Zika Virus

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Epidemiology

The first Zika virus disease outbreak in continental South America occurred in Brazil, where endemic transmission was confirmed in May 2015 [1]. Since then, up to November 2016, 10,056 cases of microcephaly or other neurologic disorders in newborn babies and infants have been reported in Brazil; 1950 of the microcephaly cases were confirmed to be infection-related. The maximum frequency of notified microcephaly in Brazil reached 49.9 cases per 10,000 newborn babies, a peak that is 24 times higher than the historical mean occurrence of microcephaly [2].

The first known cases of local Zika virus infection in the continental United States were reported in July, 2016 [3]. Soon after, the Centers for Disease Control and Prevention (CDC) established the Zika Pregnancy and Infants Registries to collect information about pregnancy and infant outcomes following laboratory evidence of ZIKV infection during pregnancy. By July 11, 2017, of 2945 completed pregnancies reported, 127 (4%) were live-born infants with birth defects, and 7 were pregnancy losses with birth defects [4].

Currently, ZIKV is a potential pandemic threat, circulating in the Americas, Pacific Islands, Southeast Asia, and the islands of Cape Verde off the coast of West Africa [5]. Although the number of cases in endemic areas different from the Americas is unknown, it is estimated that over two billion people inhabit in areas

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with proper environmental conditions for ZIKV, raising concerns about its final geographical range and ultimate clinical impact [6–8].

Pathogenesis

The exact pathogenic pathways of the immune response of the host and the molecular mechanisms involved in the complications associated with ZIKV infection are the subject of extensive research worldwide. Current knowledge of the physiopathology of the infection comes from multiple animal models, cell culture studies, postmortem evaluation of affected patients, and clinical/epidemiological studies.

ZIKV is transmitted to humans within their urban cycles mainly through bites of infected mosquitoes belonging to the *Aedes* genus (*A. aegypti*, *A. africanus*, *A. albopictus*) [9]. Perinatal infection occurs through vertical transmission from an infected expectant mother. The initial viral load allows transplacental passage, although the exact mechanisms have not been clarified [10]. Recent findings suggest that this is mediated by placental macrophages (Hofbauer cells) and cytotrophoblast cells. Thus, the virus reaches a direct pathway to fetal circulation, disseminating through developing tissue [11]. The virus has a tropism toward neuronal precursor cells over immature neurons or pluripotential stem cells [12]. There are multiple candidate receptors that could be responsible for the uptake of the virus into the developing neuron—among them the tyrosine kinase receptors of the families TYRO, AXL, and TAM—that allows this particular access to neuronal precursor cells [10]. The entrance of the virus to progenitor cells of the neural crest through the AXL receptor—a phagocytic phosphatidylserine widely shown in neuronal precursors—activates cell signaling pathways that result in the deregulation of the cell cycle and activation of apoptotic pathways [13]. Within NPCs, the virus quickly replicates, disseminating all over the underlying tissue. The result is a twofold depletion of NPCs: suppression of the proliferation of NPCs and increased cell death of both infected NPCs and non-infected cells.

After multiple replication cycles, there is a decrease in the neuronal volume and mass, leading to the clinical presentation of microcephaly. Other effects noted are the thinning of periventricular cell layers and structural disruption, which leads to alterations of the ventricular system. It has also been shown in animal models that infections during later pregnancy can lead to alterations in the neuronal differentiation and a decrease of the total number of neurons, which would also explain other neurocognitive manifestations seen in patients without microcephaly [12]. The cause of ocular and aural damage is not yet clear; however, widely accepted theories suggest direct cytotoxicity due to the virus or as a consequence of an inflammatory process. So far, it has not been possible to isolate the virus within ocular tissue [14]. It would also seem that the fetal compromise is associated with the viral strain. A study comparing different viral strains and their effect in the development of fetal brains in animal models and human neuronal organoids found that Brazilian virus strains cause a greater depletion of neuronal precursor cells and a higher disruption in neuronal monolayers when compared with African strains [15].

