

## Zika Virus Infection in Pregnancy, Review of Literature

Emre Ekmekci<sup>1\*</sup>, Servet Gençdal<sup>2</sup>, Emine Demirel<sup>1</sup> and Sefa Kelekci<sup>1</sup>

<sup>1</sup>Department of Perinatology, Faculty of Medicine, Izmir Katip Celebi University, Turkey

<sup>2</sup>Obstetrics and Gynecology Clinic, Izmir Atatürk Education and Research Hospital, Ministry of Health, Turkey

**\*Corresponding author:** Emre Ekmekci, Department of Perinatology, Faculty of Medicine, Izmir Katip Celebi University, 170 Street, 35150 Karabaglar/İzmir, Turkey, Tel: +90 (232) 244 44 44; Email: dr.ekmekci@hotmail.com

### Review Article

Volume 2 Issue 1

**Received Date:** February 22, 2016

**Published Date:** March 03, 2017

### Abstract

Zika virus infection is caused by a virus transmitted primarily by *Aedes* mosquitoes. Patients with Zika virus disease may have non-specific symptoms including mild fever, skin rash, conjunctivitis, muscle and joint pain, malaise or headache. These symptoms normally last for 2-7 days. Zika virus infection during pregnancy is a cause of congenital brain abnormalities, including microcephaly; and that Zika virus is a trigger of Guillain-Barré syndrome. Links to other neurological complications are also being investigated. In this article we tried to review epidemiology, clinical features, diagnosis and obstetric management of Zika virus infections in pregnancy.

**Keywords:** Zika Virus; Pregnancy; Microcephaly; Perinatal Infection

### Introduction

Zika virus is an arthropod-borne flavivirus transmitted by mosquitoes [1-4]. Clinical manifestations of Zika virus infection occur in approximately 20 percent of patients and include acute onset low-grade fever with maculopapular pruritic rash, arthralgia (notably small joints of hands and feet), or conjunctivitis (non-purulent). Congenital Zika virus infection is associated with severe congenital anomalies, these include congenital microcephaly (in addition to other developmental problems among babies born to women infected during pregnancy), Guillain-Barré syndrome, myelitis, and meningoencephalitis [5-6]. Zika virus infections were first detected in the Western hemisphere in February 2014 on Chile's Easter Island [7]. Currently, there is an ongoing Zika virus outbreak in the Americas, the Caribbean, and the Pacific [8-10]. Zika virus is a neurotropic virus that particularly targets neural progenitor cells [11]. Murine and human placental studies support the hypothesis that maternal infection leads to

placental infection and injury, followed by transmission of the virus to the fetal brain, where it kills neuronal progenitor cells and disrupts neuronal proliferation, migration, and differentiation, which slows brain growth and reduces viability of neural cells [11,12]. In the placenta, the virus primarily infects and replicates in placental macrophages (Hofbauer cells), and to a lesser extent cytotrophoblasts [13]. A series from Brazil described histopathological findings in tissue from two newborns with microcephaly and severe arthrogryposis who died shortly after birth and tissue from a microcephalic infant who died at age two months [14]. In these three cases, there was immunohistochemical and molecular evidence of virus persistence in the brain. The range of neuropathology included ventriculomegaly, lissencephaly (which commonly aligns with microcephaly), and cerebellar hypoplasia, all of which have been observed in other cases studied [15].

## Diagnosis

The diagnosis of Zika virus infection should be suspected in individuals with typical clinical manifestations and relevant epidemiologic exposure (residence in or travel to an area where mosquito-borne transmission of Zika virus infection has been reported, or unprotected sexual contact with a person who meets these criteria). The differential diagnosis of Zika virus infection includes: Dengue fever, Chikungunya, Parvovirus, Rubella, Measles, Leptospirosis, Malaria, Rickettsial infection, group A Streptococcus. At each prenatal visit, health care providers should screen pregnant woman for possible exposure to Zika virus and possible symptoms of Zika virus infection. Mother had typical clinical manifestations of Zika virus infection (one or more of the following: maculopapular pruritic rash, arthralgia, conjunctivitis, or fever) and relevant epidemiologic exposure during pregnancy (residence in or travel to an area where mosquito-borne transmission of Zika virus infection has been reported). The diagnosis of Zika virus infection is definitively established via real-time reverse-transcription polymerase chain reaction (rRT-PCR) for Zika virus RNA (in serum, urine, or whole blood) or Zika virus serology [16,17]. Serum and urine are the primary diagnostic specimens; whole blood is an approved specimen for some nucleic acid assays. For individuals presenting <14 days after onset of symptoms, rRT-PCR of serum (or whole blood) and urine for detection of Zika virus RNA should be performed. Any positive rRT-PCR result establishes a diagnosis of Zika virus infection and in such cases no further testing is indicated. Negative rRT-PCR results do not exclude Zika virus infection and should prompt Zika virus serologic testing (Zika virus IgM and plaque reduction neutralization test [PRNT]). The diagnostic approach is different in pregnant compared to non-pregnant individuals because Zika virus RNA can persist longer in a pregnant woman's serum (107 days after symptom onset in one case [1] and because of the potential for congenital infection, even if the mother is asymptomatic [2,3]. The main challenge pertaining to laboratory testing for Zika virus is that the window period for Zika virus identification in blood or urine by polymerase chain reaction is relatively short (within the first two weeks of infection). Fetal ultrasonography may also be indicated.

