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# Review Article
# Consequences of Zika Virus Infection During Fetal Stage and Pregnancy Safe Drugs: An Update

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## Abstract

Zika virus (ZIKV), is a member of the Flaviviridae family and cause congenital microcephaly and Guillain-Barre' Syndrome (GBS). The fetus of the mothers infected with ZIKV during first trimester are suffered from severe neurological damage like change of head shape and circumference celled microcephaly, convoluted scalp, deformed joints and vision and hearing loss. Its capability to infect fetus caused Public Health Emergency of International Concern. The information related to ZIKV infecting pregnant women and safe drugs were retrieved from the authentic published resources available on Medline, Pubmed, Pubmed Central, Science Direct and other scientific databases. The retrieved information has been compiled and analyzed. Microcephaly is a rare paediatric condition, implicated with severe consequences on fetus. The consequences of ZIKV infection to the fetus, statistical analysis summarizing association of microcephaly with ZIKV infection with other teratogenic congenital disease manifestations like ZIKV infection and about the therapies which can work for fetus and pregnant women include the use of chloroquine, amodiaquine, sofosbuvir, macrolide antibiotic azithromycin, niclosamide, albendazole/mebendazole, palonosetron and use of convalescent serum. Present review explains techniques of virus detection in fetus. Detailed case study analysis of affected fetus and the mechanism by which virus cause damage to the tissues and the target of fetus might be helpful in future to prevent the detrimental effects of the virus.

Key words: Zika virus, microcephaly, ZIKV detection, fetal infection, therapies during pregnancy, drugs

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Data Availability: All relevant data are within the paper and its supporting information files.

## INTRODUCTION

Zika virus (ZIKV) was first isolated in 1947 from the Zika forest in Uganda from Rhesus macaque and later was identified in *Aedes africanus*. During initial epoch, it was included in neglected tropical diseases due to mild pathological conditions accessible in a limited number of identified cases. The situation dramatically changed during 2014-15, when it exploded in American countries and caused an approximate 1.5 million infections[1]. Its human infections are due to mosquito bite; however person to person transmission of virus may occur through sexual contact or saliva exchange during kissing and vertically from mother to fetus[2]. The ZIKV infection is mainly remains asymptomatic and in symptomatic infection, the manifestations are often mild and are similar with symptoms of dengue including rash, fever, arthralgia, conjunctivitis, myalgia, headache and retro-orbital pain[2]. Mostly, the symptomatic ZIKV infections are self-limited and resolve within a week[3] but in severe infection it causes neurological condition called Guillain-Barre' Syndrome and also meningoencephalitis and myelitis[2,4]. The most dreadful complications occurs during pregnancy and result in severe fetal abnormalities and death. The association of ZIKV infection with the cases of microcephaly was identified in Brazil in 2014-15, when cases of microcephaly increased to 20 fold in ZIKV affected area. Since then, several epidemiological, geographic and clinical evidences have been sufficiently accumulated to confer relatedness of microcephaly and other related birth defects and ZIKV infection to mother defects[5-8]. The same has been supported by the presence of ZIKV RNA and infectious virus particle in fetus and placental tissue[9,10]. Also animal model studies using pregnant mice revealed the same detrimental effects on neuronal system of the fetus[11,12].

The severe repercussions of ZIKV infection on the fetus have compelled World Health Organization (WHO) to declare global health emergency to carry research in order to find out the amicable solutions. The major emphasis in the present review has been given on fetal detection and consequences of ZIKV infection in fetus; statistical analysis revealing the connection of ZIKV with neurological detrimental consequences and the study of its symptoms identical with other congenital diseases and different drugs, which may be used by the pregnant women efficaciously to prevent fetus from severe detrimental outcomes of ZIKV infections have been discussed.

