# Fetal repercussions of Zika virus infection during pregnancy
# Repercussões fetais da infeção por Zika durante a gravidez

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## Abstract

Recently, Zika virus infection has been rapidly spreading, rising the cases of fetal abnormalities. A review was performed from February 2016 to January 2017, selecting articles that evaluated the fetal repercussions of maternal infection, considering fetal autopsies, clinical examinations and imagiology. The most frequent abnormalities were in the central nervous system, namely microcephaly, intracranial calcifications and ventriculomegaly. Death and fetal growth restriction were also reported. Anomalies in other systems were found to a lesser extent. Despite enough evidence proving this causality, it is important to document all these changes, allowing the comprehension of the virus' full width.

**Keywords:** Zika virus; Zika virus infection; Pregnancy; Microcephaly; Emerging infectious diseases.

## INTRODUCTION

ZIKV belongs to the *Flaviviridae* family, which includes several other clinically significant viruses, such as dengue, West Nile and yellow fever viruses[1]. It is transmitted to humans through the bite of the infected mosquitoes, being the *Aedes* genus the most frequent vector[2].

Structurally, ZIKV is a positive-sense single-stranded RNA virus which contains 10,794 nucleotides encoding 3,419 amino acids[3]. This virus consists of two non-coding regions that flank an open reading frame which encodes the capsid protein, envelope glycoprotein, the membrane or precursor membrane protein, and other seven non-structural proteins involved in replication, assembly and suppression of the host's natural immunological response[4].

Phylogenetic studies reveal the existence of two main lineages, African and Asian, being that the latter originated in the course of the virus's migration from East Africa to Southeast Asia; from here, the virus spread to the Pacific Islands and French Polynesia, among other countries, all the way to the Americas[5] (Silva A.)

The virus was first isolated in 1947 from a rhesus monkey in the Zika forest in Uganda during the research into the epidemiology of yellow fever and was isolated from *Aedes africanus* mosquitoes the following year[6]. Later on, in 1952, the virus was isolated from humans also in Uganda and in Nigeria[7]. In the same decade, the species *Aedes aegypti* was identified as the most common vector for ZIKV transmission[8].

Ever since its discovery, some cases of ZIKV infection in humans in Africa, India and Southeast Asia have been reported, although they were isolated and separated in time. The first noteworthy outbreak was reported in 2007 on Yap Island in the Federated States of Micronesia[9]. In this outbreak, it was estimated that around 73% of the island's population was infected with ZIKV and some of the symptoms included rash, fever, arthralgia and conjunctivitis; however, there were no hospitalizations or deaths[9]. Another striking outbreak took place in French Polynesia between October 2013 and April 2014, this time infecting 66% of the population[10]. Due to the contemporaneous increase of Guillain-Barré syndrome during that outbreak, retrospective studies were made and successfully proved the association between ZIKV infection and Guillain-Barré syndrome[11]. These were the first documented neurologic sequelae caused by ZIKV infection. Subsequently, in 2014, the ZIKV disseminated through some of

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the South Pacific islands, including Easter Island, the Cook Islands and New Caledonia[12]. The most recent and significant outbreak was in northeastern Brazil in late 2014, which rapidly and surprisingly spread throughout the whole country; alongside with it, cases of Guillain-Barré syndrome and microcephaly significantly increased as well.[13] Since then, ZIKV quickly disseminated throughout Central and South America.

Considering this fast dissemination and its apparent consequences, on February 1st of 2016, the WHO declared ZIKV infection a Public Health Emergency of International Concern[14]. As of January 2017, this problem continues to evolve, bringing uncertainty about the repercussions of this global threat.

Although the main cause for ZIKV infection is a bite from an infected mosquito, some cases of sexual and perinatal transmission have been reported[10]. In adults, this infection is mostly asymptomatic (80%)[15]. When symptoms occur, they are mild and non-specific, and include: pruritic maculopapular rash, mild fever, arthralgia, myalgia, headache, non-purulent conjunctivitis and retro-orbital pain. Usually there is a full recovery within 1-2 weeks of onset[10,15]. Deaths are not common in this infection and are mostly limited to immunocompromised patients or in those who already have other comorbidities[16,17].

