Review Article

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# Zika Virus and Pregnancy, What is Must to Know for an Obstetrician

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**Abstract**

The rapid spread of the Zika Virus (ZIKAV) infection, had become global threat to humanity and of the concern for all over the world. Data regarding ZIKAV in pregnancy are very less, mainly from case reports that show of association between maternal ZIKAV infection, fetal microcephaly, and intracranial calcifications. Although the presently the exposure of ZIKAV is limited to western countries. But with the increasing International tourism and growing medical tourism, the possibility of future exposure from endemic to other areas, making this disease pandemic cannot be denied. The objective of this review is to present the current literature regarding ZIKAV and its effect on pregnancy and possible management of pregnant patient with potential exposure to ZIKAV.

**Keywords:** Zika Virus; Pregnancy; Diagnosis; Complications; Management.

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## Introduction

The latest Zika virus (ZIKAV) outbreak occurred throughout South and Central America, Caribbean and South Pacific and considered as epidemic [1,2]. Recently the World Health Organization (WHO) declared it a public health emergency of international concern, after getting some association between microcephaly cases and neurological disorders [3]. This single-stranded RNA arbovirus of *Flavivirus* genus was first identified in the Zika forest of Uganda, Africa in 1947 and named accordingly [4].

In May 2015, it was first reported from the Brazil [5]. and as of March 21, 2016, mosquito-borne transmission of ZIKAV had been reported in 32 countries and territories of America. Most persons infected with ZIKAV have a mild illness or are asymptomatic. However a link between ZIKAV infection during pregnancy and adverse pregnancy and birth outcomes had been described [6]. Most cases of ZIKAV infection are self-limiting and without sequelae, but there have been cases of Guillain–Barré disease post-infection [7].

## Zika Virus

ZIKAV is a single-stranded RNA virus of genus Flavivirus of the family Flaviviridae, a type of arbovirus believed to be transmitted by the aedes mosquito to humans. Mostly the zika virus infection is asymptomatic (80%). It usually causes a benign illness characterized by fever, headache, malaise, arthralgia, maculopapular rash, and conjunctivitis, which is very similar to dengue [8-11]. ZIKAV can cross the placenta. It has been detected using polymerase chain reaction (PCR) analysis of amniotic fluid of pregnancies affected with fetal structural anomaly [12]. ZIKAV has been isolated postmortem from the brain of a fetus with microcephaly [13]. The available data shows some evidence of association between maternal ZIKAV infection and fetal microcephaly, though not yet fully established [14].

### Transmission of ZIKAV

ZIKAV has been transmitted mainly by the bite of female *Aedes* mosquitoes [15]. El Niño and hot winters and summers are some favourable environmental factors for these vectors, which help in spreading this virus. The stored water is a ideal environment for breeding of *Aedes* mosquitoes [16]. But the infection can be spread through sexual intercourse [17, blood transfusion [18], and perinatal transmission [19].

### Clinical Features of ZIKA Virus Infection

The exact incubation period of ZIKAV infection is not known but most of the cases occur 3-12 days after the mosquito bites [20]. Most of the infected people are asymptomatic. But 20% may presents with mild fever, malaise, headache, skin rashes, nonpurulent conjunctivitis, muscle pain and small joints of hands and feet pain, or back pain lasting for 2-7 days. Other possible clinical features include anorexia, retro-orbital pain, edema, diarrhea, constipation, abdominal pain, dizziness, and pruritus. Due to these features it is difficult to differentiate with other arboviral diseases such as dengue and chikungunya [21]. Patients requires hospitalization is uncommon and mortality is rare [22]. Guillain-Barré syndrome has been reported in patients following suspected ZIKAV infection. Pregnant women can have ZIKAV infection in any trimester [23,24]. The incidence of ZIKAV infection in pregnant women is not known till now. The evidence available from existing data does not suggest that pregnant women are more susceptible to ZIKAV infection and it may develop more complication during pregnancy.

### Diagnosis of ZIKA Virus

At present, no commercial test available to diagnose ZIKAV infection. This infection can be diagnosed by two methods. First is to detect Viral RNA by reverse transcription-polymerase chain reaction (RT-PCR), and secondly, antiviral antibodies can be detected by either immunoglobulin M (IgM) enzyme-linked immunosorbent assay (ELISA) or plaque reduction neutralization test (PRNT). IgM antibody appears in the blood at the end of first week of illness. It may appear due to another *Flavivirus* infection due to cross reaction. This cross-reaction effect can be confirmed by using plaque reduction neutralization test (PRNT) [25]. Centers for Disease Control (CDC) recommends performing both RT-PCR and serological test to diagnose congenital ZIKAV infection. RT-PCR test is done on the serum from the umbilical cord blood or the infant within 2 days of birth. It can also be done on cerebrospinal fluid , placental tissue, and amniotic fluid. The period of viremia is very short and just about 3-5 days after onset of illness. RT-PCR is effective during the early stages of acute disease in multiple studies, with detection of the viral genome in serum, urine, saliva, and semen [17,26,27]. RT-PCR testing is thought to remain positive in serum 4 to 7 days after onset of acute illness. RNA can be isolated from urine even up to 3 weeks after the onset of acute illness [28]. A negative result does not exclude the disease.

