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Zika Virus Infection during Pregnancy; Maternofetal Risk Assessment, Transmission, Complications, and Management: A Review of the Literature

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Abstract

Zika virus (ZIKV) is a vector transmitted, arthropod-borne viral disease. People around the globe, especially pregnant females are more prone to it. Various neurological and ophthalmological congenital abnormalities make it an epidemic in Central and South Americas as well as Pacific regions. Therefore, the present review, by considering available literature, aims to evaluate the link between ZIKV infection and maternofetal damage. We used a number of electronic databases (PubMed, Google Scholar, Scopus, and Science Direct) to identify the relevant published studies. Of 200 articles found initially, 144 were selected for additional review. Subsequently, 69 articles were finally selected. ZIKV is a life threatening fetal infection. It can easily encounter developing fetus through maternal circulation. Large numbers of fetal mortalities and adult morbidities have been reported till date. WHO has reported cases of ZIKV associated fetus neural damage from 29 countries in its recent report of 2017. Though the exact mechanism of maternofetal ZIKV transmission is still inconspicuous, it is evident that in the 1st trimester the risk of developing microcephaly is at its peak, thus, maximizing the risk of various congenital anomalies. The lack of proper therapeutic and preventive measurements makes it more deleterious.

Keywords: Zika Virus, Pregnancy, Microcephaly, Transmission, Management

1. Context

The prenatal period or pregnancy is the most thrilling and vulnerable experience for both the mother and the fetus (1). Even though an intrauterine environment is safest for the fetus, it is susceptible for the infectious agents (2). These infectious agents might be teratogenic or result in congenital abnormalities with a higher rate of maternofetal morbidity (3). Today, the emergence of pandemics e.g., Ebola virus, Nipah virus, influenza, and Zika virus (ZIKV) has threaten the global village and it may be the result of Anthropocene epoch (4). It means the increasing influence of man on earth's environment in the form of urbanization, deforestation, and change in geographical distribution, which dramatically effects all forms of life on earth including, flora; fauna, and even infectious agents (5).

Zika, a Flavivirus from the family Flaviviridae (6), has a single stranded RNA (7). This arthropod-borne virus (arbovirus) (8) is transmitted through the Aedes mosquito species, namely *Ae. africanus*, *Ae. apicoargenteus*, *Ae. luteocephalus*, *Ae. aegypti*, *Ae. vitattus*, and *Ae. furcifer* (9). Besides vector transmission, the non-vector transmission occurs between the mother and fetus; during transplantation surgeries and hospital stay (nosocomial) (10), and from other substances of human origin (SoHO) (11). At first the ZIKV infection did not get much consideration as the mild fever, arthralgia, and rash developed in 20% of the cases; while, 80% of the cases were asymptomatic (12).

According to an estimation, ZIKV infected 3 - 4 million Americans in 2016 and 440000 – 1300000 Brazilians in 2015 (13). About 2.17 billion people are residents of those areas that are favorable for its dispersal (14). Since 2015, there has been a dramatic spread of ZIKV in 66 countries, whereas drastic outbreaks were also reported in 44 previously known ZIKV-negative countries (15).

The major threat of today's world is that the fetus of symptomatic ZIKV infected pregnant female can become the victim of this perilous virus. Usually, the chances of microcephaly is only 7 per 10000 live births (16), however, ZIKV increases this estimation up to several folds. Currently, World Health Organization (WHO), Centers for Dis-

ease Control and Prevention (CDC), European Centre for Disease Prevention and Control (ECDC), American Society of Reproductive Medicine (ASRM), and the International Planned Parenthood Federation (IPPF), etc., are the leading organizations that deals with the drastic effects of ZIKV on maternofetal health.

Thus, it is crucial for the gynecologists, obstetricians, and pediatricians to be cautious about the newly emerging data related to ZIKV for the appropriate maternofetal assessment in all the three trimesters of gestation period. This review aims to formulate the current literature regarding ZIKV and its hazardous effects on maternofetal health with a special emphasis on risk assessment, virus transmission, associated complications, and possible management.

