Is Zika Virus an Emerging TORCH Agent? An Invited Commentary

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ABSTRACT: Zika virus (ZIKV) is a mosquito-borne arbovirus from the family *Flaviviridae*, which had caused some epidemics since its discovery in 1947 without any significant impacts on public health. In 2015, however, a 20-fold increase in congenital microcephaly cases in northeastern Brazil was attributed to prenatally acquired ZIKV infection. Traditionally, TORCH agents have 4 common characteristics including causing a mild illness in infected mother, vertical transmission to fetus, developing several anomalies in the affected fetus, and in some instances, maternal therapy may not ameliorate fetal prognosis. Prenatal ZIKV infection has shown the aforementioned characteristics during the recent epidemics in South America and the Caribbean region; therefore, it should be considered as an emerging TORCH agent that may seriously threaten public health. Fetal ultrasound can be used as a safe, inexpensive, and easy-to-access imaging modality for detecting suspicious cases of congenital Zika syndrome in utero and suggesting confirmatory diagnostic examinations to these patients.

KEYWORDS: Zika virus, ZIKV, congenital Zika syndrome, TORCH, microcephaly, pathogenesis

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Zika virus (ZIKV) is an arbovirus from the genus *Flavivirus* and the family *Flaviviridae*. It has been named after the Zika Forest in Uganda, where ZIKV was first isolated from a rhesus monkey in 1947. Zika virus is an arthropod-borne virus (similar to other flaviviruses) with the most common vector in the current outbreaks being mosquitoes from the genus *Aedes* (such as *Aedes aegypti* and *Aedes albopictus*). To date, 76 countries and territories have reported confirmed and/or possible active mosquito-borne transmission of ZIKV worldwide. Recently, sexual transmission has been confirmed as well, but likelihood of the virus transmission via this route is not well understood yet, although it seems to be low.[1–3]

Zika virus has caused some epidemics since its discovery, but it did not attract any significant attention until recently. In the outbreaks reported up to 2013, most of the infected patients were asymptomatic and only 20% of them had mild symptoms such as fever, arthralgia, maculopapular rash, and conjunctivitis. In 2013, however, a few infected adults revealed severe neurologic symptoms during the ZIKV outbreak in French Polynesia, mostly consistent with Guillain-Barré syndrome. Subsequently in 2015, the Ministry of Health of Brazil attributed a 20-fold increase in congenital microcephaly cases in northeastern Brazil to the prenatal ZIKV infection. Therefore, another route of transmission should be present for ZIKV, which is vertical transmission of the virus from the maternal blood stream through the placenta to the fetus. Considering these facts, ZIKV was not as benign as the initial assumption anymore and was announced as a "Public Health Emergency of International Concern" by the World Health Organization in February 2016.[1,3]

The acronym TORCH was first suggested by Nahmias et al[4] in 1971 to represent 4 congenital infections, which were not easily distinguishable based on the clinical grounds. These 4 bigs were "TOxoplasmosis," "Rubella," "Cytomegalovirus," and "Herpes simplex viruses type 1 and 2."[4] Subsequently, proposed by other researchers, the letter "O" changed to stand for "Other infections" because an increasing number of infectious agents turned out to cause severe congenital abnormalities similar to the classic TORCH infections, with the most important one being Syphilis. The TORCH infections have some characteristics in common, including the following: (1) most of them cause only a mild maternal illness, (2) they may transmit from the infected mother to the fetus vertically (through the placenta or in a few infections via the vaginal canal), (3) they may cause severe fetal anomalies, and (4) treatment of the maternal infection usually does not affect the fetal prognosis significantly.[5]

Prenatal infections are responsible for 2% to 3% of all congenital anomalies.[5] Congenital anomalies, especially of the brain, may be categorized into 2 broad spectra, including: (1) *malformations*, which are the phenotypic presentation of a genetic derangement with a high recurrence risk in the next pregnancies; and (2) *disruptions*, which are caused by a disruptive insult during pregnancy (mostly early pregnancy) leading to abnormal development of a fetal organ that had the potential of normal development. The etiologies of the second category are less likely to cause fetal abnormalities in the next pregnancies because they are mostly environmental teratogens. Infectious agents (such as TORCH infections) stay on the second category.[6]

Congenital ZIKV infection characteristics are very similar to classic TORCH infections, including the following:

