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# Prevention of Mother to Child Transmission of Zika Virus and Associated Teratogenic Effects

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**ABSTRACT:** *Background:* Zika virus (ZIKV), a mosquito-borne flavivirus the same vector that causes Dengue and Chikungunya. ZIKV originated from Uganda and was first discovered in monkeys at Zika forest in 1947. Historically, ZIKV causes mild and self-limiting symptoms which can be observed in only 20folds of infected individuals. Recently, in 2015, ZIKV imaged in Brazil and has been linked to serious neurological complications including microcephaly. In 2016, the World Health Organization declared this fact as "Public Health Emergency"
*Objective:* Review on possible mother to child transmission of ZIKV in utero and its related teratogenic effect.
*Method:* Studies both in human and animal models revealed a relationship between ZIKV infection in pregnancy and neurological effects such as microcephaly in fetus and neonates.
*Result:* ZIKV has been linked with microcephaly especially when symptoms emerged in a pregnant woman during first and early second trimester.
*Conclusion:* Although there is a linkage between ZIKV and neurological effects such as microcephaly, most people still doubting as to whether the emerging problem of microcephaly is related to ZIKV infections which is known to present with mild and self-limiting symptoms.

**KEYWORDS:** Zika virus, microcephaly, aedes mosquito, congenital abnormalities, vertical transmission.

## 1 INTRODUCTION

Zika virus (ZIKV) is an arbovirus of the family Flaviviridae, mosquito-borne in the genus aedes [1], [2], [3], the same vector that transmit chikungunya, dengue and yellow fever [4]. ZIKV was first discovered in 1947 in the Zika Forest in Uganda and was isolated from the monkey [5], [6], [7], [2]. The first human cases were detected in 1952, since then, ZIKV out breaks have been reported in America, Southeast Asia, tropical Africa, and the Pacific Islands [2]. In 2007, there was ZIKV outbreak in island Micronesia and then to french polynesia [8] and different regions of the South Pacific and vantage to large epidemics in 2013 and 2014 [7], [9].

ZIKV usually results in mild and self-limiting illnesses and symptoms such as fever, conjuctivitis, skin rashes, muscle and joint pain, malaise and headache [4], [10]. Clinical features of ZIKV are analogous to those of other diseases of the same origin such as dengue and chikungunya and tend to be asymptomatic in approximately 80 folds of infected people [4], [11], [8]. ZIKV cases have been neglected until declared by the WHO as a "*public health emergency*" following an outbreak in Brazil in 2016 [5], [2], [12], [11], [8]. In February, 2017, an estimation of 3000 cases of zika related anormalies including microcephaly was reported from 29 countries with the vast majority in Brazil [5].

