Available online on 15.03.2016 at http://jddtonline.info
Journal of Drug Delivery and Therapeutics
An International Peer Reviewed Journal
Open access to Pharmaceutical and Medical research

REVIEW ARTICLE

A SHORT COMPILATION ON ZIKA VIRUS TRANSMISSION AND ITS COMPLICATION DURING PREGNANCY

Parajuli Rishi Ram*[1], Dahal Prawan[2], Pokhrel Priyanka[1], Lamichane Shreekrishna[3], Shrestha Saroj[1], Timilsina Purushottam[1]

[1]Production Pharmacist, Time Pharmaceutical Pvt. Ltd. Nepal

[2]Sr. Technical Manager, Time Pharmaceutical Pvt. Ltd. Nepal

[3]Sr. Production Pharmacist, Time Pharmaceutical Pvt. Ltd. Nepal

*Corresponding Authors Email: Positive.rishiram@gmail.com.

Received 22 Jan 2016; Review Completed 20 Feb 2016; Accepted 21 Feb 2016, Available online 15 march 2016

ABSTRACT

Zika virus, a mosquito borne flavivirus transmitted primarily by *Aedes aegypti* mosquitoes is a pathogen affecting humans. These vectors also transmit dengue and *chikungunya* virus and are found throughout much of the world, including parts of the United States. An estimated 80% of persons infected with Zika virus are asymptomatic. Microcephaly is the greater risk for the infant born from the Zika Virus infected pregnant mother. This virus also causes neurological syndromes. Zika virus disease can often be diagnosed by performing reverse transcriptase-polymerase chain reaction (RT-PCR) on serum.

Keywords: Zika Virus, Pregnancy, Microcephaly, *Aedes aegypti* mosquito, Brazil.

INTRODUCTION:

Zika virus is an emerging arthropod borne virus (arbovirus) transmitted by *Aedes* (*Stegomyia*) mosquitoes. The virus belongs to the genus *Flavivirus*, family *Flaviviridae*, and is closely related to other *Flavi* viruses such as dengue, yellow fever and *West Nile* viruses. Zika Virus is an RNA virus containing 10,794 nucleotides encoding 3,419 amino acids. Zika Virus was first isolated from a rhesus monkey in the Zika Forest of Uganda, in 1947.[1] Zika Virus was first isolated from humans in 1968, in Nigeria. Zika Virus has been considered as emergent since 2007.In 2007, an outbreak of Zika Virus occurred on YAP, the western state of Micronesia. There was 49 conformed and 59 probable cases of Zika identified. Roughly 73% of the 11,241 population was infected according to the CDC. In November 2013, an outbreak occurred in the islands of Western Polynesia, including Tahiti. As of January 13, 2014 the number of confirmed Zika cases was 361, while the number of suspected cases was over 35,000. In February 2014, New Caledonia reported 49 cases, 30 were cases imported from French Polynesia, some cases were confirmed to be autochthonous.[2]

Clinical Manifestations:

The first well-documented report of human Zika Virus disease was in 1964 when Simpson described his own occupationally acquired Zika illness at age 28. It began with mild headache. Next day, a maculopapular rash covered his face, neck, trunk, and upper arms, and spread to his palms and soles. Transient fever, malaise, and back pain developed.

By the evening of the second day of illness he was a febrile, the rash was fading, and he felt better. By day three, he felt well and had only the rash, which disappeared over the next 2 days. Zika Virus was isolated from serum collected while he was febrile.[3] In 1973, laboratory-acquired Zika Virus illness in a man was reported with acute onset of fever, headache, and joint pain but no rash which was isolated from serum collected on the first day of symptoms; the man's illness resolved in 1 week. Of the 7 Zika Virus case-patients in Indonesia, all had fever, but they were detected by hospital-based surveillance for febrile illness.[4] Other manifestations included anorexia, diarrhea, constipation, abdominal pain, and dizziness. The outbreak on Yap Island was characterized by rash, conjunctivitis, and

arthralgia. Other less frequent manifestations included myalgia, headache, retroorbital pain, edema, and vomiting.[5]

Symptoms of Zika Virus:

Zika Virus infection in humans symptoms ranges from asymptomatic to influenza like symptoms such as fever, headache, arthralgia, myalgia, malaise, anorexia, rash, asthenia, retro-orbital eye pain, oedema, lymphadenopathy, and diarrhoea. Symptoms usually begin 3-7 days after a person is bitten by an infected mosquito and last several days to a week. The illness is usually mild, and severe, disease requiring hospitalization is uncommon. There is no specific treatment for Zika virus disease. The only treatment option available is the provision of supportive care including rest, fluids, and use of analgesics and antipyretics.[6]

Figure A: lymphadenopathy; B: maculopapular rash; C: periarticular swelling.