## FETAL DETECTION OF ZIKV

Two pregnant women from state of Paraiba in Brazil, whose fetus were recognized to have microcephaly at 18 weeks and 10 weeks gestation were investigated for presence of ZIKV in their amniotic fluid. Nucleic acid was isolated from purified virus particles from the centrifuged amniotic fluid and qRT-PCR and viral metagenomic next-generation sequencing revealed the presence of ZIKV[13]. Eleven infants having congenital ZIKV infection were included in the study to mothers having confirmed lab evidence of ZIKV infection by serology or PCR. All the patients presented with microcephaly with reduced cerebral volume, lissencephaly, fetal akinesia, cerebellar, ventriculomegaly and hypoplasia. The possibility of other genetic diseases and bacterial and viral infections associated with microcephaly was excluded by laboratory testing. The ZIKV genomic RNA was present in both the maternal as well as fetal tissues including amniotic fluid, cord blood, placenta and brain in case of dead fetus. Genetic variation was observed in envelope gene in different tissues[14].

## CONSEQUENCES OF ZIKV INFECTION IN FETUS

The ZIKV infection with strain FSS13025 through subcutaneous infection in a non-human primate (pigtail macaques) at 119 day of gestation period using $10^7$ plaque forming units, revealed a lag in the growth of the fetal biparietal diameter (BPD) on the basis of weekly ultrasound. The ZIKV infected fetal brain exhibited marked reduction in posterior white matter as compared to the control fetal brain. Bilateral white matter gliosis occurred with many apoptotic and mitotic figures. No cortical malformation or abnormalities of the brainstem or cerebellum was observed. Upon delivery the presence of ZIKV viral RNA was notified in chorionic villous tissue of the placenta, the fetal brain and liver and the maternal brain, eyes, spleen and liver[15]. The findings of Waldorf *et al.*[15] were consistent with the findings of Brasil *et al.*[9] where arrest of white matter expansion was evident by MR imaging. The same arrest in fetal brain growth and neuroinvasion was observed in case of human pregnancy subject, having ZIKV infection in third trimester. In contrast to the findings of Waldorf *et al.*[15] and Dudley *et al.*[16] reported only presence of viral RNA in fetus of rhesus macaque model. In previous ZIKV infection conditions in rhesus macaques did not showed arrested brain growth with genomic RNA detection in very few organs including lymph node, bone marrow and optic nerve and the difference in result might have arose due to different amount of inoculums used. A pregnant woman, who traveled for 7 days to ZIKV infected area during 11$^{th}$ week of gestation, was found seropositive for ZIKV. Magnetic resonance imaging performed during 16-20$^{th}$ week of gestation revealed the reduction of brain circumference from 47 percentile at 16 weeks of gestation to

the 24 percentile at 20 weeks of gestation with severe brain anomalies[9]. At the 30.1 weeks' gestation, the fetal ultrasound analysis revealed brain atrophy with coarse calcifications in the white matter of the frontal lobes with head circumference was 2.6 SD below expected level. In an another case at 29.2 weeks' gestation, head circumference was 3.1 SD below expected level with asymmetrical cerebral hemispheres and thin and continuous pons and brainstem[17]. Brain calcification in both the cases is indicative of an intrauterine infection. In Paraiba state, ZIKV infection was diagnosed in six children born from mothers apparently infected with ZIKV during pregnancy. All of the children have head circumference below 10 percentile with cerebellar involvement in 2 cases and brain calcifications in 3 cases with one case of and three with brain calcifications. One neonate had severe arthrogryposis[17]. During delivery, ZIKV RNA was detected in the chorionic villous tissue of the placenta, the fetal brain and liver; and the maternal brain, eyes, spleen and liver. Arrested fetal brain growth and viral neuroinvasion are consistent with the congenital ZIKV syndrome seen in humans. The virus is found to culminate efficient infection in human cortical neural progenitor cells becoming the cause of stunted neuronal growth[18]. Head Computed Tomography (CT) of 23 infants having congenital microcephaly, in age between 3 days to 5 month, revealed calcification mainly in frontal lobe (in 69-78% of the infants) and the parietal lobe (in 83-87%)[19].

## STATISTICS OF ZIKV INFECTION AFFECTING FETUS

The ZIKV infections in French Polynesia after 2013-2014 outbreak, 8 cases of microcephaly were identified[20]. Serological and statistical analysis with mathematical modeling revealed that only 1% of the fetuses and neonates are born with microcephaly to the ZIKV infected mothers having infection during first trimester. This percentage is about 50 times higher than expected baseline value; however the results are based on small sample size, wide confidence intervals and other adverse effects on brain other than microcephaly were not been assessed[21]. Fetuses and infants with congenital Zika virus infection have shown some typical morphological features including intracranial calcifications, redundant scalp skin, arthrogryposis and clubfoot along with microcephaly.