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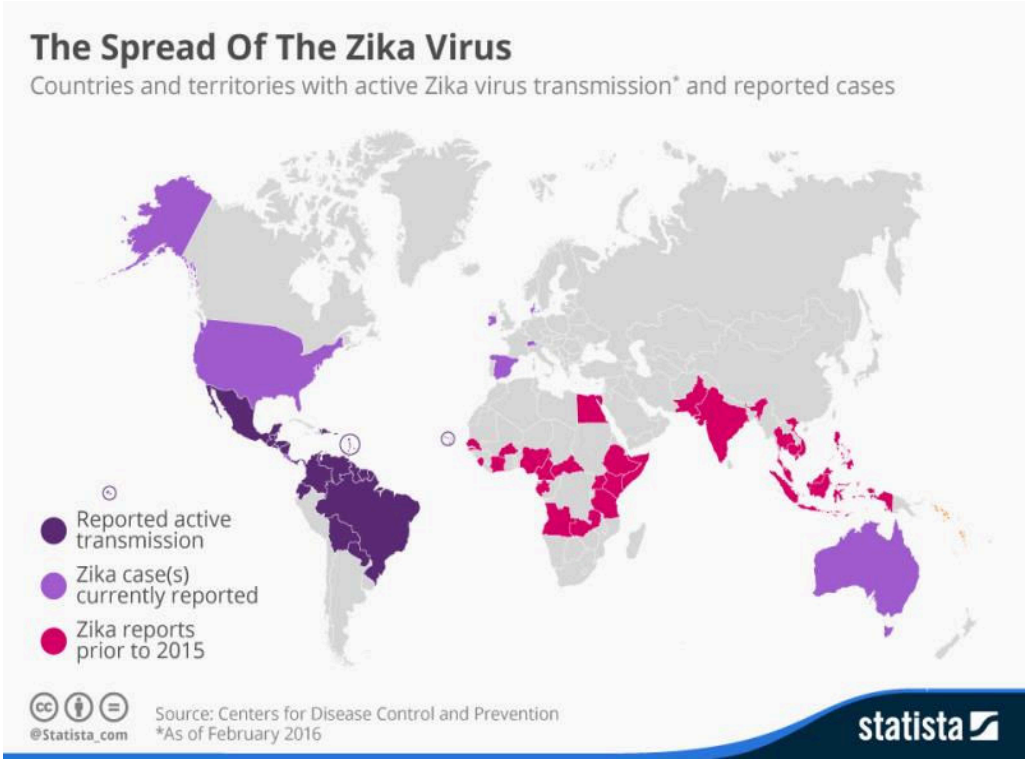


Historically, ZIKV infection have not been conceived as a world-shaking public health concern, up until 2015, when ZIKV outbreak happened in America leading to an estimated number of 1.5 million cases in Brazil [9], [10]. ZIKV infection has been associated with neurological disorders and severe congenital abnormalities [6], [5], [11], [13], [14]. Public attention was attracted to the reality that the neglected disease with self-limiting symptoms became a global health problem due to its teratogenic effects, causing innate Zika syndrome including microcephaly [15], [16] along with terrible neurological outcomes such as Guillain-Barré syndrome in adults [2], [3], [5], [10], [7], [4], [14], [8] as well as premature births and miscarriages [17].

Zika virus (ZIKV) seems to continue spreading throughout both tropical and subtropical regions of the world. Along with mosquito being the vector of ZIKV,the disease can be spread through blood transfusion, laboratory exposure, sexual contact, and from mother to child [18], [4], [12]. It was concluded by WHO and United States Centers for Disease Control and Prevention (CDC), that the causal relationship between ZIKV in pregnancy and congenital zika syndrome (CZS) is apparent in offspring hence needs attention [11], [12], [13]. This article is the review of the origin of the ZIKV, mode of transmission which includes mother to child transmission in utero and associated effects in fetus and neonates as well as possible treatment, prevention and control.

## 2 MECHANISM OF TRANSMISSION AND ZIKA VIRUS SYNDROME

The outbreak of ZIKV in America which occured in 2015–2016 outbreak established how a relatively concealed and mild mosquito-borne disease can become a global health emergency, causing congenital Zika syndrome, including microcephaly, and other neurological complications such as Guillain-Barré syndrome [3], [19], [11], [15]. Zika virus (ZIKV) continues to spread throughout the regions of the world. Transmission of ZIKV can occur through mosquito vectors of the family flaviridae, sexual contact, blood transfusion [20], or accidental laboratory exposure as well as mother to child transmission [21]. It has been reported that the transmission of ZIKV from mother to child can occur during pregnancy, delivery and breast feeding [18] [22], or close contact between the mother and her newborn [21]. However, mother to child transmission in utero is a general public concern as it is linked to congenital anomalies such as microcephaly [22], [23].

