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Zika Virus Infection during Pregnancy and its Management

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Abstract

Zika virus (ZIKV) is a mosquito-borne Flavivirus having perilous effects globally, and more particularly among pregnant females. Its current epidemic in the Pacific and in Central and South America is linked with microcephaly and other abnormalities of the central nervous system in neonates. The case reports and personal communications are the only sources containing data about ZIKV and pregnancy; however, recommendations related to managing ZIKV exposure during pregnancy are emerging rapidly. We aim to review and synthesize the existing literature about ZIKV and pregnancy and to assist clinicians to manage pregnant patients who are susceptible to ZIKV infection. This review supports the existing evidence about the causal link between microcephaly and ZIKV infection during pregnancy. Globally more than 2 billion people are the residents of the areas which are conducive to ZIKV transmission. It is estimated that in 2016 around 4 million people will be infected with ZIKV in the Americas. Looking towards the current scenario of ZIKV pandemic and its drastic consequences during pregnancy, it is quite evident that ZIKV may have massive impact both on health services and affected communities. Thus, there is a dire need to establish global public health and research response on urgent footing to minimize and preclude its deleterious impact via proper diagnosis, vaccination and treatment.

Keywords: Zika virus; Pregnancy; Microcephaly; Transmission; Management

Abbreviations:

ZIKV: Zika virus; GBS: Guillain-Barré Syndrome; RT-PCR: Reverse Transcription Polymerase Chain Reaction; CDC: Centers for Disease Control and Prevention; WHO: World Health Organization; PAHO: Pan American Health Organization

Introduction

Undoubtedly, pregnancy can be termed as one of the most exciting time in a woman's life but at the same time it may be a vulnerable period both for woman and her fetus as well [1]. News related to the outbreaks of Zika virus (ZIKV) and its association with microcephaly in the newborns is a serious global concern to the pregnant woman or those planning to conceive.

ZIKV belongs to the Flavivirus family and transmitted through daytime-active mosquitoes of the Aedes spp. Initially, ZIKV infection did not gain much attention as it was only associated with mild fever, arthralgia and rash in 20% of the patients; whereas, 80% of the infected individuals remained asymptomatic [2]. Large outbreaks of ZIKV have been seen in the Pacific (especially in the island of Yap in 2007 and in French Polynesia in 2012–14). Subsequently, the situation became grave with the increasing outbreaks of ZIKV in Central and South America (especially Brazil) in 2015–16, and thus the World Health Organization (WHO) declared the situation as a Public Health Emergency of International Concern [3].

According to the prediction of WHO, there would be 4 million cases of ZIKV infections in 2016 in the Americas solely [4] and initial estimates suggests that about 2.17 billion people are the residents of areas which are conducive to ZIKV transmission [5]. ZIKV transmission has now been confirmed in 66 countries and their adjoining areas since 2015; whereas, 49 countries and territories which were previously ZIKV-negative have also reported the first outbreak of ZIKV [6]. Various advancements in research have declared ZIKV to be a potential cause of alleviation in neurological abnormalities such as microcephaly and Guillain–Barre Syndrome (GBS), reported in these regions.

It is pivotal for the obstetricians to be vigilant about the newly developing information related to ZIKV for the proper assessment and guidance of the pregnant women or those planning to conceive. This review aims at formulating the current literature about ZIKV and pregnancy as it may assist the clinicians to manage timely and appropriately the pregnant patients with potential exposure to ZIKV.

Search Strategy

We searched PubMed, Science Direct and Google Scholar with the following keywords: "Zika virus", "Pregnancy", "Transmission", "Complications", "Diagnosis" and "Management" in several combinations in BOOLEAN and MeSH searches. The search covered the period from 2007 to September 2016.

The references of selected papers were also screened to identify relevant literature, and review articles were also cited when applicable. Due to the limited data published in scientific journals, we also explored the databases of leading organizations, such as the Centers for Disease Control and Prevention (CDC), World Health Organization, European Center for Disease Prevention and Control and Pan American Health Organization (PAHO).