Zika virus related deaths:

In 28 November 2015, the Brazil MoH has notified 3 deaths associated with Zika virus infection. The fatal cases are 2 adults and one newborn. The first fatal case is a male adult with no neurological disorders, with history of lupus erythematosus, chronic use of corticosteroid drugs, rheumatoid arthritis, and alcoholism. He was admitted as a suspected dengue case, but the final laboratory diagnosis by RTP-PCR technique was Zika virus infection.It was detected by RT-PCR in the blood and organ samples (brain, liver, spleen, kidney, lung, and heart). Additionally, Zika virus was identified through partial sequencing of the virus. The second fatal case is a 16 year old female from the state of Pará. She had no neurological disorder, and was admitted to the hospital as a suspected dengue case. The onset of her symptoms (headache, nausea, and petechiae) was on 29 September 2015 and she died in late October. Zika virus infection was confirmed by RTp-PCR.[7]

Transmission of Zika virus:

There are 18 countries and territories in the Americas that have confirmed autochthonous circulation of Zika virus in 2015 and 2016: Brazil, Barbados, Colombia, Ecuador, El Salvador, French Guiana, Guatemala, Guyana, Haiti, Honduras, Martinique, Mexico, Panama, Paraguay, Puerto Rico, Saint Martin, Suriname, and Venezuela. [8]

Zika Virus and Microcephaly:

In October 2015, the Brazil International Health Regulations (IHR) notified the detection of an unusual increase in microcephaly cases in public and private healthcare facilities in Pernambuco state, Northeast Brazil. As of epidemiological week of 2016, there were 3,530 microcephaly cases recorded, including 46 deaths, in 20 states and the Federal District. Between 2010 and 2014, an average of 163 (SD 16.9) microcephaly cases was recorded nationwide per year. [9] In January 2016, ophthalmological findings were reported in three children with microcephaly and cerebral calcifications detected by CT scans and presumable intrauterine Zika Virus infection. The three infants had unilateral ocular findings involving the macular region and loss of foveal reflex. In one child well defined macular neuroretinal atrophy was detected.On 13 January 2016, the Brazil Ministry of Health reported the detection of Zika virus genome, through the RT-PCR technique in four cases of congenital malformation in the state of Rio Grande do Norte. The cases correspond to two miscarriages and two full-term newborns (37 and 42 weeks respectively) who died in the first 24 hours of life. Tissue samples from both newborns were also positive for Zika virus by immune histochemistry.[9] This adds to the evidence reported in the Epidemiological Alert of 1 December 2015 with respect to the detection of Zika virus genome through RT-PCR technique in the amniotic fluid of two pregnant women in Paraiba, whose fetus presented with microcephaly according to the ultrasound. [10] Zika Virus transmitted by *Aedes* mosquitoes, was identified in northeast Brazil, an area where dengue virus was also circulating. By September, reports of an increase in the number of infants born with microcephaly in Zika virus-affected areas began to emerge, and Zika virus RNA was identified in the amniotic fluid of two women whose fetuses had been found to have microcephaly by prenatal ultrasound. The Brazil Ministry of Health (MoH) established a task force to investigate the possible association of microcephaly with Zika virus infection during pregnancy and a registry for incident microcephaly cases (head circumference ≥2 SD below the mean for sex and gestational age at birth) and pregnancy outcomes among women suspected to have had Zika virus infection during pregnancy. Among a cohort of 35 infants with microcephaly born during