## 3 MOTHER TO CHILD TRANSMISSION IN UTERO

Maternal ZIKV infection has been linked with congenital abnormalities such as microcephaly, brain anomalies, visual and hearing deficit and other neurological problems [24], [25], [16]. It has been rumored that vertical infections can take place in utero especially during first and early second trimester [12], during vaginal birth process by contacting infants' mucosa membranes with ZIKV contaminated blood [21], [22]. Zika infection in utero is the most significant cause of ZIKV syndrome

[22], though the mechanism of intrauterine transmission of ZIKV and pathogenesis that leads to congenital anomalies such as microcephaly is not yet clear. Nonetheless, some studies have shown that ZIKV-RNA can be found in placenta and fetal tissues [16] [26], which can provide an opportunity to diagnose maternal infection, if the maternal serological testing is not conclusive outside the optimal testing window and help to identify the cause of congenital anomalies if presented in the newborn [25]. Some studies done in animal models especially by using mice, suggested the significant vertical transmission of ZIKV following the supportive results that ZIKV crosses the placenta barrier hence affecting the fetus [16], [26], [22] .

## 4 ZIKV SYNDROME

Although the disease is self-limiting, cases of neurological manifestations and the Guillain–Barré syndrome were described in French Polynesia [3], [23] and in Brazil during ZIKV epidemics [27]. Reports from the Brazilian Ministry of Health revealed the possible relationship of ZIKV infection and microcephaly because they experienced an increased number of Zika related microcephaly cases among the newborn in the affected region [28].

Some studies rumored that, isolated ZIKV strains genome sequences from microcephaly cases in Asia and any other previous affected areas may clarify the possible mechanisms for the transmission and pathogenesis of ZIKV. This review includes some of the studies done in different areas and shows some genome sequences of ZIKV strains isolated from amniotic fluid and aborted fetal tissue such as brain [29] among others.

Mlakar, J. et.al, revealed that ZIKV positive results were obtained on Reverse Trancriptase -Polymerase chain Reaction (RT-PCR) assay in the brain sample of the aborted fetus with microcephaly [14]. Similarly, Bhatnagar J. et.al found ZIKV RNA replication in placentas from women who aborted in their first [22] and second trimesters and from the brain tissues of infants with microcephaly [16]. These are in line with some studies done in animal model which demonstrated that ZIKV degrades neuronal stem and progenitor cells leading to pathological brain changes [12], [14], [16]. All these studies revealed the detection of ZIKV in the brain which distinctly displayed the powerful neurotropism [16] [26] which can be manifested by microcephaly or any other abnormalities of central nervous system (CNS). The discovery of ZIKV- RNA in placenta and brain tissues strengthens the relationship of ZIKV and serious cerebral malformation such as microcephaly [16], [26]. Any other viruses which can as well cause congenital malformations such as other flaviviruses along with chikungunya virus, lymphocytic choriomeningitis, cytomegalovirus, rubella virus, varicella–zoster virus, herpes simplex virus, parvovirus B19, enteroviruses, and Toxoplasma gondii were ruled out [14], [30]

Phylogenetic studies displayed that the nearest strain to that of Brazil was isolated from French Polynesia and spread among the Pacific Islands, belongs to the Asian strains [31]. It is believed that ZIKV was introduced to Brazil during the world Cup in 2014. Similarly, the Phylogenetic analysis was performed and demonstrated 99.7% identity of ZIKV strain singled out from French Polynesian patient in 2013 [32]. More so, ZIKV detected in Sao Paolo, Brazil, in 2015 (KU321639) and a Cambodian strains which was detected in 2010 revealed the identity of 98.3%, besides the strains from the Micronesia outbreak in 2007 and Thailand 2016 revealed the identity of 98% [31], [28].

This explains that the ZIKV genome found in these different regions resemble each other and that of Brazil. It is as well believed that, the amino acid changes as the ZIKV moves from region to the other showing a slight difference**,** for instance, three changes were found in NS1 region (K940E, T1027A, and M1143V), one in NS4B region (T2509I), and another found in the FtsJ-like methyl-transferase region (M2634V) [20]**.** This concludes the phylogenetic analysis and evolution history of ZIKV which was deduced by neighbor-joining method under a GTR+G+I substitution model as shown in figure1 [14], [31], which imply that strains collected in all ZIKV affected areas are closely related [23].