2. Evidence Acquisition

2.1. Search Strategy

We searched PubMed, Google Scholar, Scopus and Science Direct with the following keywords: "Zika Virus", "Pregnancy", "Transmission", "Complications", "Diagnosis" and "Management" in several combinations in BOOLEAN searches. The search covered the period from 2007 to May 2017. We also explored the databases of leading organizations, such as the Centers for Disease Control and Prevention (CDC), WHO, European Center for Disease Prevention and Control and Pan American Health Organization.

2.2. Data Selection

We found 60 studies from PubMed, 86 from Google scholar, and 54 from other database such as Scopus and Science Direct. All such data constitutes qualitative and quantitative studies, peer reviews, meta-analysis, guidelines, factsheets, commentaries, etc. Of these 200 initially found articles, 56 were ambiguous studies and fall under the exclusion criteria. After the review of 144 remaining studies, 75 repeated studies were also excluded. Finally, 69 studies met our inclusion criteria and were selected for a final analysis. Further publications were recognized by a manual search of the bibliography and reference section of related papers.

3. Results and Discussions

3.1. Maternofetal risk assessment

The penetration of ZIKV in previously known virus free regions has threatened the pregnant females and their newborns. According to the WHO report in 2017 on the ZIKV situation (17), 29 countries have reported ZIKV associated microcephaly and other neurological disorders in newborns (Table 1). Similarly, a report (18) demonstrated the link between ZIKV positive pregnancy and congenital abnormalities (microcephaly and other neurological anomalies) by using Shephard's criteria and Bradford Hill criteria. Also, in a study (19), the risk of microcephaly was found to be 1% in first trimester, thus, it was named as a "period of risk". Likewise, a report (20) of CDC, based on the ad hoc microcephaly surveillance system, has identified the temporal and geospatial evidences that the ZIKV causing febrile rash illness in the 1st trimester has a strong association with microcephaly. In a postmaturm study (21) of fetal brain using RT-PCR, the high viral load was found in the placenta and umblical cord while a comparative lower load was found in the muscle, liver, lungs, and spleen.

3.2. Maternal Transmission

When an Aedes mosquito bites a human being, Flavivirus deposits in the epidermal and dermal layer of the skin. The virus then interacts with the cell surface receptor and non-specific attachment factor (e.g., heparin sulphate) through envelop protein. The C-type lecithin receptors neutralize the antibody and silence the RNA. In this way, ZIKV gain entry in the host and starts to replicate in cellular cytoplasm (22).

3.3. Fetal Transmission

There is an alarming situation due to the fact that worldwide, in a number of reported cases, maternofetal ZIKV transmission is causing congenital abnormalities related to (a) neurology such as microcephaly (23, 24); neurological calcification and growth retardation, (b) ophthalmology like retinal damage, optic nerve damage, and (c) fetal mortality (25) along with miscarriages and still births (26). The vertical transmission of ZIKV can occur either through the placenta or during labor and delivery (27). The exact mechanism by which this transmission occurs is still unknown. However, recent studies (28, 29) have tried to solve the dilemma by generating two hypotheses.

According to hypothesis I "direct transmission hypothesis", ZIKV is transmitted through the uterus secretion, trophoblastic plugs (30), and semen (31). Similarly, periconceptional ZIKV load can gain entry in amniotic fluid or yolk sac (29). Due to neurotropic properties, ZIKV can access and damage the developing brain of the fetus (29).