The prevalence of Zika virus (ZIKV) has been recently increasing. There have been outbreaks since 2007, the most recent and significant one being in Brazil at the end of 2014. Since then, ZIKV has spread to Central and South America, and as of January 2017 there were 51 countries with active transmission[18]. This expansion of the virus' transmission has led to a large increase of cases not only of microcephaly, but also other abnormalities within and outside the central nervous system (CNS). The objective of this review of the literature is to describe all documented fetal structural abnormalities associated with ZIKV published to date.

## METHODS

A review of the literature was carried out from February 2016 (when the WHO declared the ZIKV infection a Public Health Emergency) until January 2017, using the MEDLINE database. For the initial research on the virus, we had no restriction on the publication year, and looked for articles with the keywords "Zika virus structure", "Zika virus pathogenesis" and "Zika virus outbreaks". The focus of the investigation were the fetal repercussions of the ZIKV infection; therefore, we looked for articles whose evaluations took into account fetal autopsies, clinical examinations and imaging techniques during pregnancy and/or in the live births. In the beginning of the research, there was very little information on this topic, since it was arising at the moment. However, during its course, more and more information was available. Consequently, we restricted it to some keywords such as "Zika virus and pregnancy", "Zika virus and microcephaly" or "fetal repercussions of Zika virus". We excluded every article that did not focus on the fetal repercussions of the ZIKV infection, such as the ones about consequences of this infection in the pregnant woman, or those based merely on suspicions, without clinical examinations, imaging techniques or autopsies. The case review articles were all published from 2016 onwards.

## CASE REVIEWS OF FETAL INFECTION

Between October 2015 and May 2016, 7,534 suspected cases of microcephaly in Brazil have been reported, 1,384 of which were confirmed; of these, 207 had in fact ZIKV infection, which was laboratory-confirmed[19]. Of all the 7,534 suspected cases of microcephaly, there were 273 intrauterine or neonatal deaths, 59 of which were actually confirmed to have microcephaly or other CNS malformation[19].

Colombia is the second most affected country by the ZIKV infection in the American continent, and as of October 2016, there were 95,898 suspected and 8,826 confirmed cases of ZIKV infection; out of the reported cases of pregnant women with confirmed and suspected ZIKV infection, 47 cases of microcephaly were associated with ZIKV infection, 213 cases were excluded and 342 cases are under investigation[20]. There was an increase in the incidence of congenital malformations in September and a tendency to increase even more in the subsequent months.

During the period of the research, 13 articles reporting fetal anomalies due to ZIKV were found. The anomalies found in several organ systems are summarized in Table I.

The first ever confirmed case of this association was reported in February 2016; a 25 year old Slovenian woman was infected with ZIKV in Brazil at the end of the first trimester of pregnancy[21]. The patient had symptomatic disease during the 13th week of gestation

**TABLE I. FETAL CHANGES ASSOCIATED WITH ZIKA VIRUS INFECTION**

| Organ System | Anomalies | Reference |
|---|---|---|
| Central nervous | Microcephaly | 21, 22, 24-29, 31-33 |
| | Ventriculomegaly | 21-24, 26-28 |
| | Cerebellar hypoplasia | 21, 22, 27, 28 |
| | Intracranial calcifications | 21, 24-28 |
| | Cerebral atrophy | 23, 24, 26, 27 |
| | Agyria | 21, 24, 28 |
| | Hydrocephaly | 21, 28 |
| | Hydranencephaly | 25, 27 |
| | Parenchymal brain hemorrhages | 26, 27 |
| | Hypertonicity, clonus, hyperreflexia, abnormal movements, spasticity and seizures | 26, 28 |
| | Degeneration of the spinal cord and brainstem | 21 |
| Musculoskeletal | Arthrogryposis, clubfoot, congenital hip dysplasia | 25-28 |
| Visual | Pigmentary maculopathy and chorioretinal atrophy | 27-30 |
| | Optic nerve atrophy/pallor | 27, 28, 30 |
| | Coloboma | 27, 30 |
| | Intraocular calcifications | 27 |
| | Microphtalmia/anophtalmia | 27 |
| | Cataract | 27 |
| Auditory | Hearing deficits | 26, 27, 31 |
| Others | Fetal growth restriction | 21, 25, 26, 31, 33 |
| | Hydrops fetalis | 25 |
| | Hydrothorax | 25 |
| | Fetal demise | 25-27, 31-33 |