Although the information about the presence of ZIKV in the amniotic fluid of pregnant women with microcephaly fetuses is scarce in the literature, Benjamin I, et.al., detected ZIKV in two women's amniotic fluid, and they all presented with symptoms of ZIKV infection in their first trimester of pregnancy in Brazil [26], [33]. Ultrasonography confirmed microcephaly in their early second trimester for instance 21–22 weeks' gestation and revealed terrible fetal brain injury related to ZIKV vertical transmission [26].

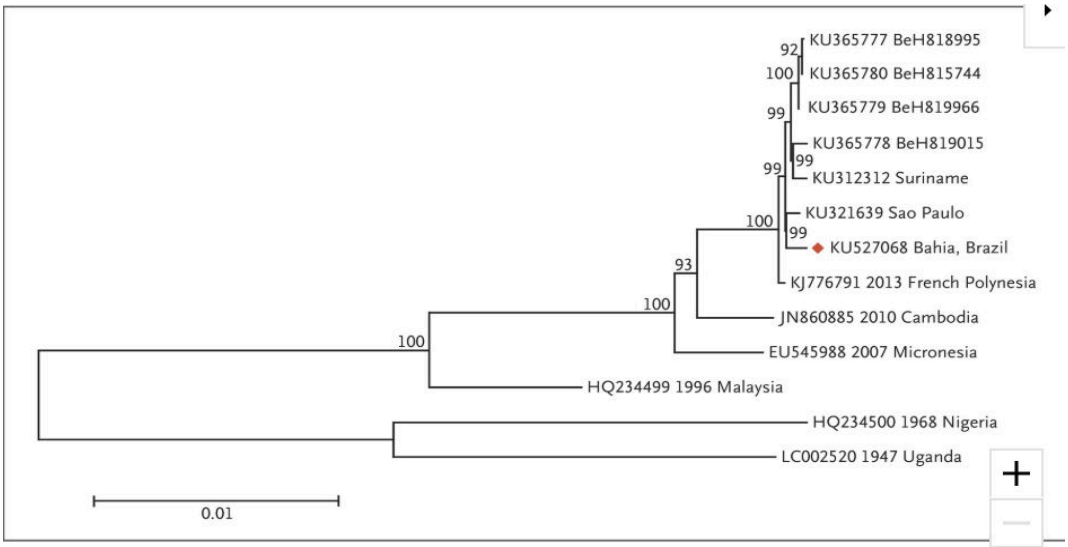


***Fig. 1. Phylogenetic Analysis of ZIKV Complete Genome [31]***

At 28weeks gestation, amniotic fluid tests confirmed the existence of ZIKV genomes and Zika antibodies which was conformable with intrauterine viral transmission which would happen during first and early second trimester of pregnancy [26], [33]. Other tests for similar viruses were ruled out and ZIKV found negative in blood and urine [26], [30]. Nonetheless, Calvet et.al, revealed the presence of ZIKV in amniotic fluid of which they managed to detect it before the woman delivered [34] and a similar study found ZIKV in amniotic fluid from women who were suspected to have ZIKV in the first trimester and lost their fetuses on the way [35].

All the same, in the similar study done in mouse model, ZIKV was innoculated directly in the amniotic fluid, some through intravenous route and vaginally revealed no clinical signs of disease but some evidence of zika viral replication were present [36], [37]. Mice that were inoculated in the uterus showed intrauterine growth retardation (IUGR) and microcephaly [37] and abortion noted in mouse with direct inoculation of ZIKV in the amniotic fluid, and yet, fetal abnormalities in mouse models were only observed when the virus is introduced directly in the gravid uterus, amniotic fluid or intravenous injection [36]. This supporting the possibility that Zika virus can pass through placenta to the fetus and affect the fetus' growth and development along with cell differentiation.

