ZIKA VIRUS IN PREGNANT WOMEN: EPIDEMIOLOGICAL ANALYSIS FROM JANUARY TO MAY 2016 AT IPATINGA, MINAS GERAIS, BRAZIL

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ABSTRACT

The Zika fever is the most recent arbovirus in Brazil, declared in November 2015 by the Ministry of Health (MOH) as a public health emergency. Since then there has been transmission of ZIKA virus (ZIKAV) in several Brazilian states. The maternal-fetal transmission of ZIKAV can be demonstrated throughout pregnancy, there is still no complete knowledge about the clinical manifestations of infection caused by ZIKAV, data on pregnant women infected by ZIKAV are limited. This is a quantitative and qualitative exploratory study, through desk research and literature. The public used in the study were 32 pregnant women confirmed with ZIKAV infection in the period from January to May 2016 in the city of Ipatinga, Minas Gerais. Data were analyzed using the SPSS program. The ZIKAV infection during pregnancy is considered one of the causes of microcephaly, and congenital anomalies. The diagnosing by ZIKAV infection is performed by RT-PCR technique, available free exam for pregnant woman's through the Unified Health System (UHS). In the study period there were no cases of microcephaly related to ZIKAV infection despite the high number of confirmed cases in Ipatinga city. The most effective way of prevention is the combating *Aedes* mosquito outbreaks. The aim was to discuss the main features of ZIKAV, knowing the complications related to infection during pregnancy, present epidemiological data of pregnant women who were infected with the virus during pregnancy and which were notified and confirmed with the ZIKAV by UHS in the city of Ipatinga, Minas Gerais in the period of January to May 2016, and describes the measures to prevent and control vector.

KEYWORDS: Zika, gestation, transmission, microcephaly, epidemiology.

1. INTRODUCTION

The Zika fever is the latest arbovirus in Brazil. It is a disease caused by virus Zika (ZIKAV) originating from Africa, was first isolated in 1947 in Zika forest, Uganda from the serum sample from a monkey *Rhesus*[1,2].

The first transmission of ZIKAV on the American continent was identified in Brazil in May 2015. The virus circulation in Brazil's Northeast was confirmed from the viral isolation in suspected cases of Dengue[1,2].

The Ministry of Health declared public health emergency in November 2015; then the World Health Organization has identified the situation as an emergency of international concern in February 2016, encouraging initiatives for research and disease control in Brazil[3].

Ever since there has been transmission of ZIKAV in several Brazilian states, expanding to countries in the Americas and Europe. On February 18, 2016 cases of the disease had been confirmed in more than 32 countries and territories around the world[2,3].

Regions infested by *Aedes aegypti*, the main vectors of the disease, can contribute to the circulation of ZIKAV and other arboviruses simultaneously as dengue (DENV) and Chikungunya (CHIKV)[3].

The aim of this study was to discuss the main features of ZIKAV, knowing the complications related to infection during pregnancy, present epidemiological data of pregnant women who were infected with the virus during pregnancy and which were notified and confirmed by the National Health System (SUS) in the Ipatinga city – Minas Gerais State, Brazil, over the period January to May 2016, and also describes the measures for prevention and control.

2. MATERIAL AND METHODS

This is a quantitative and qualitative exploratory study, through document search and literature review. The study of the universe is composed of 32 pregnant women reported and confirmed with involvement by Zika virus in the period from January to May 2016 in the

Ipatinga city, Minas Gerais, Brazil. The collection of epidemiological data such as number of reported cases and confirmed cases during the period from January to May 2016 were held in June 2016 in Epidemiological Surveillance sector of Ipatinga and the Ministry of Health website. Data were separated by categories, then most relevant variables were selected through IBM SPSS, using simple statistics. The literature review were made selecting national and international articles available online in full text dated after the year 2013, using the databases Google Scholar, PubMed and SciELO. The keywords used were: Zika virus, pregnant women, microcephaly, mechanism of action, transmission, screening, diagnosis and treatment. an analytical reading and selective was made of the information contained in the sources of interest according to the quality and relevance of the content to the topic in order to achieve the goals in research.