Serologic testing is an option after the acute phase. ZIKAV IgM is detectable in the serum by at least 4 days after symptom onset, but may not become positive until 2 weeks. Serologic testing, however, has significant limitations as there is considerable cross-reaction between ZIKAV and other viruses, such as dengue and chikungunya. The revised guidelines recommendations are that a PRNT titer higher than ten should be interpreted as evidence of infection with that specific flavivirus infection when the PRNT to the other flavivirus or flaviviruses tested is lower than ten. If PRNT titer lower than ten to a specific flavivirus will be interpreted as no evidence of infection with that virus and if PRNTs are positive (ie, ten or higher) to multiple flaviviruses, this will be interpreted as evidence of recent infection with a flavivirus [29]. It is suggested that like other Flaviviruses ZIKAV IgM persists in serum up to six months [30]. The updated guidance from the CDC recommends that Zika virus rRT-PCR on urine specimens should be done within 14 days and on serum with urine testing within 7 days after illness onset. A positive Zika rRT-PCR result demonstrates current Zika virus infection but a negative rRT-PCR result does not rule out virus infection, and immunoglobulin M antibody testing should be performed.

The only diagnostic test currently authorized by the US Food and Drug Administration (FDA) for Zika virus testing of urine is the CDC Trioplex rRT-PCR assay [31] others infections like dengue, chikungunya, parvovirus, Rubella, measles, *Leptospira*, malaria, rickettsial infection, and Group A *Streptococcus also causes arthritis*. Travelers from ZIKAV-affected areas with positive IgM antibody for dengue but negative IgG antibody for dengue on convalescent sera should be tested for ZIKAV infection [32,33].

### Complications of ZIKA Virus

ZIKAV infection has rapid spread in course and it affects the neurological system. Guillain–Barre syndrome may be associated with ZIKAV infection [34]. In October 2013 approximately 10,000 ZIKAV cases were registered and there were many cases of meningoencephalitis and autoimmune

thrombocytopenia-like complications [35]. Recently, ZIKAV infection in pregnancy was identified to be associated with microcephaly of newborn children. This finding has drawn the attention significantly. One study done in Brazil suggested that first-trimester ZIKAV infection in pregnant women carries more risk of microcephaly [36].

A causal association was proposed between microcephaly and ZIKAV infection due to following: (1) increased incidence rate of microcephaly coinciding with the ZIKAV outbreak and (2) two case report of pregnant women with symptoms of ZIKAV infection, fetal microcephaly, and amniotic fluid positive for ZIKAV by RT-PCR methods [37]. Later on, Brazil a newborn was found to have multiple anomalies and microcephaly had neonatal death shortly after birth, and ZIKAV RNA was issolated [38]. This strengthened the association between ZIKAV infection and microcephaly further [39,40].

In ZIKAV infection, there is also chance of ophthalmological involvement. In Brazil infants were found to have macular pigment mottling and loss of foveal reflex. one case having well-defined macular atrophy and in other Chorioretinal scarring with other ocular abnormalities [41,42]. Recently ZIKAV has been suggested to have neurotropic character after detected by the RT-PCR method during performing autopsy [43].

**Management of ZIKA Virus Infection**

There is no particular treatment for ZIKAV infection. Management is only supportive and symptomatic that involves rest, adequate hydration, and appropriate nutrition. Acetaminophen may be used for relieving fever. Nonsteroidal anti-inflammatory drugs and aspirin should be used cautiously to avoid hemorrhagic complications after dengue infection. Till date, no vaccine is available [21,22]. In response to the WHO statements and international concerns regarding the ZIKV outbreak, International Society for Ultrasound in Obstetrics and Gynaecology had given the following guidance for ultrasound during pregnancy.

**Ultrasound Assessment of ZIKA Virus Infected Pregnant**

In females with ZIKAV exposure and symptoms, positive Flavivirus serology or proven ZIKAV infection, or in those with exposure and/or symptoms but who have not had positive serology results, referral for detailed ultrasound assessment is appropriate as follows.