## Congenital Infection

The risk for vertical transmission exists throughout pregnancy and in offspring of both symptomatic and asymptomatic mothers [9,16-18]. The magnitude of risk of birth defects resulting from in utero exposure to Zika

virus is uncertain. Estimates of the overall risk of any birth defect or abnormality among fetuses and infants of women infected with Zika virus during pregnancy range from 6 to 42 percent [19,20]. Features of congenital Zika virus syndrome described in case reports and small case series. However, the full spectrum of the syndrome is still being investigated.

## Microcephaly

The World Health Organization (WHO), the United States Centers for Disease Control and Prevention, and other scientific groups have concluded that the Zika virus can cause microcephaly [6,21]. In some cases, congenitally infected offspring of women with first or second trimester Zika virus infection have a normal head circumference at birth but subsequently develop microcephaly in the first year of life [22]. Estimates of the risk of microcephaly with in utero Zika virus exposure range from 1 to 4 percent [19,20,23]. There is no standard definition for diagnosis of microcephaly. The WHO has defined microcephaly as follows: Occipitofrontal circumference (head circumference) greater than two standard deviations below the mean or less than the third percentile based on standard growth charts for sex, age, and gestational age at birth [5,6].

## Central Nervous System Abnormalities

Central nervous system abnormalities include ventriculomegaly; intracranial calcifications, especially along the gray matter-white matter junction, which is unusual as calcifications are punctate with other congenital infections [24].

## Positional Abnormalities

Positional anomalies, such as club foot and arthrogyposis, have been observed and may be of neurogenic origin [25].

## Adverse Pregnancy Outcomes

Adverse pregnancy outcomes include fetal loss (miscarriage, stillbirth) [19,26,27], impaired fetal growth [19,27], and hydrops fetalis [28]. Placental insufficiency is the mechanism postulated for fetal loss later in pregnancy.

## Pregnancy Management

There is no specific treatment for Zika virus infection. Management consists of rest and symptomatic treatment including drinking fluids to prevent dehydration and administration of acetaminophen to relieve fever and pain

[29]. The World Health Organization (WHO) has issued initial guidance on psychosocial support for patients and families affected by Zika virus infection and associated complications [30]. Ultrasound is the major modality used to screen for congenital Zika virus infection. Magnetic resonance imaging (MRI) is more sensitive for diagnosis of fetal brain abnormalities [31]. It is appropriate when clarification of ultrasound findings would impact pregnancy management. In women infected early in pregnancy, ultrasound findings associated with fetal infection may be detected as early as 18 to 20 weeks of gestation, but are usually detected in the late second and early third trimesters of pregnancy [32-34]. The United States Centers for Disease Control and Prevention (CDC) and ACOG suggest fetal ultrasound examination every three to four weeks to look for signs of congenital Zika virus infection and monitor fetal growth in pregnant women with laboratory evidence of recent Zika virus infection [35,36]. If the ultrasound examination is abnormal, amniocentesis for diagnosis of fetal infection should be considered. The indications for diagnostic amniocentesis, the appropriate gestational age for testing, and the interpretation of the test results are uncertain. Decisions regarding amniocentesis should be tailored to individual clinical circumstances [37].

The sensitivity and specificity of Zika virus rRT-PCR testing of amniotic fluid for diagnosis of congenital infection are not known and likely depend on timing of amniocentesis after onset of maternal infection [38]. A positive rRT-PCR result on amniotic fluid should be considered suggestive of fetal infection [17]. If the fetus is abnormal and rRT-PCR is negative, evaluation for other causes of the fetal abnormalities should be considered [39]. However, the duration of amniotic fluid PCR positivity is unknown, so a negative rRT-PCR does not definitively exclude fetal Zika virus infection [40].

Infected fetuses are at risk for stillbirth, which may be related to hydrops fetalis or growth restriction, although the exact mechanism is unknown. If antenatal testing is performed (eg, non-stress test, biophysical profile) and results are abnormal, early delivery may be appropriate depending on the clinical scenario.

### Delivery

Timing and route of delivery are determined according to routine obstetric policies and standards. The appropriate location for delivery should be decided by late third trimester [41].