## CONGENITAL ZIKV INFECTION COMPARISON WITH OTHER CONGENITAL INFECTIONS

Other well established congenital infections include toxoplasmosis, rubella, cytomegalovirus (CMV), herpes, syphilis and Parvovirus B19 (TORCH)[22]. Brain calcification is common as in toxoplasmosis and citomegalovirus infection with much severe hearing abnormalities. Ocular deformities are common to all Rubella, Herpes and CMV are common with ZIKV in hearing defects. Microcephaly is also common in all except Parvovirus B19[23]. The common molecular detection method for ZIKV is Reverse-Transcription Polymerase Chain Reaction (RT-PCR) and/or quantitative Real-Time PCR (qRT-PCR) and among the large numbers of microcephaly (4180 notified cases) in very few infants (6 tested positive) ZIKV has been detected. In the case of congenital Zika, no long lasting infection as in case of rubella and CMV congenital infections or undetectable low levels of viral loads are the possibly causes behind it[24]. Three children with microcephaly showed gross macular pigment mottling and foveal reflex loss[25].

## THERAPIES WORKING IN THE WOMB

The ZIKV infects the fetus developing in the womb, hence the therapies also be targeted there; which may work during the period of pregnancy and have proven record of safety in pregnant women as well as fetus. The drugs to be used must be able to cross the placenta in order to reach to developing fetus; brain and neural cells being the main target, the ability to cross blood brain barrier is desirable character of the therapeutics. Following are some drugs, which have been enlisted by FDA, which are safe for women during pregnancy with no apparent adverse effects and have anti-ZIKV activity (Table 1).

**Chloroquine:** Chloroquine has demonstrated to have antiviral activity against a large spectrum of viruses[26]. It has been given in case of malaria (400 mg week$^{-1}$) and no increment in birth defects was observed[27]. The ZIKV is known to cross blood brain barrier and infect central nervous system[28,29]. Chloroquine protects human Brain Microvascular Endothelial Cells (hBMEC), from ZIKA infection[30]. Also the concentration of hydroxychloroquine in the brain is 4-30 times higher than in the plasma[31] and chloroquine showed antiviral activity in mice at the maximum tolerated dose[32], so local inhibition of ZIKV infection is predicted. It inhibits the endosome acidification, thereby preventing fusion of the envelope protein of flaviviruses with the endosomal membrane. Optimal uptake of the drug is between the range of 10-20 μM L$^{-1}$ and such steady and safe plasma concentrations might be sufficient to maintain the endosomal pH at neutral in order to prevent viral replication of those depending upon acidic pH for infectivity. A 16 μM L$^{-1}$ transient or steady state whole blood concentration of chloroquine, has no adverse cardiovascular