3. LITERATURE REVIEW

Zika virus

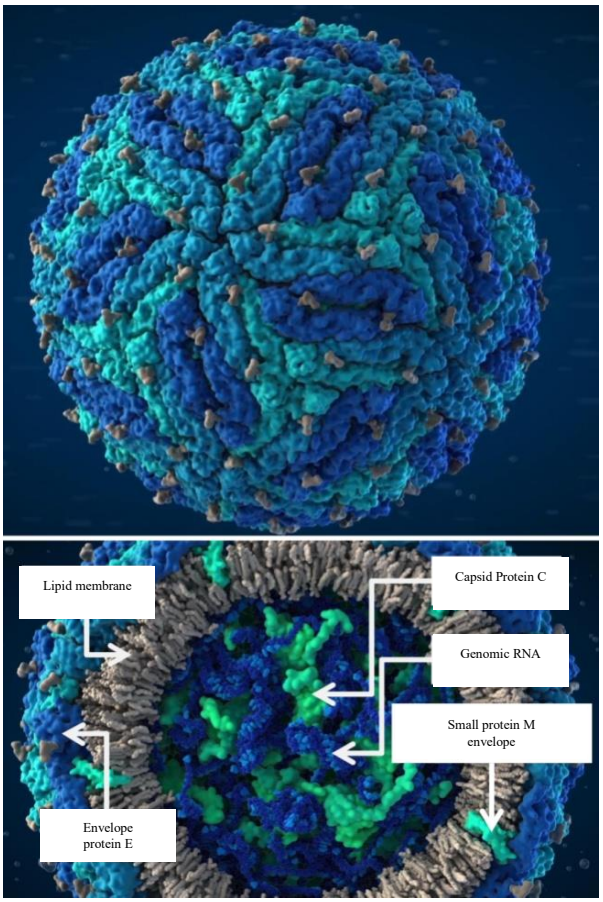

Figure 1. ZIKAV structural model in 3d. **Source:** http://visual-science.com/projects/zika/3d-model/.

The ZIKAV is an emerging arbovirus, belongs to the genus *Flavivírus*, family *Flaviviridae*[1,4]. The ZIKAV is enveloped, it has icosahedral capsid; its genome is composed of single-stranded RNA and positive polarity with approximately 10.8 kilo-size bases. The genome contains a region 5'and 3' untranslated yielding a coding region that synthesizes the structural proteins the capsid (C), pre-membrane/ membrane (prM) and envelope (E) (Figure 1) and 7 non-protein structural (NS1, NS2a, NS2B, NS3, NS4A, NS4B and NS5). These are proteins that coordinate the viral replication and inhibit the response of the immune system[5,6].

To replicate, the ZIKAV binds to the cell membrane, the cell releases its RNA which happens to be processed by the cellular machinery for the production of viral proteins and new viruses (Figure 2)[5,6].

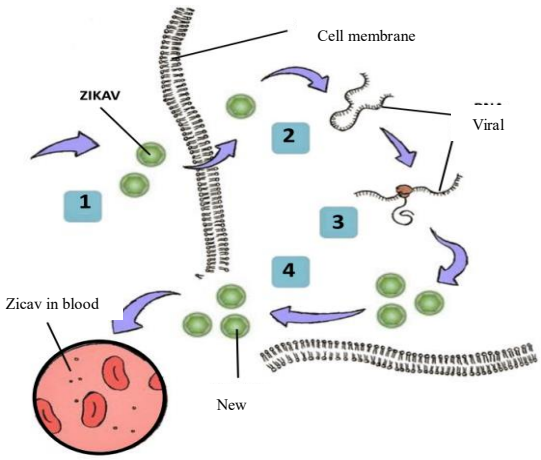

Figure 2. Simplified scheme of ZIKAV replication. (1) ZIKAV enters the bloodstream; (2) Within the cell, the virus releases its RNA, (3) that is processed by cellular machinery (4) generating new ZIKAV that disrupt the cell, being free in the circulation. **Source:** http://www.nano-macro.com/2015/05/zika.html.