Clinical Findings

Adult Infection

In ZIKV, the ratio of symptomatic to asymptomatic patients is about 20% [16]. In symptomatic patients, the incubation period of ZVD ranges from 3.5 days for the human healthy volunteer to 6–10 days for returning travelers and blood donors [17–19]. Symptoms last for approximately 1 week [20]. During the Yap State, French Polynesia, and Brazil outbreaks, the described symptoms present in the majority of cases were maculopapular rash (present in 80–98%), fatigue (80%), fever (~70%), diffuse body aches (e.g., arthritis, arthralgia, or myalgia, ~60%), and conjunctivitis (50–60%) [20, 21]. In contrast to nonpregnant patients, fever is present in less than 30% of pregnant women with ZVD [22].

Congenital Infection

A causal relationship exists between prenatal ZIKV infection and microcephaly and other serious brain anomalies in offspring [23]. The spectrum of abnormalities is broad and includes neurological impairments, fetal akinesia deformation sequence (i.e., arthrogryposis), growth restriction, and ophthalmologic alterations—hence the term congenital Zika syndrome (CZS, Table 1) has been recommended [24]. The CDC has developed case definitions for congenital ZIKV infection and ZVD [25]. It should be noted that a large case series from Brazil showed that approximately 20% of infants with congenital ZIKV infection have normal head circumference

Table 1 Clinical characteristics of congenital Zika syndrome

Epidemiology	Approximately 6% of infants born to Zika virus-infected pregnant women[a]
Clinical Findings	Central nervous system • Microcephaly • Ventriculomegaly • Calcifications • Neuronal migration defects • Limb contractures/arthrogryposis Ophthalmic • Chorioretinitis • Macular injury • Atrophy Other • Sensorineural hearing loss • Congenital heart disease
Diagnosis	Pregnant woman: serum IgM, blood and urine PCR Infant: blood, urine, and cerebrospinal fluid PCR
Treatment	Supportive
Prevention	Mosquito control (DEET, netting, avoiding travel to endemic areas) Barrier contraception to prevent sexual transmission from infected partner

[a]In the United States, incidence during 2015–2016 Brazilian outbreak may have been much higher

[26]. Figure 1 shows an overlap between congenital ZIKV infection, rash during pregnancy, neuroimaging findings, and head size.

In Brazil, among 125 women who developed rash during pregnancy and had positive results for ZIKV on PCR testing, there were 58 adverse pregnancy outcomes (46%), including 9 cases of fetal death. The majority of these affected newborns had CNS abnormalities including microcephaly, cerebral calcifications, cerebral atrophy, ventricular enlargement, and hypoplasia of cerebral structures [22]. Preliminary data from the US Zika Pregnancy Registry shows that the impact of the Zika epidemic in the United States is lower than was reported from the Brazilian epidemic. Among 442 completed pregnancies in women with laboratory evidence of possible recent ZIKV infection, 271 pregnant women (61%) were asymptomatic, and 167 (38%) were symptomatic. Overall, there were 26 (6%) fetuses or infants with birth defects. The proportion of infants with birth defects was the same in mothers with or without symptoms. Unlike the Brazilian study, no birth defects were reported among pregnancies with maternal infection in the second or

