treatment consists mainly of symptoms management by using antipyretics and analgesics to scale back fever and pain, and supportive care measures that include rest and forestall dehydration [28,29].

Although there's no yet approved targeted treatment for Zika infection, several agents are being studied, like drugs that regulate innate immune pathways mediated or suppress viral replication [10,30]. In pregnancy, neutrally active compounds like NMDA blockers are thought to possess the potential to manage the fetal neuronal damage caused by vertical transmission [10].

PREVENTION

The key measure to prevent Zika virus infection is protection against mosquito bites and vector control measures [31]. Personal protection measures consist of wearing long-sleeve, preferably light-colored clothing, that cover as much of the body surface, using physical barriers such as closed doors and windows, and using insect repellent on skin or clothing [28]. When used as indicated, Environmental Protection Agency (EPA)-registered insect repellent, were proven to be safe and effective, even for pregnant and breastfeeding women [32]. Resting and sleeping in screened or air-conditioned rooms and using mosquito nets is also recommended [33]. Infected persons should take the same basic precautions to protect themselves from mosquito bites in order to reduce spread [10].

Other measures include using a condom when living in an area with active Zika transmission and continue to do so for at least eight weeks after returning from this area, or at least six months after the cessation of symptoms. Travelers returning from Zika endemic areas, who want to donate blood, should be deferred until the risk of infection has passed, at about 28 days after returning from the affected area [33].

ZIKA VIRUS INFECTION AND PREGNANCY

Pregnancy represents a particular condition characterized by unique immunological regulatory mechanisms. Those mechanisms ensure that the maternal organism will not reject the partially allogenic fetus but also make the pregnant woman extra susceptible to infections. In addition, the imma-

ture immune system of the fetuses makes them more vulnerable to various infectious agents that the mother may contract [34,35].

It is well documented that different viruses can be transmitted vertically and cause congenital infections [34,35]. Zika virus can infect the placenta and pose great threat to pregnancies [36] by causing adverse pregnancy and fetal outcomes, such as miscarriage, microcephaly [4] or other damage to the central nervous system and severe developmental disabilities in children [6].

Zika virus infection in pregnancy has similar symptoms as those described in nonpregnant individuals [9]. Main clinical manifestations are described in order of frequency as follows: maculopapular, pruritic rash (44-93% of cases), headaches (53-62%), myalgia, or arthralgia (39-64%), conjunctivitis (36-58%) and lymphadenopathy (40%) [7,9]. Guillain-Barré syndrome is rarely associated with Zika virus infection during pregnancy, with only one case reported in literature [9,37,38].

However, in 2015, Brazilian physicians began to report a significant increase in the occurrence of microcephaly in newborns, which was possible linked to maternal Zika virus infection during pregnancy [2,39]. It wasn't until then that it raised global health concerns and discouraged pregnant women from traveling to areas affected by the Zika virus [40]. A retrospective analysis of birth defects in offspring born following the Zika virus outbreak in French Polynesia between 2013 and 2014 revealed particular abnormalities in brain development in newborns from mothers affected by Zika virus during pregnancy [7,41].

Diagnosis of Zika virus infection in pregnancy includes serum and urine molecular testing, as well as serological testing. Detailed evaluation of fetal anatomy by ultrasound is indicated between 18 and 22 weeks of gestation, and ultrasound scans should be performed every 3 or 4 weeks, to identify fetal anomalies associated with Zika virus infection [10].

CONGENITAL ZIKA SYNDROME

Although microcephaly attracted the most attention as the most important consequence of Zika virus infection in pregnancy, an increasingly spectrum of fetal anomalies associated with in utero Zika virus transmission continues to be identified. This new congenital malformation syndrome is currently referred to as 'congenital Zika syndrome' (CZS) [39].