1. Accurate assessment of gestational age: Accurate estimation of gestational age (GA) is very important to monitor appropriate fetal growth, especially head circumference (HC) growth. Before 14 weeks fetal crown–rump length (CRL) measurement is most accurate method for GA assessment. If not available then a careful history should be taken to know the last menstrual period and gestational age and compared with the first reliable ultrasound. The use of HC for gestational age estimation, especially in the third trimester, should be avoided.
2. Baseline ultrasound scan: In cases referred < 14 weeks: Measurement of fetal CRL, biparietal diameter (BPD) and HC and assessment of fetal anatomy [44]. In cases referred ≥ 14 weeks: Fetal biometry, including BPD, HC, abdominal circumference (AC) and femur length (FL) and assessment of fetal anatomy is done [44,45]. Measurement of the lateral ventricles and transcerebellar diameter is taken [46]. In addition, assessment for intracerebral findings is done to rule out other congenital infections, including presence of calcifications, periventricular or intraventricular echogenicities and irregularly shaped lateral ventricles [47].
3. Subsequent ultrasound scans: Ultrasound assessment as described above should be performed every 4–6 weeks. In these cases interval growth is important and helps in making diagnosis and reduce false-positive rates.
4. Deviation from normal: If ultrasound assessment shows a fetal Head circumfertence of 2 SD below the expected mean for gestational age, or fetal brain abnormality like intracranial calcifications or ventriculomegaly are present then referral to a specialist center for detailed assessment, including neuro-sonography of the fetal brain [46]. Most fetuses in which the only finding is a HC of 2 SD below the mean for gestational age usually represents the lower end of the normal population distribution. So these fetuses should have an interval scan in 2–3 weeks [48,49]. In cases in which subsequent scans show a further decline in fetal HC growth, to below–3 SD, or in those with definitive coexistent brain abnormalities, further assessment should be done. Discussion of the advantages and risks of an amniocentesis for ZIKAV, RT-PCR should be done after expert virology advice. The mother should be counseled about indefinitive sensitivity and specificity of this test for detecting congenital infection and chances of the fetus being affected is also unknown. However, if there is fetal brain abnormality on ultrasound and a positive ZIKAV infection on RT-