Level of Threat to Pregnant Women

The hasty dissemination and penetration of ZIKV in previously virus free regions pose a significant threat to pregnant women and their fetus. A French Polynesian study elucidated that since the major brain development of fetus took place in first trimester so ZIKV infection in the early pregnancy is more strongly linked with microcephaly than infections involved in the later trimesters of pregnancy [7]. Moreover, the effects of expansion of ZIKV in formerly unexposed populations may not be observed for a couple of months, for instance the delayed observations of microcephaly and fetal malformations were seen in French Polynesia [7] and Brazil [8]. On 25 June 2016, almost 8165 cases of microcephaly were reported in Brazil and they were suspected to have an association with ZIKV infection. Upon investigation of 5104 cases, 1638 cases i.e., 32% were confirmed to be associated with ZIKV [9]. Data from French Polynesia demonstrated that the risk of microcephaly from ZIKV infection was 1% in the first trimester [7]. This data was obtained through passive surveillance of only ~30% of general practice clinics and there are chances that it gives an underestimation of the real picture. It might be possible that some mothers had miscarriage or stillbirth or they have not visited clinics. Data depicting the outbreaks of ZIKV in Brazil has not yet been reported. This relatively low risk has to be balanced with the large population exposure and high incidence of ZIKV in some regions (e.g., ~70% in French Polynesia [7] and Yap [2]). It is still not clear that why microcephaly and other congenital abnormalities linked with ZIKV infection have become so conspicuous in the recent outbreaks. It can be proposed that the mutations involved in ZIKV strains, host or other cofactors might be responsible for this recent epidemic. The vastly increasing epidemic of ZIKV has enabled the detection of associated complications.

Perinatal Transmission

Apprehensions related to the transplacental transmission of ZIKV from mother to fetus have alleviated since a number of reports have confirmed the strong association between maternal ZIKV exposure and fetal congenital abnormalities such as microcephaly [2,10]. The vertical transmission of ZIKV can occur either through placenta or during labor and delivery [11]. Data elucidating the vertical transmission rate and the probable period of transmission of ZIKV has yet to be synthesized. In French Polynesia, two cases of perinatal transmission of ZIKV were reported between December 2013 and February 2014, and it is believed that the transmission might have taken during the delivery [11]. The testing of maternal serum, breast milk and salvia, and the infant's serum, saliva and urine for ZIKV RNA detected through reverse transcription polymerase chain reaction (RT-PCR) were reported. Nevertheless, the tests were not done consistently for every case, thus leading to the perplexing of the interpretation of the data. In Case 1, the mother suffered from rashes just two days before the delivery and her serum RT-PCR ZIKV RNA was found positive two days after the delivery. The infant breastfed upon delivery and breast milk RT-PCR ZIKV RNA was positive three days after the delivery. Moreover, RT-PCR ZIKV RNA serum and saliva test of the infant were found to be positive three days after delivery. In Case 2, the mother experienced a pruritic rash, myalgia and mild fever on postpartum day 3. Upon diagnosis it was revealed that she had positive serum RT-PCR ZIKV RNA on both postpartum days 1 and 5; whereas, she had a negative test on postpartum day 8. The new born was breastfed on postpartum day 3 and breast milk RT-PCR ZIKV RNA turned out to be positive on postpartum day 8. The RT-PCR ZIKV RNA serum test of the infant was negative at delivery and on postpartum day 3; whereas, it converted to a positive test on postpartum days 4 and 7. The urine test of the infant revealed positive RT-PCR ZIKV RNA on day 8 and subsequently it became negative on postpartum day 9. The pregnancy of Case 2 was complicated because she was also suffering from gestational diabetes. As a result, her infant suffered from hypoglycemia and neonatal jaundice, which was most probably due to the gestational diabetes. The aforementioned data fails to answer the important query that if ZIKV can be transmitted through breastfeeding [12]. Although, the salvia of both of the mothers of case 1 and 2 tested positive for ZIKV but this result might be due to certain contamination [11].

Complications during Pregnancy

Microcephaly is the major anomaly associated with ZIKV infection during pregnancy. Microcephaly can be described as a condition in which the fetus or infant has a head circumference (HC) smaller than expected for gestation or age. Depending upon the cause, microcephaly can be categorized as primary (mainly from genetic causes) and secondary (non-genetic causes such as infection or disruption of brain vasculature) [3]. The criteria which can be used to define microcephaly vary. Looking towards a more stringent definition, microcephaly is a HC of three standard deviations (SD) below the mean. This definition encompasses all those who have a clinically significant microcephaly, which in turn is associated with grave intellectual impairment, developmental delay and various other complications. According to a less stringent definition, microcephaly is a HC of two SD below the mean. This definition is presently used in Brazil for diagnosing postnatal microcephaly. It is an established fact that almost 33% of infants who have a HC between two and three SD below the mean suffers from moderate to severe intellectual impairment [13]. As far as the ZIKV infection is concerned, a unanimous definition of microcephaly is particularly important for the sake of in utero diagnosis. This task is technically quite difficult and it has been facilitated by the recently released guidelines from the Society for Maternal Fetal Medicine [14]. The evidence for strong

association between ZIKV and microcephaly is now strongly and widely accepted [3,15] (Table 1).