CZS comprises a large variety of features that includes, besides microcephaly and fetal brain damage, a broad spectrum of developmental abnormalities, like musculoskeletal and ophthalmic [3]. Additionally, other abnormalities described include

fetal growth restriction, craniofacial malformations, pulmonary hypoplasia, genitourinary malformations and arthrogryposis [34,39,42].

Based on mouse models and human cell cultures, studies have shown that Zika virus is able to cross the placental barrier and infect the fetal brain, especially neural progenitor cells, and cause apoptosis of this cells [5,43-45]. Apoptosis of neural progenitor cells could inhibit neuronal-cell differentiation and contribute to microcephaly and other neurodevelopmental abnormalities [5,9,46]. In congenital Zika syndrome the microcephaly is usually more severe than the one observed in other genetic forms of microcephaly, reflecting the massive neuronal cell apoptosis and necrosis [9]. Besides, infection of the placenta may contribute to intrauterine growth-restriction and other fetal abnormalities [5].

Vertical transmission of Zika virus has been described in all stages of pregnancy, but during the first trimester, and between weeks 14 and 17 of gestation, there is the highest risk of central nervous system damage [3,47,48]. Thus, the impact on fetal growth and development may continue to occur also during the third trimester [3,49]. Lately, different patterns in the manifestations of congenital Zika syndrome have emerged, being correlated to the gestational timing of maternal Zika virus infection [3,49].

By causing congenital malformations similar to those produced by infectious agents that are responsible for the TORCH syndrome (toxoplasmosis, rubella, cytomegalovirus, and herpes simplex), some claim that Zika virus can also be considered a TORCH agent [39,50].

The CZS has been defined by five distinctive features, focusing on brain development anomalies like microcephaly and brain calcifications, ocular abnormalities and defects of the extremities including congenital contractures and hypertonia [39,51].

Microcephaly is defined by a fetal head circumference more than two standard deviations below the mean for age and gender [11,52]. Severe microcephaly is defined as a head circumference bellow third percentile for gender and age [39,53]. Risk of microcephaly has been reported from 1% to 15% in patients with prenatal confirmed Zika virus infection [9]. Ultrasound and magnetic resonance imaging (MRI) may show cortical disorders, ventriculomegaly, hydrocephaly, cerebral calcifications, cortical development abnormalities, lissencephaly and pachygyria or agyria [9,54,55,56]. Central nervous system abnormalities may also be present in newborns exposed to the virus, but with a normal head circumference [9].

Ocular, musculoskeletal, genitourinary, and pulmonary abnormalities have also been found to be

part of CZS, drawing attention on its complexity and making this virus a burden for the Public Health Services. Birth defects potentially associated with Zika virus infection are summarized in the Table 1 [36,39].

TABLE 1. Birth defects potentially associated with Zika virus infection [39]

Type	Exemple
Neurologic	Microcephaly Hydrocephalus Lissencephaly Polymicrogyria Pachygyria Agyria Ventriculomegaly Holoprosencephaly Corpus callosum anomalies Intracerebral calcifications
Ocular	Chorioretinal atrophy Optic nerve atrophy Vascular anomalies Macular abnormalities
Musculoskeletal (craniosynostosis)	Craniofacial anomalies Arthrogryposis Acetabular dysplasia Clubfoot
Genitourinary	Hypospadias Cryptorchidism
Other	Intrauterine growth restriction Pulmonary hypoplasia Anasarca Single umbilical artery

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CONCLUSIONS

Although Zika virus infection is usually a mild and self-limited disease in non-pregnant patients, it was associated with a surge in the number of cases of microcephaly and fetal abnormalities when it affects pregnant women. The risk of the fetus being affected by the virus is higher if the transmission of the virus occurs during the first trimester of pregnancy, but the impact on fetal development was also reported during the second and the third trimester. Because of this features, Zika virus infection has become a public health issue that requires intense further investigations. Prevention measures, including vector control, avoiding mosquitos, and using condoms are effective and special attention should be given to prevention of mosquito bites among pregnant women, women of reproductive age and young children.

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