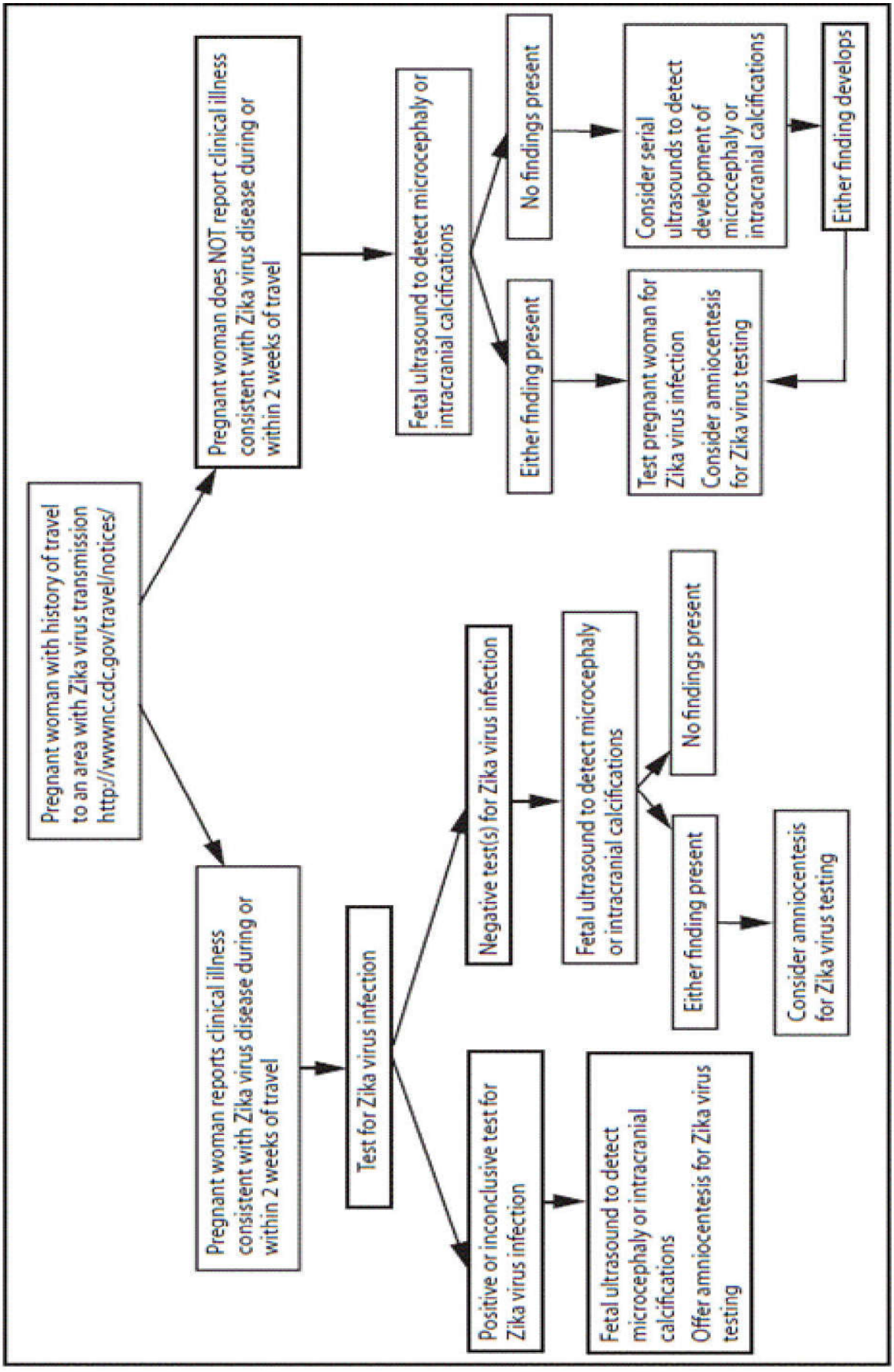


**Fig. 1:** CDC Interim guidance for pregnant women with history of travel to an area with ZIKV transmission

PCR test, the chances of association between the two are high. Fetal brain magnetic resonance imaging can be done if available to detect abnormalities not visible on ultrasound. Pregnancy termination may be discussed depending on local laws, gestational age and severity of brain abnormalities. Uncertainties regarding the condition should be discussed.

5. Postnatal assessment: After birth of infant standardized HC measurements should be undertaken and compared with standards after taking GA at birth and sex [50,51]. The use of a single cut-off regardless of GA is not recommended [52]. Whenever laboratory confirms the maternal or fetal ZIKAV infection placental histopathological examination and ZIKAV testing of placental tissue and umbilical cord blood should be done [53]. Babies with congenital ZIKAV infection should be followed up into childhood for signs of any adverse effects.

**Prevention of ZIKA Virus Infection**

The CDC guidelines for pregnant ladies travelling to an area with ZIKAV transmission and recommendations for screening, testing, and management after returning from travel. Pregnant females who travelled to an area with ZIKAV transmission and having two or more symptoms of ZIKAV disease (acute onset of fever, maculopapular rash, arthralgia, or conjunctivitis) during or within 2 weeks of travel, or who have fetal microcephaly or intracranial calcifications on ultrasound, should be tested for ZIKAV infection.

Pregnant females with laboratory evidence of ZIKAV infection should have serial ultrasound examination for fetal growth and anatomy These infected pregnant females should be managed in maternal-fetal medicine or by infectious disease specialist with expertise in pregnancy management.

CDC recommendations for Considering Travel to an Area of Zika Virus Transmission: All pregnant females should postpone travel to areas where ZIKAV transmission is ongoing [54]. If anyhow one has to travel to such area then advised to strictly avoid mosquito bites and to ensure protection for entire day [55,56]. Mosquito prevention strategies include wearing full length clothes to cover hands and feet, using insect repellents, using permethrin-treated clothing and gear, and staying in screened-in or air-conditioned rooms.

CDC recommendations for History of Travel to an Area of Zika Virus Transmission: All pregnant females should give history of travel to such area during their antenatal visit. Pregnant females with history of travel to an area with ZIKAV transmission should be evaluated for ZIKAV infection and tested in accordance with CDC Interim guidance (Figure1).

Because of the similar clinical presentation patients with symptoms should also be evaluated for dengue and chikungunya virus infection, in accordance with existing guidelines [58,59]. Reverse transcription-polymerase chain reaction (RT-PCR) testing for symptomatic patients is done with onset of symptoms within the previous week.

Immunoglobulin M (IgM) and neutralizing antibody testing should be performed on specimens collected ≤ 4 days after onset of symptoms. Testing of asymptomatic pregnant women is not recommended in the absence of fetal microcephaly or intracranial calcifications. Zika virus RT-PCR testing can be performed on amniotic fluid [24]. To reduce sexual transmission, men who live in or planned to visit a ZIKAV-infected area should use barrier during sex with their pregnant partners.

Ongoing Researches on Zika Virus: The National Institute of Allergy and Infectious Diseases is trying to find out antiviral drugs against ZIKAV. They are also working on Zika vaccine. A live attenuated ZIKAV vaccine, and a genetically engineered vesicular stomatitis virus vaccine is being researched on.

**Conclusion**

ZIKAV infection, a new public health emergency, which needs to be addressed urgently. There are several unknown facts about the pathogenesis, transmission, complications, and treatment of ZIKAV till date. Majority of the cases are asymptomatic. Affected patients should be kept under close observation. In 2016-17, the vaccine of Zika is expected to arrive. In absence of any definitive treatment and vaccine, prevention of the disease is the best measure.

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