### Breast Feeding

Transmission of Zika virus through breast milk has not been reported [42], although the virus has been detected in breast milk [43,44].

### Prevention

To protect against Zika virus infection in pregnant women should; avoid travel to areas with known mosquito transmission of Zika virus, adhere to mosquito protective measures, adhere to measures to protect from sexual transmission of Zika virus, adhere to recommendations regarding blood donation, adhere to recommendations for standard infection precautions. There is no vaccine for prevention of Zika virus infection, but a vaccine is under development.

### References

1. Petersen LR, Jamieson DJ, Powers AM, Honein MA (2016) Zika Virus. *N Engl J Med* 374(16): 1552-1563.
2. Musso D, Gubler DJ (2016) Zika Virus. *Clin Microbiol Rev* 29(3): 487-524.
3. Anderson KB, Thomas SJ, Endy TP (2016) The Emergence of Zika Virus: A Narrative Review. *Ann Intern Med* 165(3): 175-183.
4. Focosi D, Maggi F, Pistello M (2016) Zika Virus: Implications for Public Health. *Clin Infect Dis* 63(2): 227-233.
5. World Health Organization (2016) Consensus on causal link between Zika and neurological disorders.
6. World Health Organization (2016) Zika situation report.
7. Gatherer D, Kohl A (2016) Zika virus: a previously slow pandemic spreads rapidly through the Americas. *J Gen Virol* 97(2): 269-273.
8. Fauci AS, Morens DM (2016) Zika Virus in the Americas-Yet Another Arbovirus Threat. *N Engl J Med* 374(4): 601-604.
9. Hennessey M, Fischer M, Staples JE (2016) Zika Virus Spreads to New Areas - Region of the Americas, May 2015-January 2016. *MMWR Morb Mortal Wkly Rep* 65(3): 55-58.

10. Chen LH, Hamer DH (2016) Zika Virus: Rapid Spread in the Western Hemisphere. *Ann Intern Med* 164(9): 613-615.
11. Costello A, Dua T, Duran P, Gülmezoglu M, Oladapo OT, et al. (2016) Defining the syndrome associated with congenital Zika virus infection. *Bull World Health Organ* 94(6): 406-406A.
12. Garcez PP, Loiola EC, Madeiro da Costa R, Luiza MH, Pablo T, et al. (2016) Zika virus impairs growth in human neurospheres and brain organoids. *Science* 352(6287): 816-818.
13. Quicke KM, Bowen JR, Johnson EL, McDonald CE, Ma H, et al. (2016) Zika Virus Infects Human Placental Macrophages. *Cell Host Microbe* 20(1): 83-90.
14. Martines RB, Bhatnagar J, de Oliveira Ramos AM, Helaine PF, Silvia, et al. (2016) Pathology of congenital Zika syndrome in Brazil: a case series. *Lancet* 388(10047): 898-904.
15. Hazin AN, Poretti A, Turchi Martelli CM, Huisman TA, Microcephaly Epidemic Research Group, et al. (2016) Computed Tomographic Findings in Microcephaly Associated with Zika Virus. *N Engl J Med* 374(22): 2193-2195.
16. Centers for Disease Control and Prevention (2016) Emergency Preparedness and Response Recognizing, Managing, and Reporting Zika Virus Infections in Travelers Returning from Central America, South America, the Caribbean, and Mexico.
17. Petersen EE, Staples JE, Meaney-Delman D, Marc F, Sascha RE, et al. (2016) Interim Guidelines for Pregnant Women During a Zika Virus Outbreak-United States, 2016. *MMWR Morb Mortal Wkly Rep* 65(2): 30-33.
18. European Centre for Disease Prevention and Control (2016) Rapid Risk Assessment: Zika virus disease epidemic: potential association with microcephaly and Guillain-Barré syndrome, fourth update.
19. Brasil P, Pereira JP, Moreira ME, Ribeiro Nogueira RM, Damasceno L, et al. (2016) Zika Virus Infection in Pregnant Women in Rio de Janeiro. *N Engl J Med* 375(24): 2321-2334.
20. Honein MA, Dawson AL, Petersen EE, Jones AM, Lee EH, et al. (2017) Birth Defects Among Fetuses and Infants of US Women With Evidence of Possible Zika Virus Infection During Pregnancy. *JAMA* 317(1): 59-68.
21. Rasmussen SA, Jamieson DJ, Honein MA, Petersen LR (2016) Zika Virus and Birth Defects--Reviewing the Evidence for Causality. *N Engl J Med* 374(20): 1981-1987.
22. van der Linden V, Pessoa A, Dobyns W, James AB, Helio van der Linden, et al. (2016) Description of 13 Infants Born During October 2015–January 2016 With Congenital Zika Virus Infection Without Microcephaly at Birth-Brazil. *MMWR* 65(47): 1343-1348.
23. Cauchemez S, Besnard M, Bompard P, Dub T, Guillemette-Artur P, et al. (2016) Association between Zika virus and microcephaly in French Polynesia, 2013-2015: a retrospective study. *Lancet* 387(10033): 2125-2132.
24. Soares de Oliveira-Szejnfeld P, Levine D, Melo AS, Amorim MM, Batista AG, et al. (2016) Congenital Brain Abnormalities and Zika Virus: What the Radiologist Can Expect to See Prenatally and Postnatally. *Radiology* 281(1): 203-218.
25. van der Linden V, Filho EL, Lins OG, Camila VV, Regina CR, et al. (2016) Congenital Zika syndrome with arthrogryposis: retrospective case series study. *BMJ* 354: i3899.
26. Mlakar J, Korva M, Tul N, Poljšak-Prijatelj M, Mraz J, et al. (2016) Zika Virus Associated with Microcephaly. *N Engl J Med* 374(10): 951-958.
27. Carvalho FH, Cordeiro KM, Peixoto AB, Tonni G, Moron AF, et al. (2016) Associated ultrasonographic findings in fetuses with microcephaly because of suspected Zika virus (ZIKV) infection during pregnancy. *Prenat Diagn* 36(9): 882-887.
28. Sarno M, Sacramento GA, Khouri R, do Rosário MS, Costa F, et al. (2016) Zika Virus Infection and Stillbirths: A Case of Hydrops Fetalis, Hydranencephaly and Fetal Demise. *PLoS Negl Trop Dis* 10(2): e0004517.
29. Centers for Disease Control and Prevention (2016) Zika Virus: Symptoms, Diagnosis, & Treatment.
30. World Health Organization (2016) Psychosocial support for pregnant women and for families with microcephaly and other neurological complications in