Hypothesis II is referred to as "placenta mediated transmission". ZIKV gains entry in cells via numerous surface receptors such as dendritic cell-Specific Intercellular adhesion molecule-3-Grabbing non-integrin (DC-SIGN), AXL, tyrosine-protein kinase receptor (Tyro3), and T-cell immunoglobulin and mucin domain 1 (TIM-1) (32, 33). The

Table 1. Zika Virus Associated Microcephaly Cases Reported Till 2017

Country	No. of Cases Reported	Total No. of Cases Reported Per Continent
South America		2849
Argentina	2	
Bolivia	14	
Brazil	2366	
Colombia	86	
French Guiana	16	
Suriname	2	
Paraguay	2	
Trinidad and Tobago	1	
North America		126
Canada	2	
Dominican Republic	22	
Grenada	1	
Guadeloupe	13	
Guatemala	15	
Haiti	1	
Martinique	19	
Puerto Rico	11	
USA	42	
Central America		14
Costa Rica	2	
El Salvador	4	
Honduras	1	
Nicaragua	2	
Panama	5	
Europe		3
Slovenia	1	
Spain	2	
Asia		3
Thailand	2	
Viet Nam	1	
Oceania		9
French Polynesia	8	
Marshall Islands	1	
Northwest Africa		9
Cape Verde	9	

Table 2. Transmission

Transmission	Description
1. Maternal transmission	
i	Vector mediated
ii	Non-vector mediated
2. Fetal transmission	
Hypothesis 1	Direct transmission
Hypothesis 2	Placenta mediated transmission

major sites for expression of AXL is developing cerebral cortex, astrocytes, radial glial cells, microglia, and endothelial cells; however, Tyro3 and DC-SIGN expression is either relatively low or completely absent (34). After gaining access to the cell, ZIKV RNA starts replication. Afterwards, it shows antiviral response by up regulating of TLR3 mRNA, retinoic acid-inducible gene-I (RIG-I) and melanoma differentiation-associated gene 5 (MDA-5) mRNA. The silencing of TLR3 results in up regulation of viral replication, however, type I interferon (IFN) response remains unaffected. Thus, with treatment of IFN-α, IFN-β, or IFN-γ there will be the dose-dependent inhibition of viral replication (32). IFN-λ is responsible for protection of the placenta; however, the placental transmission of ZIKV is still possible (35).

Hypothesis II is further demonstrated by a study (36) that concluded some interesting facts about ZIKV by using 3D organ cultures. It was concluded that (i) at an early pregnancy stage, ZIKV actively replicates in both deciduous and chronic-villi tissues, (ii) at the mid stage of pregnancy, ZIKV replicates more rapidly in deciduous tissues than chronic-villi tissues, (iii) ZIKV up regulated apoptosis in the placenta. If the ZIKV infected pregnancy is not a miscarriage, then the virus, before 10 weeks of gestation, starts interfering molecular synthesis and disrupting placenta signals during neurogenesis. The other assumptions for neurogenesis inhibition are; placental inflammatory response and gene mutation.

The ZIKV infected placenta can't function normally. Thus, insufficient placenta leads to growth retardation and microcephaly. Surprisingly, the result of autophagy in both ZIKV infected placental cell and fibroblast is different. As autophagy in the placental cells prevents the viral replication (37) while in skin fibroblasts ZIKV itself stimulates autophagy, which in turn causes increase ZIKV loads (32).

3.4. Complications during Pregnancy

3.4.1. Neurological Problems

Microcephaly is the major abnormality related to the ZIKV infection in pregnancy. Microcephaly is a condition

in which the head circumference of a newborn is less than the estimated range. Microcephaly can be characterized on the basis of cause, (a) primary (genetic causes) and (b) secondary (non-genetic causes) (12).

There is a strong association between ZIKV and microcephaly (12, 18, 38), which was been declared as public health emergency of international concern (PHEIC) by WHO (39). In a study (40), postmortem examinations of 7 neonates were performed. Their mothers most likely came in contact to ZIKV during their 1st trimester. The longevity of neonates was 30 minutes to 6 days after birth. All cephalic examinations revealed a decrease in brain weight and ventriculomegaly. While 2 neonates suffered from cerebellar hypoplasia, 1 from pachygyria, 1 from arthrogryposis, and in 1 morphologic microcephalus changes occurred, the head circumference was still within range.