Transmission

The ZIKAV is predominantly transmitted by blood-sucking mosquito bite of Aedes genus and may be of the species *Aedes aegypti* or *Aedes albopictus* (Figure 3)[1,4,7].

There are other forms of transmission and may be of mother to child (intrauterine); blood transfusions and through sexual intercourse. The ZIKAV has been detected in semen, blood, urine, amniotic fluid, saliva and bodily fluids found in the brain and spinal cord[8,9].

During the first weeks of ZIKAV infection, the virus can be isolated from the bloodstream. When the mosquito bites a human infected with viremia during this period, it acquires the virus can transmit to others[10].

The Aedes mosquitoes that carry the ZIKAV feed on human blood preferably, and can sting multiple people in a single meal. They live in close proximity to human

habitations. The bites occur mainly during the day, and usually lay eggs both in and close to places with standing water; They can be found in most of the Americas[10,11].

The maternal-fetal transmission of ZIKAV was demonstrated throughout pregnancy. The full spectrum of results that may be associated with congenital infection is unknown[12].

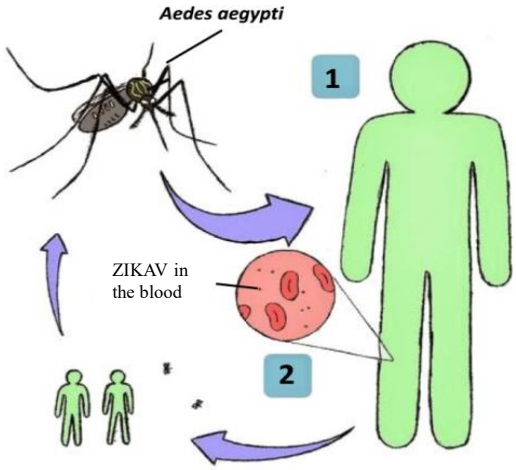

Figure 3. Simplified scheme of transmission ZIKAV by *Aedes aegypti*. (1) The *Aedes aegypti* mosquito bites an infected person and acquires the virus; (2) transmit the virus through bites another person. **Source:** http://www.nano-macro.com/2015/05/zika.html.

It is believed that the vertical transmission of ZIKAV occurs similarly to other TORCHS (transmitted infections fetus). The layer of syncytiotrophoblast cells (SYN) isolated from post-partum placenta showed extensive resistance to viral action, it seems likely that the fetus viruses go through pathways that do not involve replication in this cell layer SYN[13].

As suggested by a recent study on the ZIKAV held in placental cells in the first and second trimester of pregnancy, the extravillous trophoblast (TEV) can be an entry portal for microorganisms, because it enables them to overcome the SYN barrier. However, it is unclear how pathogens reach these cells. As TEV are hidden in the decidua basalis, possibly, these cells are exposed to maternal blood and/ or infected immune cells during the vascularization[12,13].

Although SYNs isolated from postpartum placenta and SYNs exposed to the virus from the first quarter to be resistant to infection ZIKAV, it is possible that the ZIKAV to replicate in the early stages of pregnancy, or has other placental cells as a target. The ZIKAV RNA has been detected in placenta, fetal microcephaly[10,13].

The infection ZIKAV has an incubation period of three to twelve days[14].

Zika virus during pregnancy

About the clinical manifestations of infection caused by ZIKAV, there is still no complete knowledge. It can be considered that the infection is benign, but in Brazil have been registered many cases of Guillain-Barré Syndrome (GBS) days after development of clinical infection[1].

The data on pregnant women infected ZIKAV are limited. There is no evidence to suggest that pregnant women are more susceptible to infection, or are more severely affected[12].

Pregnant women can be infected ZIKAV in any trimester of pregnancy, and the reported symptoms during pregnancy are similar to non-pregnant individuals. May have mild fever (or absence of fever), rash, arthralgia (joint pain), itching in the body and conjunctivitis. The disease is self-limited and lasts up to a week. Severe cases are unusual[12,14,15,16].