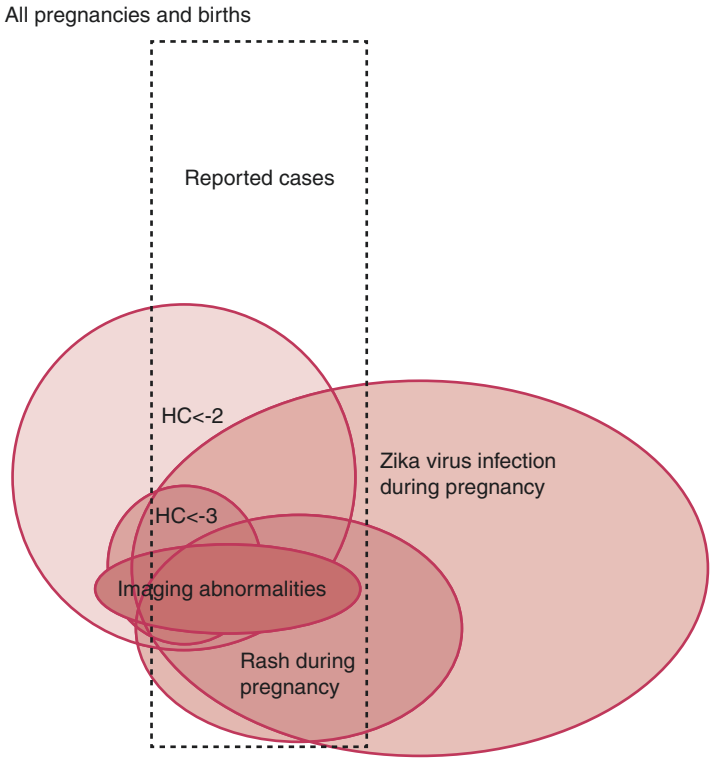

Fig. 1 Overlap between ZIKV, rash during pregnancy, neuroimaging findings, and head size [26]. França GVA, Schuler-Faccini L, Oliveira WK, Henriques CMP, Carmo EH, Pedi VD, et al. Congenital Zika virus syndrome in Brazil: a case series of the first 1501 livebirths with complete investigation. The Lancet. 2016;388(10047):891-7. DOI: https://doi.org/10.1016/S0140-6736(16)30902-3. Creative Commons Attribution License (CC BY)

Table 2 Adverse pregnancy outcomes by trimester of maternal Zika virus infection

	Moderate[a] *n* (%)	Severe[b] *n* (%)	Overall *n* (%)
First trimester (*n* = 34)	0	11 (32.4%)	11/34 (32.4%)
Second trimester (*n* = 64)	1 (1.6%)	7 (10.9%)	8/64 (12.5%)
Third trimester (*n* = 47)	1 (2.1%)	2 (4.3%)	3/47 (6.3%)
Any trimester (*n* = 145)	2 (1.4%)	20 (13.8%)	22/145 (15.2%)

[a]Moderate adverse outcomes: severe osteomuscular impairment or 4–5 of 7 items affected in the Hammersmith Functional Motor Scale

[b]Severe adverse outcomes: pregnancy loss, microcephaly, or 6–7 items affected in the Hammersmith Functional Motor Scale

third trimester, while 11% of pregnancies with ZIKV infection during the first trimester presented with birth defects [27].

In Cali, Colombia, there is an ongoing follow-up of a cohort of infants born to mothers who consulted during pregnancy for Zika-related symptoms and were confirmed to have ZVD by blood PCR. Data for 145 infants has been obtained, 46% of whom had adverse outcomes, including 15% of infants with moderate or severe impairments (Table 2).

The contrasting findings between the epidemics in these three different regions were also reported in the distinct waves of ZIKV that occurred in Brazil, with incidences of infection-related microcephaly varying from 49.9 cases per 10,000 live births during the first wave in the northeast region to 3.2–15 cases per 10,000 live births during the second wave in other Brazilian regions. The reasons for the difference in the impact of ZIKV infection during pregnancy among different regions or countries are not clear [2].

Central nervous system findings. Neurologic impairment is the most common consequence of congenital infection. In an observational study from Brazil, 11 infants with congenital Zika virus infection were followed up from gestation to 6 months of age. Although most infants with CNS compromise had microcephaly, some patients had head circumference measurements that were consistent with their gestational age, as brain atrophy was compensated by an enlargement in ventricular size [24]. A common pattern of brain atrophy and changes associated with disturbances in neuronal migration were observed, resulting in findings such as microcephaly, a reduction in cerebral volume, ventriculomegaly, multifocal dystrophic calcifications, cerebellar hypoplasia, and lissencephaly [24, 28, 29].

Ophthalmic findings. Infants with congenital Zika frequently develop ocular manifestations. Of 29 Brazilian patients born with microcephaly with a presumed diagnosis of congenital ZIKV, 35% had ocular abnormalities [30]. Furthermore, the 43 Colombian and Venezuelan patients clinically diagnosed with congenital Zika syndrome had bilateral ophthalmic manifestations. The most common findings were focal pigmental mottling, with a predilection for the macular area, and chorioretinal atrophy and scars. Optic disk abnormalities as well as congenital glaucoma (12% of cases) were also described [31].