Similarly, a study (41) demonstrated a case in which a 25 years old woman developed symptoms of the ZIKV infection at 13 weeks of gestation. Ultrasonography at the 14th and 20th week was normal, however, at the 29th week fetal anomalies were seen and at 32nd week intrauterine growth retardation was confirmed and then pregnancy was terminated on request of the mother. On the autopsy, the body weight, length, and head circumference was found to be lower than the reference range along with signs of calcification in cortex, villi, and decidua.

Hence, it is confirmed now that congenital ZIKV syndrome during pregnancy can be the reason of brainstem and cerebellar hypoplasia, gross calcification of the brain parenchymal layer, ventriculomegaly, delayed myelination, and lissencephaly (lack of normal convolutions in cerebral cortex) (42, 43). Contrary to other maternofetal neuro degenerative viruses, ZIKV is the most fatal one. Thus, a surveillance system that can identify the ZIKV infected infant and asymptomatic ZIKV positive pregnancy is needed (44). Microcephaly can also be a result of genetic predisposition (45) and excessive prenatal alcohol intake (46).

The presence of ZIKV in the fetal brain can cause microcephaly (41, 47) because this virus impairs neuronal division and differentiation or neurogenesis in the fetus. Therefore, it results in weakly growing neural progenitor stem cells, which in turns cause deregulation of cell cycle deregulation with caspase-3-mediated apoptosis (48).

3.4.2. Guillain-Barre Syndrome

Guillain-Barre syndrome (GBS) is an immune-mediated complication associated with the ZIKV infection. GBS affects the peripheral nervous system (PNS). It may result in peripheral neuropathy, which leads to muscle paralysis and death (49). Flavivirus, other than ZIKV, may also be the causative agents for GBS (50). A clear association between ZIKV infection and GBS has now been established in French Polynesia (51) and other regions where ZIKV morbidity rate is high (52).

3.4.3. Vision Impairment and Other Anomalies

A ZIKV infected infant is at a higher risk of developing microcephaly along with visual defects like focal macular pigment mottling, chorioretinal atrophy with a predilection for the macular area, and congenital glaucoma (53). The possible mechanism for the development of blindness in newborns is the expression of AXL in the neural retina (34, 54). Therefore, a cross-sectional study (55) was conducted on 32 ZIKV infected infants. On examination, it was revealed that overall 26% of infants had no eye contact, 52% couldn't make social smile, while retinal impairment was found in 28%, and impaired optic nerve was in 17%, with optic nerve hypoplasia in 8%. Therefore, ZIKV can damage internal and external layers of retina and choroid (56). A cross-sectional study (57) in Brazil was conducted on 40 infants. It was revealed that though all mothers had normal ocular functions, the infants developed fundus, optic nerve, and macular abnormalities with microcephaly. Likewise, the ZIKV infection is also associated with hearing impairment, however, this anomaly is rare (16).

3.5. Management Approaches

3.5.1. Diagnostic Strategies

The interpretation and confirmation of ZIKV lab findings is difficult. Lab test facilities are available and accessible in many states of US healthcare settings and CDC. Reverse transcription polymerase chain reactions (RT-PCR) test, immunoglobulin (Ig) test, ultrasound and sonography are the usually adopted diagnostic strategies for the ZIKV infection (Table 3).

CDC recommends RT-PCR analysis of suspected individuals (21), however, IgM antibodies test can give false positive results due to the fact that IgM can cross react with other strains of Flaviviridae members (18). Hence, healthcare provider must be vigilant enough to report the ZIKV infection case to a local health department.