### 4.1 CONGENITAL ZIKV RELATED MICROCEPHALY

WHO defined microcephaly as an infants' rare condition where the brain is under developed antenatally or stopped growing postanatally leading to abnormal smaller head size as compared to infants of the same sex, age and ethnicity [38], [39], [40]. Microcephaly has been linked with ZIKV due to the world-shaking emerging number of infants with microcephalus following ZIKV outbreak in Brazil [38], [41], [42]. It is hypothesized by WHO and other studies that ZIKV in pregnancy can cause congenital brain anomalies such as microcephaly [38], [41] hence needs public attention and response.

Some studies where the mice models were used found that ZIKV replicates effectively in the embryonic brain by targeting neuronal progenitor cells and revealed that infected brains were smaller [43] with hypertrophied ventricles and a thin cortex [19]. These studies discovered that prenatal transmission of ZIKV is concodant with fetal abnormality such as microcephalic physical appearance [41], [42]. Similarly, the relationship of zika infection and fetal brain abnormalities were noticeable on electron microscopy aggregation that were agreeable with ZIKV detection in the fetal brain [28]. The findings on electron microscopy suggested the possible persistence of ZIKV in the fetal brain, perhaps due to the immunologically secured environment for the virus. The number of viral copies were substantially detected higher in the fetal brain than in the serum obtained from adult ZIKV infected patients but similar to those in semen [26].

More so, in Venezuela, there was a microcephaly case related to the current ZIKV infection, which was confirmed by PCR in amniotic fluid and cord blood at 4 weeks and 3 days after infection [26], [44]. Furthermore, In Colombia, ZIKV was revealed by real-time PCR in amniotic fluid at 10 weeks and in cord blood at 28 weeks after infection [45]. Likewise, Benjamin I, et.al revealed that ZIKV can be perceived by PCR in amniotic fluid as well as in umbilical cord blood in early pregnancy or more than 14 days after infection [26], [44]. These results support the perspective that ZIKV crosses the placental barrier and beef up the causal association between ZIKV and microcephaly along with other neurological disorders [26]. Intrauterine viral level suggests

the persistent replication and partially vindicated by the reduced immune system response of the fetus, as seen in the of congenital cytomegalovirus [26]

These similar cases presented and characterized by seriously affected CNS and gross intrauterine growth retardation [30]. The placenta calcification and low placental–fetal weight ratio [12], signaled possible damage to the placenta trophoblast and induce cellular apoptosis leading to disruption of placenta barrier [40], [30]. Other studies found that ZIKV crosses the placenta barrier hence infect the fetus and suppress fetal growth which eventually leads to birth defects such as microcephaly [40]. Similar studies done in the pregnant mouse model revealed that ZIKV crosses the placenta barrier and invades neuroprogenitor cells of the fetal brain [46] causing apoptosis leading to cell death hence impairing neural development [40], [36], [30].

## 5 Risk of Vertical Transmission in Utero

In 2015, microcephaly detection in Brazil alarmed investigation of the outbreak in other areas such as French Polynesia where the results revealed about 17 new born babies with brain malformation including microcephaly. In early 2016, French polynesia reported to WHO about their linkage between Zika and Guillain-Barré syndrome [28], [43] .

It was documented that prenatal ZIKV transmission can occur at any stage of pregnancy and there is a correlation in the manifestation of the CZS physical appearance and the maternal gestational timing of ZIKV infection [12]. It has been discovered that the highest risk period for CNS is maternal infection is first [41] and early second trimester [12], [36]. It was documented in a study of affected neonates that among 183 cases of decisive CZS with microcephaly, 77% of their mothers rumored of having symptoms in the first trimester [41], 18% in the second trimester and 5% in the third trimester [12], which concludes that the greatest risk of ZVS occurs in the early stages of life in utero.