Table 1: Repurposed drugs for ZIKV inhibitory action in pregnant women

| Drugs | Drug usage | Known modus operandi | FDA status/ fetal safety* | References |
|---|---|---|---|---|
| Chloroquine | Antimalarial/antiviral | Inhibits the endosome acidification | C | Savarino and Shytaj[26], Stins *et al.*[30] and Akpovwa[33] |
| Amodiaquine | Antimalarial drug | Amodiaquine-heme complex is toxic to parasitic membrane | C | Adjei *et al.*[34] and Malone *et al.*[63] |
| Sofosbuvir | Inhibit hepatitis C NS5Bprotein | Inhibit ZIKV polymerase in a dose dependent manner Protect human neuroepithelial stem cells and brain organoids | B | Onorati *et al.*[37] |
| Azithromycin | Antibiotic | Inhibit the ZIKV replication in glial cell lines and human astrocytes | B | Workowski and Bolan[39], Lin *et al.*[40] and Retallack *et al.*[43] |
| Niclosamide | Broad antiviral | Inhibit virus propagation by neutralizing the endosomal pH | B | Xu *et al.*[44] |
| Albendazole/Mebendazole | Anti-helminths | Inhibit microtubules polymerization, Decreases absorption of glucose by intestinal parasite | C | Ndibazza *et al.*[45] and Acs *et al.*[48] |
| Palonosetron | Antiemetic | Inhibits viral entry, RNA synthesis and viral egress of ZIKV | B | Pascoalino *et al.*[49] and Barrows *et al.*[50] |
| Quinacrine hydrochloride | Antimalarial | Histamine N-methyltransferase inhibitor | C | Balasubramanian *et al.*[64] |
| Mefloquine | Antimalarial drug | Affect feeding capacity of parasite | B | Balasubramanian *et al.*[64] and McDonagh *et al.*[65] |
| Daptomycin B | Lipopeptide antibiotic for gram positive bacterium | Oligomerize on bacterial membrane and form pore | B | Barrows *et al.*[50] |
| Auranofin | Antirheumatic agent | Inhibitor of thioredoxin reductase | C | |
| Clofazimine | Anti-bacterial/leprosy treatment | Bind to guanine bases of DNA and prevent it acting as template for replication | C | |
| Deferasirox | Chelation of intracellular iron; renal failure and cytopenias | Orally active ion chelation | C | |
| Methoxsalen | Used for psoriasis | Form photo adducts and inhibit DNA synthesis, cell division and epidermal turnover | C | |
| Micafungin | Echinocandin antifungal drug | Inhibit enzyme essential for fungal cell-wall synthesis | C | |
| Sertraline-HCl | Antidepressant | Anti-flavivirus | C | |
| Fingolimod | For treating multiple sclerosis | Binds to S1P receptors and acts as a functional antagonist | C | |
| Ivermectin | Treatment of certain worm infections | Anti-flavivirus | C | |
| Digoxin | Antiarrhythmic | $Na^+$-$K^+$ pump inhibitor | C | |
| Seliciclib | Anticancer | Cyclin-Dependent Kinase (CDK) inhibition and cause apoptosis | C | Xu *et al.*[44] |

*On the basis of studies, the drugs has been assigned risk categorizes (A, B, C, D and X) by FDA; where A and B category pose least risk to pregnant women and fetus, Risk category B drugs: Animal studies represent no risk on fetus but no controlled study carried out on pregnant women, Risk category C drugs: Some teratogenic effects have been seen on fetus with no control studies on pregnant women but potential benefits may outweigh the risk

impact and is sufficient to prevent viral replication along with overproduction of immune-modulators linked with few viral infections. This concentration must be maintained in patients body through intravenous infusion till the viremia in the body reached to undetectable levels[33].

**Amodiaquine:** It is again an antimalarial drug and through autophagy inhibition, it posses antiviral activity. The drug is generally safe to be used during pregnancy and have no side effects; however, there are reports on amodiaquine-associated cardiovascular effects[34].

**Sofosbuvir:** It is recommended as FDA approved class B drug[35,36], which has been used by a limited number of pregnant women and no increased incidences of malformation or harmful effects on human fetus has been observed. Sofosbuvir was predicted to be fit between the palm and fingers region of ZIKV RNA polymerase using molecular modeling and inhibits ZIKV polymerase in a dose dependent manner. Human neuroepithelial stem cells and brain organoids can be protected by sofosbuvir[37],it also induce increased rate of A-to-G mutations like ribavirin an another ribonucleoside analog[38].

**Macrolide antibiotic azithromycin:** Azithromycin (AZ) is generally considered as safe for use in pregnant women with sexually transmitted infections or respiratory infections[39]. No adverse effects have been on fetal health[40]. Oral administration lead to reach concentrations to approximately 2.8 μM in the placenta, from where it is rapidly transported to amniotic fluid and umbilical cord plasma[41]. It tends to accumulate in fetus and adult brain in a concentration ranging from 4 to 21 μM[42]. At this concentration AZ inhibit the ZIKV replication[43]. In the experiment of Retallack *et al.*[43] using primary human tissue, high susceptibility of radial glia and astrocytes than neurons was demonstrated. Azithromycin, a common and pregnancy safe antibiotic is shown to reduce ZIKV replication in glial cell lines and human astrocytes[43].

**Niclosamide:** It is a FDA approved category B drug, indicating no risk to foetuses. As per WHO recommendations, niclosamide is safe to use during pregnancy as it is not mutagenic or teratogenic and posses no embryotoxicity. It's a broad antiviral and inhibit virus propagation by neutralizing the endosomal pH and attenuating the viral membrane fusion, a crucial step of viral entry inside the cell[44].