The ZIKAV infection during pregnancy (Figure 5) is considered one of the causes of microcephaly, congenital defect wherein the head and the baby's brain are lower than expected in comparison with babies of the same age and sex[17].

In addition to microcephaly, they were found other problems in fetuses infected ZIKAV before birth, such as eye defects, hearing loss and impaired growth [12,17].

There are reports that during pregnancy can occur placental insufficiency, intrauterine growth restriction, cerebellar atrophy, ventricular dilatation and intracranial calcifications. Congenital anomalies induced ZIKAV as neurological and eye disorders may present even without microcephaly[12,13,17].

Based on the available evidence it is believed that non-pregnant women who has infected ZIKAV, is not at risk of birth defects in future pregnancies[17].

Scientists are collecting data to better understand the extensions and the impact of infection ZIKAV in pregnant women in order to clarify potential health problems that can cause infection[12,17].

Diagnosis

The diagnosis of infection ZIKAV can be performed by clinical examination; serology, through the identification of IgG and IgM antibodies; addition to the RT-PCR technique of molecular biology. Currently, only the RT-PCR technique is available[14,18].

The RT-PCR is a method used to identify the virus in early infection stage. Amplification of the genetic material (RNA) virus from patient samples allows to check the presence or absence of the individual ZIKAV[12,14,18].

It is necessary to perform a differential diagnosis of people infected with dengue virus due to similarities of symptoms, in order to establish appropriate measures for each case[14,18].

Flowchart diagnosis by the Unified Health System in Ipatinga, MG

The care of pregnant women with suspected infection ZIKAV the Unified Health System (SUS) begins with the

attendance of pregnant women to the Unit Basic Health (UBS) nearest your home; where health professionals will follow to diagnostic and monitoring measures[19,20].

Pregnant without rash is referred for prenatal care in primary health care; while pregnant with reporting or rash signs of infection, rash or fever without apparent cause is served by the health team of the unit which will evaluate other infectious disease; performing differential diagnosis for syphilis, HIV, toxoplasmosis, rubella. The rash onset date is noted in the pregnant woman's card, and the suspected case is reported in Zika form. It is filled also a mirror record of medical records, with the pregnant woman's data, which is attached to the notification form and forwarded to the Municipal Epidemiological Surveillance (VIEP)[19,20].

Then the mother is conducted to collect material for viral isolation (blood or urine) in the municipal laboratory. The samples collected are directed to clinical laboratory of Ezequiel Dias Foundation (FUNED). The embodiment of obstetric Ultrasound may be important for the morphological analysis of the fetal skull and displaying internal structures of the brain. If the ultrasound detect morphological or microcephaly change, the pregnant woman is sent to a referral service[20,21].

When the result of viral isolation for ZIKAV is negative, it is necessary to investigate other causes of symptoms through prenatal care in primary care. The positive results for ZIKAV are available by VIEP, and the mother is directed to consult with an infectious disease physician, who may order tests at its discretion; and consultation in prenatal high risk, which will follow up the monitoring of gestational development[20,21].

Before the release of the viral isolation result there is a connection with the team of psychologists, nutritionists, psychiatrists, gynecologists and obstetricians of the "Support Center for Health" (NASF) to support pregnant women awaiting the results, with priority focus in prevention and promotion of physical and mental health[19,20].

4. RESULTS AND DISCUSSION

In the period January-May 2016 were 13,973 reported cases of suspected infection of pregnant women ZIKAV in Brazil, with 5,925 laboratory confirmed cases (42.4%). There were 1,551 confirmed cases for microcephaly and/ or changes in the central nervous system (CNS) suggestive of congenital infection[22].

In Minas Gerais, in the same period, it was reported 877 suspected cases, corresponding to 6.27% of the cases in relation to Brazil. laboratory were confirmed 230 cases (26.23%), corresponding to 3.88% of the cases in relation to Brazil. Of the cases reported in Minas Gerais, 5.25% were discarded because they had negative results for infection ZIKAV and 68.52% were still under investigation. There have been three confirmed cases of microcephaly and/ or changes in the CNS suggestive of congenital infection[22].