Table 1: Evidence for a causal link between ZIKV and microcephaly

1. Epidemiological and clinical findings
Increase in microcephaly cases coincides with increase in ZIKV transmission (with a 6-month delay).
Data modeling shows that the main period at risk is the first trimester of pregnancy.
Of the microcephaly cases investigated in Brazil, 32% were linked to ZIKV.
Case study: Miscarriage of a baby with microcephaly was positive for ZIKV (including in its brain), but negative for other known infectious causes of microcephaly.
2. Laboratory studies
ZIKV can infect human neural progenitor cells and attenuate their growth *in vitro*.
Primary human placental macrophages and trophoblasts are permissive to ZIKV infection *in vitro*.
3. Animal models
Mouse model of ZIKV display signs of microcephaly.
4. Analogy to related viruses
Rubella virus, another Flavivirus, causes microcephaly when infection occurs during pregnancy.

Another grave complication associated with ZIKV infection is GBS. GBS is an immune-mediated disease afflicting the peripheral nervous system causing debilitating peripheral neuropathy leading to muscle paralysis, and may result in a serious consequence i.e., death in certain cases [16]. Other viruses such as those belonging to Flaviviruses may also be responsible for GBS [17]. A clear association between ZIKV infection and GBS has now been established in French Polynesia [18].

Numerous other cerebral abnormalities associated with congenital ZIKV syndrome during pregnancy includes brainstem and cerebellar hypoplasia, gross calcification of the brain parenchyma, severe ventriculomegaly, delayed myelination and lissencephaly (absence of normal cerebral folds) [19,20]. In contrast to other viruses in pregnancy that exert their effects both on neural tissues and on other body organs, ZIKV have a debilitating effect on neural tissues specifically. Recently, two reports of neuroimaging of 46 infants with likely ZIKV-associated microcephaly verified severe brain damage in almost all the cases [19-21].

Potential Mechanisms Linking Zika virus and Microcephaly

Once the microcephaly develops in utero (hereafter microcephaly), impaired neurogenesis takes place in fetus which either results in decreased number of neural progenitor stem cells or impaired neuronal division and differentiation [22]. Multiple non-infectious causes or agents responsible for microcephaly have been demonstrated such as genetic predisposition [23] and prenatal alcohol exposure [24].

Detection of ZIKV in the brain tissue of microcephalic fetuses [25,26] and the *in vitro* evidence that ZIKV can cause the infection of neural progenitor cells and weaken their growth, serve as the supportive evidence establishing ZIKV infection as a cause of microcephaly [27]. If the human cortical neural progenitor cells are infected that it may lead to cell cycle dysregulation and caspase-3-mediated apoptosis [27]. Entry of ZIKV in to the cells is mediated via numerous surface receptors such as DC-SIGN, AXL, Tyro3, and, to a lesser extent, TIM-1, with a major role for AXL [28,29]. The AXL receptor which is present in the brain tissue of the fetus is expressed to a large extent in the cells of developing cerebral cortex, including radial glial cells, microglia, astrocytes and endothelial cells; however, the expression of the receptors i.e., Tyro3 and DC-SIGN is either low or completely absent [30]. The possible mechanism for the development of blindness in babies born to ZIKV infected mothers involve the expression of AXL in the outer margin of the neural retina and in cells of the ciliary marginal zone adjacent to neural retina [30,31]. Once the virus gains entry and replication of ZIKV RNA takes place, a potential antiviral response is initiated with the upregulation of TLR3 mRNA as well as RIG-I and MDA-5 mRNA. The silencing of TLR3 leads to strong upregulation of viral replication but it does not affect the type I interferon (IFN) response. If the infected cells are treated with IFN-α, IFN-β, or IFN-γ then it results in the dose-dependent inhibition of viral replication [28], thus proposing the potential therapeutic approaches in the times to come. ZIKV could be transferred to the fetal brain by transplacental passage or through diffusion into the amniotic and yolk sacs during the process of embryogenesis [32]. Undoubtedly, the placental cells are protected against ZIKV infection via IFN-λ response but despite of this the transplacental means of transmission is plausible [33]. It is still quite ambiguous that whether these protective mechanisms holds true in the early pregnancy.

A recent study has revealed that the human placental macrophages as well as the trophoblasts permitted the productive ZIKV infection [34]. This *in vitro* evidence is further strengthened by the ex-vivo findings of ZIKV detection in chorionic villi. It demonstrated that ZIKV can cause the placental infection, most probably through the maternal blood. Some other routes responsible for fetal ZIKV infection in early pregnancy may include leakage through the trophoblastic plugs or diffusion of ZIKV into the amniotic and yolk sacs as they are formed. The presence of ZIKV in semen has also been identified which might make the early embryo susceptible to ZIKV, thus elucidating the strong support of sexual transmission of ZIKV [35], though it cannot be declared as the main route of infection in embryo.

If the placenta is infected through ZIKV then placental functions could be altered leading to the growth restriction of fetus as well as placental insufficiency, which in turn is described for ZIKV infections associated with microcephaly [7,8,25]. The anomalous autophagy of placenta could have negative effects on the placental functions. Autophagy in the placental cells precludes the viral replication [36]. The situation is different for in skin fibroblasts where ZIKV cause the stimulation of autophagy, which in turn is linked with increased ZIKV loads [28].