- the context of Zika virus: Interim guidance for health-care providers. *Emergencies preparedness, response.*
31. Griffiths PD, Bradburn M, Campbell MJ, Cooper CL, Graham R, et al. (2016) Use of MRI in the diagnosis of fetal brain abnormalities in utero (MERIDIAN): a multicentre, prospective cohort study. *Lancet* 389(10068): 538-546.
  32. World Health Organization (2016) Pregnancy management in the context of Zika virus infection. Interim guidance update.
  33. Oliveira Melo AS, Malinge G, Ximenes R, Szejnfeld PO, Alves Sampaio S, et al. (2016) Zika virus intrauterine infection causes fetal brain abnormality and microcephaly: tip of the iceberg? *Ultrasound Obstet Gynecol* 47(1): 6-7.
  34. Bromley B, Benacerraf BR (1995) Difficulties in the prenatal diagnosis of microcephaly. *J Ultrasound Med* 14(4): 303-306.
  35. <http://www.acog.org/About-ACOG/News-Room/Practice-Advisories/Practice-Advisory-Interim-Guidance-for-Care-of-Obstetric-Patients-During-a-Zika-Virus-Outbreak#Figure1>.
  36. CDC (2016) Update: Interim Guidance for Health Care Providers Caring for Pregnant Women with Possible Zika Virus Exposure-United States. *MMWR* 65(29): 739-744.
  37. The American Congress of Obstetricians and Gynecologists (2016) Practice Advisories.
  38. Besnard M, Lastere S, Teissier A, Cao-Lormeau V, Musso D (2014) Evidence of perinatal transmission of Zika virus, French Polynesia, December 2013 and February 2014. *Euro Surveill* 19(13).
  39. Centers for Disease Control and Prevention (2016) Questions and Answers for Obstetrical Healthcare Providers: Pregnant Women and Zika Virus Infection.
  40. The American Congress of Obstetricians and Gynecologists (2016) Practice Advisory: Interim Guidance for Care of Obstetric Patients During a Zika Virus Outbreak.
  41. Vouga M, Baud D (2016) Imaging of congenital Zika virus infection: the route to identification of prognostic factors. *Prenat Diagn* 36(9): 799-811.
  42. Karwowski MP, Nelson JM, Staples JE, Marc F, Katherinae EFD, et al. (2016) Zika Virus Disease: A CDC Update for Pediatric Health Care Providers. *Pediatrics* 137(5): e20160621.
  43. Fleming-Dutra KE, Nelson JM, Fischer M, Staples JE, Karwowski MP, et al. (2016) Update: Interim Guidelines for Health Care Providers Caring for Infants and Children with Possible Zika Virus Infection--United States, February 2016. *MMWR Morb Mortal Wkly Rep* 65(7): 182-187.
  44. Cavalcanti MG, Cabral-Castro MJ, Goncalves JL, Santana LS, Pimenta ES, et al. (2017) Zika virus shedding in human milk during lactation. An unlikely source of infection? *Int J Infect Dis* S1201-S9712(17): 30045-30050.