According to Table 1 of frequencies you can see that in Minas Gerais most cities had 1 case; 85.4% had number of cases less than or equal to 7. As a city presented many cases greater than 40.

Table 1. Frequency of cases of pregnant women affected by ZIKAV by city in the state of Minas Gerais in the period from January to May 2016.

Number of cases	F	%	% accumulative
1	24	50	50
2	11	22,9	72,9
3	3	6,3	79,2
4	2	4,2	83,3
7	1	2,1	85,4
10	1	2,1	87,5
13	1	2,1	89,6
15	1	2,1	91,7
25	1	2,1	93,8
28	2	4,2	97,9
41	1	2,1	100
Total	48	100	

Source: The authors, 2016.

The municipalities of Minas Gerais State with the highest number of laboratory confirmed cases were Montes Claros (17.83%), Belo Horizonte (12.17%), Sete Lagoas (12.17%) and Ipatinga (10.87%)[20,22].

Physical and environmental characteristics may explain the epidemic observed in the study area. Ipatinga for example, it is located in a region of high average temperatures and humidity, conditions that can contribute to the reproduction of the Aedes mosquito in periods of rain, and consequently favor the transferability not only ZIKAV, but also of the Dengue virus (DENV) and Chikungunya virus (CHIKV)[23].

The standard deviation of Minas Gerais (Table 2) was higher compared to the Ipatinga, this means that the number of cases of pregnant women with confirmed ZIKAV in Ipatinga are closer to the average when compared to Minas Gerais. Analyzing the maximum and minimum value of cases it is noticed that in Ipatinga the number of cases per district varied from 1 to 6 cases, while in Minas Gerais the number of cases per town ranged from 1 to 41 cases.

In Ipatinga, between January and May 2016 were reported 141 cases of pregnant women suspected infection ZIKAV, with laboratory confirmed 32 cases (22.7%) distributed in 13 districts of the municipality, as shown in Figure 1; and there were no confirmed cases of microcephaly related to infection ZIKAV the study period.

Table 2. Statistical data of pregnant women affected by ZIKAV in Ipatinga (in neighborhoods) and Minas Gerais (for cities) in the period January to May 2016.

		Ipatinga	Minas Gerais
N		13	48
Mean		2,46	4,79
Median		2	1,5
Mode		1	1
Standard deviation		1,613	8,558
Interval		5	40
Minimum		1	1
Maximum		6	41
Percentile	25	1	1
	50	2	1,5
	75	4	3

Source: The Authors, 2016.

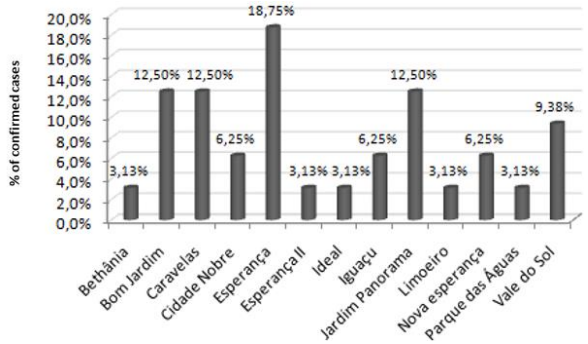

Figure 1. Distribution neighborhood confirmed cases of ZIKAV in pregnant women in Ipatinga, Minas Gerais, in the period from January to May 2016. **Fonte:** The Authors, 2016.

The Esperança neighborhood had a higher number of confirmed pregnant women with laboratory infection ZIKAV, followed by the districts Bom Jardim, Caravelas and Jardim Panorama showed 4 cases each; and Sun Valley, with 3 cases. On Table 3 it was found that 92.3% of the number of cases neighborhoods have less than or equal to 4[20,22].

Table 3. Frequency of cases by pregnant neighborhood affected by ZIKAV in Ipatinga, in the period January-May 2016.

Number of cases	F	%	% accumulative
1	5	38,5	38,5
2	3	23,1	61,5
3	1	7,7	69,2
4	3	23,1	92,3
6	1	7,7	100
Total	13	100	

Source: The Authors, 2016.