Other manifestations. As well as neurologic and ophthalmic abnormalities, other manifestations of CZS have been described. Congenital heart disease was present in

13.5% of 103 infants with presumed CZS. Sensorineural hearing loss was present in 5.8% of children born with microcephaly and laboratory evidence of congenital ZIKV infection [32]. Arthrogryposis, foveas in the knees or elbows due to limb contractures in utero, and redundant scalp skin in infants with normal head circumference are also common findings [22, 33].

Diagnosis

Maternal Diagnosis

Current diagnosis of ZIKV is based on molecular detection of viral RNA through polymerase chain reaction (PCR). Genetic material can be detected in serum or plasma from the expectant mother within 2 days of the beginning of the symptoms and up to 7 days after the symptomatology has started. In urine, it is detected up to 14 days later, but there are reports that have isolated the virus up to 20–39 days later [34]. Compared with serum, urine has shown higher responsiveness and a wider detection window. The CDC diagnosis protocol recommends taking both samples, as well as ZIKV IgM serology, as soon as possible through 12 weeks after symptom onset in pregnant women with recent possible ZIKV exposure and symptoms of ZVD [35].

Serological methods detect IgM-ELISA from 4 to 5 days after the start of the symptoms up to 12 weeks or more after the symptomatology has started. Even though false negatives occur, a negative result at least a week after the start of the symptoms is a strong evidence against ZIKV infection [36]. Due to the high degree of cross-reactivity with other flaviviruses, a positive or in conclusive IgM-antibody result must always be confirmed with a plaque reduction neutralization test (PRNT), generally only available in reference laboratories. This decreases the usefulness of serology, particularly in countries with high dengue endemicity [37]. With a confirmed diagnosis in an expectant mother or its high clinical suspicion, it is recommended to perform an amniocentesis and RT-PCR on the amniotic fluid to confirm the fetal infection.

Fetal Testing

Fetal diagnosis can be challenging; amniotic fluid samples can produce negative results in spite of fetal infection, and likewise, positive results can be obtained without fetal abnormalities. Thus, close monitoring through ultrasound and fetal magnetic resonance in the search of premature congenital malformations is recommended [38].

Newborn Testing

RT-PCR analysis of serum, urine, and CSF of the newborn suspected of having ZIKV infection is recommended during the first 2 days of life; however, there are multiple reports that reveal isolation of the virus for weeks to months after being

born [28]. If fetal or maternal infection is confirmed or highly suspected due to clinical manifestations, a thorough assessment of the newborn must be performed with neuroimaging (preferably brain magnetic resonance or ultrasound), ophthalmologic assessment and monitoring, hearing studies, and a detailed neurological examination. In symptomatic cases at birth, it is recommended to perform an echocardiogram, electroencephalogram, hepatic function testing, and exploration of possible musculoskeletal malformations. CDC has implemented a guide for infant neuroimaging and infant and placental Zika virus testing, which is currently being revised and updated [39].

Treatment

There is no specific treatment or antiviral drug for ZIKV infection. Recommendations include the treatment of symptoms with acetaminophen for fever or pain and an antihistaminic for pruritic rash and hydration [19]. For congenital Zika syndrome, multidisciplinary follow-up care, including infectious diseases, neurology, ophthalmology, audiology, speech, occupational therapy, and physical therapy, is important in order to maximize the functional outcome.

Prevention

Primary prevention of the ZIKV infection consists of avoiding mosquito bites and the performance of vector control. Among the recommended measures are clothing that covers exposed parts of the body, use of repellents, and adequate physical barriers such as closed windows, screens, and mosquito nets [40]. In expectant mothers who live or come from areas where the virus is circulating, consultation upon recent infection symptomatology must be emphasized, highlighting that for one third of congenital cases there was no history of rash during pregnancy [26].

In order to prevent sexually transmitted infections, it must be noted that viral particles have been isolated in semen up to 10 weeks after the beginning of the symptoms, within the female genital tract up to 2 days after the beginning of the symptoms, and that sexual transmission has been documented up to 44 days after the beginning of the symptoms [41, 42].

Transmission of virus by blood transfusion has also been documented [43]. Given that most of the infections are asymptomatic, the best strategies to prevent infections by transfusions are the evaluation of nucleic acids in the donor blood or inactivation of the pathogen [44]. There are about 40 vaccine candidates under development; however, they are not expected to be available for some years. It is unknown whether Zika infection produces a permanent immunity [45].

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