and the pregnancy carried on without complications until the 29th week, when she noticed reduced fetal movements. The ultrasonography at 32 weeks showed fetal growth restriction, microcephaly, ventriculomegaly, a diminished trancerebellar diameter and several calcifications spread throughout the brain and the placenta[21]. The pregnancy was terminated and the autopsy revealed microcephaly, open sylvian fissures, agyria, internal hydrocephaly of the lateral ventricles and calcifications in the cortex and subcortical white matter in the frontal, occipital and parietal lobes[21]. Nonetheless, the cytoarchitecture of the fetal brain was preserved. There was also diffuse astrogliosis with focal astrocytic outburst into the subarachnoid space. The brain stem and spinal cord suffered from degeneration in the long descending tracts, predominantly in the lateral corticospinal tract. $6.5x10^7$ ZIKV RNA copies per milligram of tissue were identified exclusively in the brain, with no further lesions in any other organ, which demonstrates this virus' neurotropism[21]. Some of these alterations in the brain were also reported in the same month by ultrasonography at 21 and 22 weeks of gestation in women who had ZIKV infection symptoms[22]. About one month later, a case of a confirmed infection of a Finnish woman in Central America during the 11th week of pregnancy was described; at 20 weeks of gestation, the fetal head circumference had decreased from the 47th to the 24th percentile and ultrasonography and magnetic resonance imaging showed cerebral atrophy and ventriculomegaly[23]. One month after this last case, another one was described in Brazil, and it exposed some of the same brain anomalies, such as microcephaly, ventriculomegaly, intracranial calcifications, cerebral atrophy and agyria[24].

In Salvador, Brazil, a case of a 20 year old pregnant woman was reported. The ultrasound at 26 weeks detected fetal growth restriction, microcephaly, hydranencephaly, brain calcifications, hydrothorax, ascites and subcutaneous edema[25]. Once again, the virus was only identified in the CNS (cerebral cortex, medulla oblongata and cerebrospinal fluid) and placenta. An induced labour was performed at 32 weeks due to fetal

demise and the stillbirth showed signs of arthrogryposis[25].

A case-control study from Rio de Janeiro, Brazil, enrolled 345 women who described acute febrile illness with a rash during pregnancy and were followed to determine pregnancy and infants outcomes, comparing cases positive for ZIKV infection during pregnancy (53%) to those who were negative[26]. Some of the described abnormalities included cerebral calcifications, cerebral atrophy, ventricular augmentation and hypoplasia of cerebral structures. These adverse outcomes happened in fetuses of women who were infected between 6 and 39 weeks of gestation, except the calcifications, which were only seen in infants whose mothers were infected at a maximum of 34 weeks[26]. Cerebral parenchyma hemorrhages were also detected, and in one case the mother had been infected at 39 weeks. Out of the live births, 42% had abnormalities on imaging or examination, and out of those, 63% had grossly abnormal neurological examinations, showing hypertonicity, clonus, hyperreflexia, spasticity and seizures[26]. 9% of the fetuses exposed to ZIKV and 5.3% of fetuses in the control group were small for gestational age (p=0.06). Microcephaly was detected in 2 infants exposed to ZIKV (1.7%), both infected in the first trimester of pregnancy, and it was not displayed in any of the infants of the control group[26]. This study confirms that ZIKV infection causes severe and recurrent problems in the CNS development in utero, as well as in general fetal development, being that in this cohort, such problems affected 46% of fetuses and 42% of live-born infants[26].