On every visit, the healthcare giver must evaluate the travel history of the patient and any symptom of the ZIKV infection in case the pregnant female traveled to ZIKV infected prevailing areas and was later tested for IgM. However, the tests resulted into ZIKV negative then as per ASRM guidelines it does not rule out the risk of ZIKV infection (18, 61). Similarly, females who are inhabitant of high ZIKV infection prevailing areas must be monitored with great care. If the woman is suspected for the ZIKV infection on the basis of symptoms, then required diagnostic tests must be carried out. However, in the absence of symptoms, the diagnostic strategy must involve IgM test at her

Table 3. Diagnostic Strategies for Zika Virus Infection

Diagnostic test	Time of sample collection	Reference
Serum RT-PCR	ZIKV symptom arise in 1st week of gestation	(58)
Urine RT-PCR	Two weeks after onset of symptoms	(21)
Serum and urine RT-PCR	Less than a week after onset of symptoms	(59)
ZIKV-IgM	4 days after onset of symptoms; asymptomatic woman after 2-12 weeks of exposure or during first visit to healthcare setting or having travel history to suspected area	(18, 60)
Fetal Ultrasonography	3-4 week after exposure or onset of symptoms	(18)
Ultrasound	Asymptomatic ZIKV positive 8-12 weeks pregnancy	(60)

first prenatal visit following serological test in the late 2nd trimester. Additionally, an ultrasound for fetal anomalies must be carried out in asymptomatic ZIKV infected women at 18 - 20 weeks of pregnancy (18, 60, 61). If the female is positive for serological and RT-PCR test then an ultrasound must be carried out at every 3-4 weeks (58). Supplemental ultrasound is mandatory for asymptomatic exposure, because the time from exposure of ZIKV to the appearance of clinical symptoms is not obvious till date. (60). In case if anatomic abnormalities are confirmed through ultrasound then amniocentesis for determining ZIKV infection must be performed.

3.5.2. Medications

There is no specific treatment like any vaccine or antiviral agent available for ZIKV positive pregnant woman. As per WHO guidelines (62) only symptomatic treatment can be given, e.g. non-steroidal anti-inflammatory drugs (NSAIDS) or aspirin can only be used if the patient is negative for dengue virus strain tests. Acetaminophen can be used to relief headache in the dose at which it treats a fever. While itchy rashes can be treated with chlorpheniramine (1st line treatment) and emollient lotions like calamine lotion, it has no fetal safety evidence.

Trials for developing vaccines and therapeutic agents are going on by various researchers around the globe (63). In a study (64), Emricasan inhibited caspase-3 activity and protected neural progenitor cells while food and drug administration (FDA) approved Niclosamide for anthelmintic treatment also showed inhibition of ZIKV replication. Similarly, in a study (65), hematological derived antibody from ZIKV infected patients had protected the fetuses of mice from ZIKV.

3.5.3. Preventive Measures

As there is no vaccine available for preventing ZIKV, therefore, WHO (62) and CDC (66) recommends pregnant females to protect themselves every time from mosquitoes by using mosquito repellents and larvicides, covering skin, eliminating standing pools of water, and by using screens on doors and windows.

3.6. Limitations

Our study is limited to epidemiology, prevalence, and complications related to maternofetal ZIKV infection. Thus, the major limitation of the present review is that the authors were unable to demonstrate the mechanisms of all listed complications associated with the ZIKV infection due to insufficiency of available data.

4. Conclusions

The ZIKV infection is the most prevailing syndrome in the global village. Its mortality rate is comparatively low in adults as compared to fetus, neonates, and infants. There are several factors that contribute in its inappropriate diagnosis, (a) time between exposure and development of first clinical symptom is poorly understood, (b) false positive or negative results of diagnostic tests, and (c) patient remain asymptomatic for long time. Similarly, lack of therapeutic and preventive measures make it more dreadful. The present review concludes that there is a global coverage of ZIKV infection and all the above-mentioned preventive strategies are not long-lasting, especially for maternofetal health hazards. Thus, it is recommended that strong preventive measures such as gene drive (gene is inserted in mosquito that will prevent incubation of vector) must be adopted.

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