Management of Pregnant Women

Interpretation of the results of laboratory tests used for diagnosing or confirming ZIKV infection is quite intricate. Facilities for testing ZIKV are presently accessible at the CDC and various state health departments in the USA. When the symptoms of ZIKV infection began to appear during the first week, the diagnosis can be confirmed through RT-PCR on serum [37]. The RNA of ZIKV can be detected in urine two weeks after the onset of symptoms, thus now it is recommended by CDC that ZIKV RT-PCR must be performed on urine sample collected <14 days after onset of symptoms in patients who are suspected to be the sufferers of ZIKV infection [38]. If the samples are collected from the patients in less than 7 days the onset of symptoms than serum testing must be performed along with urine testing to confirm the diagnosis [39]. ZIKV specific IgM antibodies can be detected after 4 days of onset of illness and these antibodies last for about 2 to 12 weeks. One must remain vigilant while interpreting the results on the basis of IgM antibodies because they may cross react with other Flaviviruses and thus may give false positive results [40]. ZIKV infection is a matter of serious concern so all the healthcare providers must report the suspected Zika cases on urgent footing to their local health department. Guidelines pertaining to the collection and submission of fetal tissues and body fluids for testing ZIKV infection are available at the CDC website (http://www.cdc.gov/zika/hc-providers/testing-for-zikavirus.html).

Initial Evaluation in Areas without Active Mosquito-borne Transmission

Assessment of the pregnant patients for potential exposure must be carried out by the healthcare providers on every visit. This must include the evaluation of the travel history of the patients and their sexual partners, and to look into the symptoms consistent with ZIKV infection.

The pregnant women, whose symptoms are consistent with ZIKV infection either during or within two weeks of travelling, must be tested for ZIKV infection through RT-PCR and IgM serological testing. The pregnant women who are asymptomatic but have a travel history must be tested for ZIKV antibody IgM 2 to 12 weeks after exposure [41]. In this situation a negative result does not definitely rule out ZIKV infection, but it would be an indication that a recent ZIKV infection did not occur and may preclude the need for serial ultrasonography. Fetal ultrasonography with a particular focus on intracranial calcifications or microcephaly must be carried out within 3 to 4 weeks after the exposure to ZIKV or symptoms development [40]. The algorithm which may act as a supporting tool for diagnosing a pregnant woman with possible ZIKV exposure, who is not a resident of the area with active ZIKV transmission can be found at http://www.cdc.gov/mmwr/volumes/65/wr/mm6512e2. htm#F1_down [40].

Initial Evaluation in Areas with Active Mosquito-borne Transmission

Women who are the residents of areas in which there is active mosquito-borne transmission of ZIKV must be monitored for symptoms on every visit to the healthcare provider. In case the symptoms appear in these women then diagnosis should be carried out through serum RT-PCR and IgM detection. However, if the women remain asymptomatic, then current strategy involves obtaining IgM at her first prenatal visit with a subsequent serological test in the late second trimester. Moreover, asymptomatic women must go for an ultrasound at 18–20 weeks of pregnancy to determine any abnormalities in the fetus [40,41].

Further Testing

If the results of serological and PCR tests of the pregnant patient comes out to be positive for ZIKV infection then successive ultrasounds must be done every 3–4 weeks [37]. The history of ZIKV infection in uterus and the time from the exposure to the appearance of clinical symptoms is still anonymous. Due to this reason, supplementary ultrasound examinations must be carried out even in the case of asymptomatic exposure, even though the time interval at which it should occur is not clear [41]. If certain anatomic abnormalities such as like microcephaly or intracranial calcifications are seen through ultrasound then amniocentesis for determining ZIKV infection may also be considered.

Conclusions

The current outspread of ZIKV and its deleterious effects on pregnant women or those planning to conceive is an alarming situation and thus is a matter of global concern. ZIKV pose a global threat to pregnant women and strong evidences have proved the association of ZIKV with microcephaly and multiple other cerebral abnormalities. The congenital complications associated with ZIKV and its potential long-term negative consequences demands a strong and timely global public health and research response to alleviate and preclude its negative impact on health, social and economic sector, and to advance the development of vaccines, therapeutics, and better diagnostics.

Further research must be done for identifying and determining the potential transmission routes and to elucidate the effect of ZIKV infection in pregnant and non-pregnant women. Since, the healthcare providers are a main source of informing the public so they must keep an eye on the recommendations of CDC and WHO in this regard. Focused discussion must be carried out between the clinicians and pregnant women who have recently traveled in the areas with ZIKV outbreaks or those planning such travel. Dissemination of accurate information to the public may aid in the prevention and future spread of ZIKV infection and thus its negative consequences on health can be minimized.

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