August–October 2015 in eight of Brazil's 26 states and reported to the registry, the mothers of all 35 had lived in or visited Zika virus-affected areas during pregnancy, 25 (71%) infants had severe microcephaly (head circumference >3 SD below the mean for sex and gestational age), 17 (49%) had at least one neurologic abnormality, and among 27 infants who had neuroimaging studies, all had abnormalities. Tests for other congenital infections were negative. All infants had a lumbar puncture as part of the evaluation and cerebrospinal fluid (CSF) samples were sent to a reference laboratory in Brazil for Zika virus testing; results are not yet available. Further studies are needed to confirm the association of microcephaly with Zika virus infection during pregnancy and to understand any other adverse pregnancy outcomes associated with Zika virus infection.CDC recently tested samples from two pregnancies that ended in miscarriage and from two infants with microcephaly who died shortly after birth. All four cases were from Brazil and were positive for Zika virus infection, indicating that the infants had become infected during pregnancy. Zika virus was present in the brain of the full term infants, and genetic sequence analyses show that the virus in all four cases was the same as the Zika virus strain currently circulating in Brazil. All four mothers reported having experienced a febrile rash illness during their pregnancies.[11]

Zika Virus and neurological syndromes:

During the Zika virus outbreak in French Polynesia,74 patients had presented neurological syndromes or auto-immune syndromes after the manifestation of symptoms consistent with Zika virus infection. Of these, 42 were classified as Guillain-Barré Syndrome (GBS) out of which 24 (57%) were male, and 37 (88%) had signs and symptoms consistent with Zika virus infection.[8] In July 2015, Brazil reported the detection of patients with neurological syndromes who had recent history of Zika virus infection in the state of Bahia. There were 76 patients with neurological syndromes identified, of which 42 (55%) were confirmed as GBS. Among the confirmed GBS, 26 (62%) had a history of symptoms consistent with Zika virus infection. In addition, on 25 November 2015, the AMRC of the Oswaldo Cruz Foundation reported that Zika Virus infection was found in 10 of the 224 suspected dengue patients whose samples were analyzed for Zika virus infection. Seven of the 10 samples analyzed corresponded to patients with neurological syndrome. In January 2016, El Salvador reported the detection of an unusual increase of GBS .On average, El Salvador records14 cases of GBS per month (169 cases per year), however, between 1 December 2015 and 6 January 2016 there were 46 GBS recorded, two of which died. 25 (54%) were male and 35 (76%) were over 30 years old. All were hospitalized and treated with immunoglobulin. Of the deceased patients, one had a history of multiple underlying chronic diseases. In 22 patients whose information was available, 12 (54%) had febrile rash illness between 7 and 15 days prior to the onset of GBS.

Currently, similar situations are being investigated in other countries of the Americas. These findings are consistent with a temporal and spatial link between Zika virus circulation and the increase of GBS. Although the etiopathogenesis and associated risk factors have not yet been well established, Member States should implement surveillance systems to detect unusual increases in cases and prepare health services for care of patients with neurological conditions. Zika virus can cause other neurological syndromes such as meningitis, meningoencephalitis and myelitis.

Sexual Transmission:

Zika Virus transmission by sexual intercourse has been suggested by Foy et al., who described a patient who was infected in southeastern Senegal in 2008. After returning to his home in Colorado, United States, he experienced common symptoms of Zika Virus infection and symptoms of prostatitis. Four days later, he observed signs of hematospermia, and on the same day, his wife had symptoms of Zika Virus infection. Transmission by semen was suggested as the wife of the patient had not traveled out of the United States during the previous year and had sexual intercourse with him 1 day after he returned home. Zika Virus infection of the patient and his wife was confirmed by serologic testing, but the presence of Zika Virus in the semen of the patient was not investigated.[12]

CDC Interim Guidelines:

CDC has developed interim guidelines for health care providers in the United States caring for pregnant women during a Zika virus outbreak. These guidelines include recommendations for pregnant women considering travel to an area with Zika virus transmission and recommendations for screening, testing, and management of pregnant returning travelers. Health care providers should ask all pregnant women about recent travel. Pregnant women with a history of travel to an area with Zika virus transmission and who report two or more symptoms consistent with Zika virus disease (acute onset of fever, maculopapular rash, arthralgia, or conjunctivitis) during or within 2 weeks of travel, or who have ultrasound findings of fetal microcephaly or intracranial calcifications, should be tested for Zika virus infection in consultation with their state or local health department. Testing is not indicated for women without a travel history to an area with Zika virus transmission. In pregnant women with laboratory evidence of Zika virus infection, serial ultrasound examination should be considered to monitor fetal growth and anatomy and referral to a maternal-fetal medicine or infectious disease specialist with expertise in pregnancy management is recommended. There is no specific antiviral treatment for Zika virus; supportive care is recommended. [13]