1. Zika virus infection is asymptomatic or just mildly symptomatic in most of the infected pregnant women following horizontal transmission of the virus to the mother via mosquito bite or sexual contact.[3]
2. It has been suggested that ZIKV is transmitted to the fetus vertically through the placenta. The classic TORCH agents usually interfere with the normal placental growth and function. They may cause inflammatory responses (such as villitis and intervillositis) or vascular thrombosis leading to placental infarction and scarring. None of these pathomechanisms, however, has been demonstrated to occur in ZIKV infection. Instead, it has been proposed that the maternal decidua, fetal placenta, and umbilical cord are highly permissive to ZIKV. *Hofbauer cells* (macrophages with fetal origin), which are naturally occurring components of the placental stroma, proliferate significantly in response to ZIKV infection. Recently, ZIKV RNA has been isolated from Hofbauer cells, and the tropism of ZIKV to these cells has been demonstrated in experimental studies on human term placentas. The virus shedding into the placental stroma after replication in the Hofbauer cells may infect other cells (such as stromal fibroblasts). Considering these facts, it seems that *Hofbauer cells* play a crucial role, as the main target cells, in transplacental transmission of ZIKV to the fetus.[7–13]
3. The neurotropism of ZIKV has been confirmed in the studies on postmortem examination of human fetuses and animal models. Neural progenitor cells are the primary target of ZIKV, but other immature neurons may be also affected to a less degree. The virus causes abnormal differentiation of the neural progenitors or induces apoptosis in these cells, and hence interferes with the normal fetal brain development. The pathomechanism of abnormalities seen in congenital Zika infection is best explained by the "*fetal brain disruption sequence (FBDS)*," originally described by Russell et al in 1984. A *sequence* is defined as morphologic anomalies that are caused secondary to a malformation or disruption. Accordingly, FBDS is defined as partial fetal brain destruction due to a disruptive agent leading to a reduction in the intracranial hydrostatic pressure, which results in the subsequent collapse of the fetal skull. Fetal brain disruption sequence is clinically characterized by severe microcephaly, overlapping skull sutures, prominence of the occipital bone, and scalp rugae.[6,13–17]
4. Prenatal ZIKV infection causes severe congenital anomalies, mostly in the central nervous system (CNS). The constellation of these abnormalities in an infected fetus is known as "*congenital Zika syndrome (CZS)*." The principal neuroimaging findings in CZS include microcephaly (ie, head circumference 2-3 SD less than mean at a given age), brain parenchymal calcifications (mostly punctate in shape, band-like in distribution, and located at or just below the corticomedullary junction), brain atrophy with secondary ventriculomegaly, subependymal pseudocysts, malformations of cortical development (mostly polymicrogyria and less likely lissencephaly-pachygyria spectrum), agenesis/hypoplasia of the corpus callosum, cerebellar and brainstem hypoplasia, and myelination abnormalities. Overlapping sutures, small fontanels, and a pointed appearance of the occipital and frontal regions may be evident in the skull. Other possible findings in CZS are ocular abnormalities (such as perimacular lesions, optic nerve abnormality, and chorioretinal atrophy), sensorineural hearing loss, and arthrogryposis. In addition, CZS has been associated with an increased risk of intrauterine growth restriction and miscarriage. It should be emphasized that although *microcephaly* is the most common finding in CZS; there are a few reports of CZS cases with severe brain anomalies but normal head circumference at birth. Therefore, it seems that ZIKV can cause a wide spectrum of abnormalities in the fetal CNS.[1,17,18]

In summary, according to the similarities between ZIKV and classic TORCH agents, ZIKV should be considered as an emerging TORCH infection, which has been suggested and agreed by some other authors as well.[12,13,19] To date, 29 countries and territories have reported a total number of 2656 cases of congenital microcephaly and/or CNS anomalies potentially related to the prenatal ZIKV infection, with most of them originated in Brazil (2366 cases).[2] It has been estimated that CZS develops in 1% to 13% of fetuses that their mothers are infected during the first trimester of gestation. In addition, it seems that fetal prognosis in the CZS correlates highly with the time of infection (ie, infection occurring during early pregnancy deteriorates the fetal outcome more than the infection acquired during late pregnancy).[3,20]

When discussing about neurologic complications caused by ZIKV, it is of paramount importance to differentiate between *prenatally* and *postnatally* acquired infections. Although ZIKV may cause severe CNS anomalies in the infected fetuses, disease course is less benign in the infected adults with most (80%) of the cases being completely asymptomatic. A few recent reports, however, have indicated the possible relationship between a number of severe neurologic complications (including Guillain-Barré syndrome, transverse myelitis, meningoencephalitis, and acute disseminated encephalomyelitis) and postnatally acquired ZIKV infection in rare instances. These acute neurologic complications are most likely caused by neuronal damage and demyelination due to the host's humoral and cellular mediators (ie, cross-reactivity and autoimmunity), which is different from the

pathomechanism of CZS (ie, direct invasion and injury of fetal neural progenitor cells by the virus).[21,22]

In the endemic regions, prenatal screening for CZS may be performed by ultrasound as an easy-to-access and relatively inexpensive imaging method. Subsequently, fetal magnetic resonance imaging may be used as a complementary study for more precise evaluation of the suspected fetuses. Amniotic fluid real-time reverse transcription polymerase chain reaction (rRT-PCR) can reveal the virus RNA in the amniotic fluid and may be performed as a diagnostic testing in the pregnancies suspected for CZS based on imaging studies. Amniotic fluid may also be analyzed for ruling out other causes of microcephaly (such as other congenital infections and genetic disorders). In addition, maternal blood/serum/urine should be examined by molecular or serologic testing for maternal ZIKV infection.[23]

Currently, there is no approved drug for treatment of ZIKV infection in adults, and supportive care is only recommended. Following strategies are proposed to reduce the number of CZS cases: (1) vector control in the endemic regions, (2) offering contraceptive methods to the women residing in the endemic areas, (3) sexual abstinence or barrier use during intercourse by the men residing in or recently returning from an endemic area, and (4) travel ban to the regions with active virus transmission for the pregnant women. Furthermore, possible future vaccination against ZIKV will reduce the number of CZS cases significantly, similar to what happened to the congenital rubella syndrome.[24]

Author Contributions

MZM was responsible for the conception, data collection, drafting the article, and final approval of the article.

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