**Anti-helminths (Albendazole/mebendazole):** A randomized controlled trial in Entebbe, Uganda revealed that albendazole use during pregnancy had no effect on maternal anemia, birth weight, perinatal mortality, or congenital anomalies[45]. However a cross study conducted in Sri Lanka, when mebendazole, was given to the pregnant women in 2nd trimester, it was not found associated with significant increase in major congenital defects but its use during first trimester should be avoided[46]. With that the absorption rate of mebendazole is less than albendazole, teratogenic effects of mebendazole are less in human as evidenced by a study conducted on 192 pregnant women[47]. It has been found non fetotoxic in a small study with mean larger gestation period and higher birth weight of fetus[48].

**Palonosetron:** Palonosetron is a compound with antiemetic properties and is being used to treat chemotherapy-induced nausea and vomiting. If potentially inhibits viral entry, RNA synthesis and viral egress of ZIKV from the host cell. It can be administered orally or intravenous route with higher (97%) bioavailability and long half life (40 h)[49] and experiments of Barrows *et al.*[50] also supports the same phenomenon. It's a FDA class B drug and in pregnant mice and rabbits, treated with 921 and 1841 times respectively the human dose, no evidence of harm to fetus or fertility was observed.

**Use of convalescent serum:** The ZIKV neutralization has been documented by human convalescent serum by Plaque Reduction Neutralization Test (PRNT)[51]. In ICR mice fetus, reduction in infected brain cells was documented when the pregnant mice was treated with convalescent serum intra-peritoneally. Till the time no effective measure for ZIKV treatment is obtained, the convalescent serum might be used to treat pregnant women. Wang *et al.*[52] demonstrated protection from microcephaly by in pregnant mice model by reducing caspase 3 activated cells using convalescent serum. The serum is able to reverse cortical plate and Ventricular Zone (VZ)/subventricular zone thinning. The antibodies in the serum are able to cross both the placenta and blood brain barrier so as to prove its utility to treat infected pregnant women.

Few more drugs, which may be readily chosen from the FDA approved list, are given in Table 1.

Besides these, continuous research is going on to identify more effective therapeutics and drugs against the dreadful ZIKV as it has affected the human health worldwide. New avenues comprising of emerging and upcoming therapeutic strategies may be explored to encounter this infectious pathogen with futuristic perspectives. These include cytokines, RNA interference, RNA polymerase inhibitors, neutralizing antibodies, egg yolk antibodies (IgY), drugs designed to target the Fc receptor interactions, Toll-Like Receptors (TLRs), heat shock proteins, nano-medicines and nanotechnology based drugs[53-59]. Besides these several other alternatives viz. employing the use of probiotics, herbal formulations and several plant metabolites etc. are also to be exploited since these are known to possess antiviral action[60-62].

## CONCLUSION AND FUTURE PERSPECTIVE

The ZIKV, a member of Flaviviridae family, causes brain injury to the fetus. Microcephaly is a rare pediatric condition, implicated with severe consequences on fetus and his or her parent's life. Detailed case study analysis of affected fetus and the mechanism by which virus cause damage to the tissues and the target of fetus might be helpful in future to prevent the detrimental effects of the virus. As the infection to fetus occurs within the womb, the therapies must be started during pregnancy stage only. There is an urgent need of searching new efficient drugs for treatment with proven safety records. The search of a new drug usually takes decades to develop, so drug repurposing is the best option till that time and in fact many of the drugs previously used for treating another ailment including chloroquine, amodiaquine, sofosbuvir,

azithromycin, niclosamide, albendazole/mebendazole and palonosetron. In future more drugs might be evaluated for searching more efficacious drugs against ZIKV.

## SIGNIFICANCE STATEMENT

1. Present review encompasses the information regarding the Zika virus infection in fetal stage resulting in severe brain damage and microcephaly evidenced by reduced head circumference. Other congenital infections, resulting in congenital zika virus infection like symptoms also have been discussed
2. Present review discuss about the FDA approved drugs, which have been tested against Zika and are considered as pregnancy safe drug

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