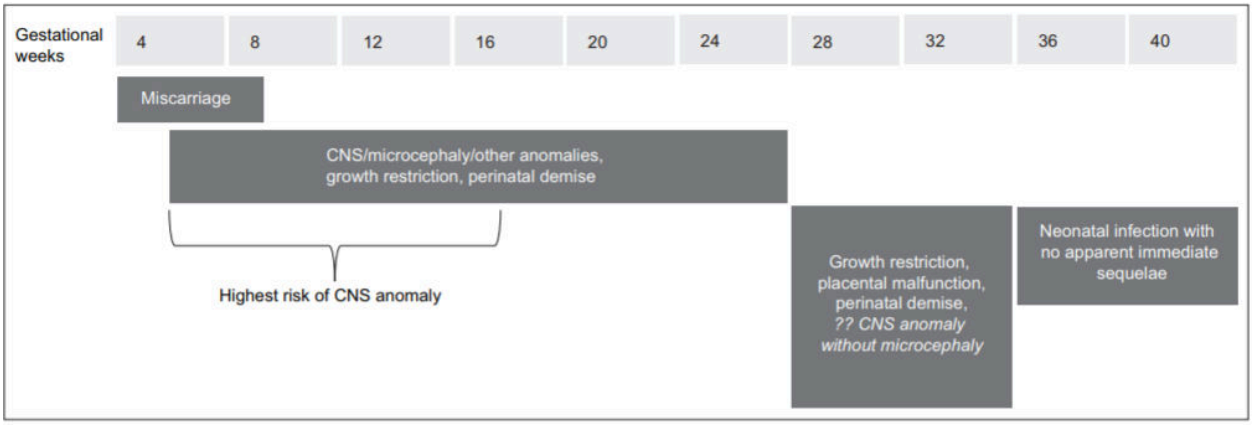


***Fig. 2. Maternal gestational timing of ZIKV infection and fetal phenotype [12]***

Women who were infected before 7-8 weeks of gestation aborted and ZIKV RT-PCR revealed the presence of infection in the serum of the mother and products of conception [12]. In general, ZIKV vertical transmission occurrences believed to be low with highest risk of fetal complication during the first and early second trimester [14], [41], [47], as shown in the figure2 [12]. An increased number of information signaled that ZIKV is vertically transmissible and typically during perinatal period through the placenta.

## 6 Treatment Prevention and Control

ZIKV infection is self-limiting [27] with no cure [28], so only supportive treatment which focuses on signs and symptoms is provided [20]. Nonetheless, the complications in the fetus are irreversible and nasty. Therefore, it is very important to prevent the ZIKV by following public health measures such as vector control as the backbone of the risk reduction for ZIKV infection [12]. Pregnant women should avoid visiting endemic areas especially in their first and second trimester. In an inevitable situations, the women who stays or works in affected areas, should take strict measures to reduce the risk of mosquito bite and practice safe sex by using a condom [12], [41]. Reduce mosquito bites by wearing long sleeved clothes and pants, using arthropod repellent, and insecticide treated mosquito nets, keep the windows shuts to keep mosquitoes out when indoors and using air conditioner [12].

Precautions should be considered to minimize ZIKV infection in pregnant women to reduce the incidence of CZS. WHO released an epidemiologic alert with recommendations, such as vector control, active surveillance of all individuals staying, entering in the country or returning from endemic areas as well as isolation of infected individuals in the room with air-conditioner to prevent transmission [12]. However, as studies found that only 20% of ZIKV infected individuals are symptomatic, some of these strategies can be ineffective because of the huge number of unrecognized cases, yet infected individuals may not be confined. Alertness in identification of first cases of ZIKV infections is critical for immediate response in mobilizing resources for vector control to prevent further spreading of the virus.

## 7 CONCLUSION

Prenatal ZIKV infection is connected with an important risk of fetal involvement of CNS and IUFD, in particular when the infection occurs during the first and second trimester. The infinite risk of CZS is relatively low even with current localized ZIKV outbreak; however, public and health workers should maintain a pictorial perspective of ZIKV effect on pregnancy. Due to the linkage of ZIKV and neurological effects including microcephaly, expectant mothers should be provided with appropriate and consistent counselling and planned obstetric surveillance by considering the maternal gestational timing in relation to ZIKV.

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