Diagnosis:

During the first week of illness, Zika virus disease can often be diagnosed by performing reverse transcriptase-polymerase chain reaction (RT-PCR) on serum. Serology assays can also be used to detect Zika virus-specific IgM and neutralizing antibodies, which typically

 ISSN: 2250-1177 CODEN (USA): JDDTAO

develop toward the end of the first week of illness. Plaque-reduction neutralization testing (PRNT) can be performed to measure virus-specific neutralizing antibodies to confirm primary flavivirus infections and differentiate from other viral illnesses. Laboratory evidence of maternal Zika virus infection can include Zika virus RNA detected by RT-PCR in any clinical specimen; or positive Zika virus IgM with confirmatory neutralizing antibody titers that are ≥4-fold higher than dengue virus neutralizing antibody titers in serum. Testing would be considered inconclusive if Zika virus neutralizing antibody titers are < 4-fold higher than dengue virus neutralizing antibody titers.

Challenges in interpreting Zika virus testing:

RT-PCR test may not demonstrate Zika virus RNA in a woman with Zika virus infection if the period of viremia has passed. Serum serologic testing can be performed, however, cross-reactivity with related flaviviruses (e.g., dengue and yellow fever viruses) is common. Plaque-reduction neutralization testing (PRNT) can be performed to measure virus-specific neutralizing antibodies to Zika virus, but neutralizing antibodies may still yield cross-reactive results in persons who were previously infected with another flavivirus, such as dengue, or has been vaccinated against yellow fever or Japanese encephalitis.

Prevention:

There is no specific medication and Vaccines found yet for the treatment of Zika Virus Infection. Treatment is generally supportive and can include rest, fluids, and use of analgesics and antipyretics. Fever should be treated with paracetamol and acetaminophen. Although aspirin and other nonsteroidal anti-inflammatory drugs are not typically used in pregnancy, these medications should specifically be avoided to reduce the risk for hemorrhage. Preventing mosquito bites is the only way to avoid becoming infected**.** The mosquito that spreads Zika is very aggressive and bites during the day and early evening.

- Using insect repellent containing picaridin, oil of lemon eucalyptus, is safe and effective and long lasting protective. Pregnant & breast feeding women should choose an EPA-registered insect repellent and use it according to the product label after applying the sunscreen cream.
- When weather permits, wear long-sleeved shirts and long pants.
- Use air conditioning or window/door screens to keep mosquitoes outside.
- Use a mosquito bed net while sleeping.
- Help reduce the number of mosquitoes by emptying standing water in the surrounding.

CONCLUSION:

In this way after a long time span of about half a century later its first eruption in humans, *Aedes aegypti* vector of Zika Virus, still stretch to no end and has tremendously influenced health status of many people, among which pregnant ladies are at top most risk since fetus gets directly invaded leading to microcephaly along with other congenital complications. The present disease burden suggests for conduction of high scientific research and clinical trials promptly in order to control the most alarming disease pattern of the evolving global scenario. Although, about 80% of persons infected with Zika virus are assumed to be asymptomatic, In contrast, symptoms may include maculopapular rash, fever, headache, anorexia, diarrhoea, constipation, joint and abdominal pain, myalgia, edema, dizziness, and vomiting. There is a possible association between Zika and microcephaly (abnormally small head and brain) in newborns. It is suspected that women who get infected with Zika virus may pass the virus to the developing fetus if they are pregnant. However, there are many causes of microcephaly in babies, but evidence on Zika virus infection causes microcephaly has not been confirmed. Thus more study is needed to understand this possible relationship.

ACKNOWLEDGEMENT:

The corresponding author expresses deep gratitude to all the friends for their co-operation and guidance in searching various articles and journals for completion of this review and also grateful to authors, editors & publishers of all those articles, journals and books from where the literature for this article has been reviewed & discussed.

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How to cite this article:
Parajuli RR, Dahal P, Pokhrel P, Lamichane S, Shrestha S, Timilsina P, A short compilation on zika virus transmission and its complication during pregnancy, Journal of Drug Delivery & Therapeutics. 2016; 6(2):52-56

 ISSN: 2250-1177 CODEN (USA): JDDTAO