Although the most frequent and best studied alterations were those in the CNS, an increasing number of studies has been arising, suggesting the impact of the ZIKV in other systems. The involvement of the musculoskeletal system was documented in several cases. In the Salvador case, the fetal autopsy showed signs of arthrogryposis[25]. In the case-control study in Rio, foveas in the elbows and knees as a result of limb contractures in utero were reported[26]. Another study also described the presence of musculoskeletal anomalies secondary to CNS dysfunction, such as arthrogryposis, clubfoot and congenital hip dysplasia[27]. The latter was reported in a case in Pernambuco as well[28].

Reports of ocular abnormalities have also been progressively increasing. Chorioretinal anomalies (involving or not the macula) were the most prevalent ones, suggesting the children could have reduced vision. The ophthalmological exams revealed alterations in the macula, such as chorioretinal atrophy, pigment stippling and focal pigment mottling of the retina[26-30]. Optic nerve atrophy was detected in three studies through pallor in the ocular assessment[27,28,30]. Other defects consisted in coloboma, intraocular calcifications, microphtalmia, anophtalmia and cataracts[27,30]. One of these studies detected ocular abnormalities in 10 of 29 patients with microcephaly, whose mothers had had ZIKV infection during pregnancy (34.5%)[30]. However, a causal link has not been established for all the ocular anomalies. Hearing deficits were also reported[26,27,31].

Fetal demise appears to be a consistent bad outcome[25-27,31-33]. The Salvador case described above suggested there could be a link between ZIKV infection and hydrops fetalis and fetal demise, although the mechanism remains unknown[25].

Likewise, fetal growth restriction has also been documented as a prevalent result in the event of maternal ZIKV infection during pregnancy.[21,26,31,33].

## CONCLUSION

There has been sufficient evidence to establish a causal relationship between the ZIKV infection during pregnancy and neonatal structural anomalies[21,34]. Besides this fact, there has not been any other explanation for the defects detected in the studies mentioned above and there is also documented proof in tissue biopsies of congenital ZIKV infection; along with that, other viruses that could have the same repercussions have been excluded in the majority of studies. Despite extensive research, there is no alternative hypothesis for the microcephaly and all the other brain defects observed.

The timeframe in order for malformations to occur is throughout the pregnancy; although only the fetuses whose mothers were infected in the first trimester had malformations related to embryogenesis, abnormalities in the CNS were detected in fetuses infected until 39 weeks of gestation[26].

Even though the most frequent anomalies were those involving the CNS, other systems have also been affected. Microcephaly has been the most discussed fetal malformation when it comes to ZIKV infection. This may be, in part, because this virus is more active in developing countries, meaning more precarious diagnostic methods and a delayed search for medical assistance. Therefore, it could be the most common

abnormality simply because it is easily perceived in the clinical exam, while other defects may go unnoticed. There have been other prevalent findings in the CNS, such as ventriculomegaly, cerebral and cerebellar hypoplasia and intracranial calcifications, among others. In nearly all the studies, fetal growth restriction and fetal demise were documented. Although in a smaller proportion, anomalies found in other systems have proven to be more prevalent and should also be a major source of concern. These consist of hearing deficits, hydrothorax and hydrops fetalis. Nevertheless, the most frequent alterations outside the CNS were optical.

After establishing these causal relationships, other concerns take place. First of all, it is urgent to determine the full extension of the malformations; if there are similarities between ZIKV and other teratogens, there could be a phenotype expansion and more defects could exist besides the ones we know of at the moment. In second place, it is important to clear the differences in the birth defects according to the different periods of time in pregnancy during which the mother was infected. Finally, determining factors that may alter the outcome of an already adverse pregnancy is also relevant, such as severity of the infection, coinfection with another virus, previous contact with another flavivirus causing an existing immune response, and also the genetic background of the mother and the fetus[34].

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