The neighborhoods that had the highest number of cases are populated and are in areas with high rainfall, urban infrastructure deficiencies, low socioeconomic conditions, resulting in ideal places for mosquito vector populations of breeding, favoring their survival throughout the year and the rapid transmission of arboviruses[23].

Treatment, prevention and control

Treatment for ZIKAV is symptomatic. There are only treatment for relief of symptoms using analgesics and antipyretics, anti-inflammatories for reducing pain in joints and muscles, eye drops three to six times daily as lubricant, antiallergic drugs. It is important to rest and stand for seven days and eat foods rich in minerals and vitamins, drink plenty of fluids for fast recovery[18].

The bloodsucking mosquitoes of the genus Aedes have shown extraordinary capacity for biological adaptation making it difficult to extinction. The fight against these mosquitoes is highly recommended to avoid the incidence of new cases of infection ZIKAV. The awareness and mobilization of the population are essential to avoid environments conducive to the development of vectors[24].

Measures to eliminate areas where mosquitoes develop is to cover water tanks with screens or covers, preventing access vector; musketeers use in windows and doors; regularly clean the roof gutters, do not leave bottles, gallons, tires and any objects that hold water exposed to rain[24,25].

Individual protection should be carried out through the use of repellent on exposed skin and clothing, particularly in pregnant women. The use of clothes that minimize skin exposure is recommended to provide protection against bites during the day when mosquitoes are most active[24,25].

There is no vaccine against the disease. The most effective form of prevention is to combat the mosquito Aedes outbreaks typical of urban areas of tropical and subtropical climate and use of repellents [18].

It is essential the participation of society together with government agencies in the battle against the mosquito. A vector control program is able to reduce the probability of a viremic human blood serve as power supply for the *Aedes aegypti* and *Aedes albopictus*[25].

5. CONCLUSION

Through the research conducted, it was observed that the Zika fever is an arbovirus that recently arrived in the Americas, especially in areas infested by *Aedes aegypti*, one of the main vectors that can contribute to the circulation of ZIKAV and other arboviral diseases such as dengue and Chikungunya.

The media has widely reported the increasing number of suspected and confirmed cases of pregnant women

affected by ZIKAV in Brazil and the possible complications related to the virus to the fetus, such as microcephaly, eye abnormalities and neurological disorders. Studies are still under development to understand the real impact and the extent of infection, seeking to clarify potential health problems that can cause infection.

It is not known for sure what the means of transmission of ZIKAV, studies point to have isolated the virus in semen, blood, urine, amniotic fluid, saliva, and other bodily fluids. It is believed that the mother-to-child transmission can occur at any gestational period.

The consultation of the pregnant woman to the doctor is very important for the diagnosis, monitoring gestational development and fetal development, as well as guidance for prevention of other diseases.

Due to the high cost to perform the RT-PCR molecular biology, it is necessary to develop more affordable diagnostic methods in order to expand the investigation of cases in the general population; not only in pregnant women and fetuses.

In Brazil, laboratory were confirmed 5,925 cases of pregnant women affected by ZIKAV the study period, occurring 1,551 confirmed cases of microcephaly. In Minas Gerais it was confirmed only 3 cases of microcephaly associated with infection ZIKAV. However, in Ipatinga, despite the high number of confirmed cases of affected pregnant women, there were no cases of microcephaly related ZIKAV the study period, which does not rule out the possibility of the occurrence of cases in the future.

There are no vaccines against the disease, prevention should be held collectively and individually, limiting the spread of mosquito vectors, which are common in urban areas of tropical and subtropical climate, using repellents, covering water tanks, sanitation, do not leave water accumulated in tires, roofs, gutters.

Therefore, efforts are needed to further studies clarify the extent and impact of infection-tion, in order to guide researchers in the development of vaccines and other medicines to contribute to the health of pregnant women, fetuses, and elsewhere, preventing the incidence of new neurological cases of microcephaly and involvements related to ZIKAV.

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