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Short Communication

The role of pregnant women with rash in the Zika virus sentinel surveillance

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Abstract

Introduction: The state of São Paulo has been monitoring cases of microcephaly and pregnant women presenting with acute rash, through CeVeSP. **Methods:** This was a descriptive study focusing on pregnant women with rash and the outcome of their pregnancy, based on the notifications through the CeVeSP. **Results:** During 2016, 2,209 cases of pregnant women with rash were reported and investigated. Of these, 36.6% were confirmed. Of the pregnant women who tested positive for ZIKV, 6.4% did not have a favorable outcome. **Conclusions**: Our results allowed the characterization of pregnant women exposed to ZIKV and the outcome of pregnancy.

Keywords: Pregnant women. Zika virus. Microcephaly.

Zika virus (ZIKV) is a *flavivirus* related to yellow fever, dengue fever, West Nile virus infection and Japanese encephalitis[1]. ZIKV is usually transmitted to humans through the bite of mosquitoes of the genus *Aedes*. Although there are several species of this genus, *Aedes aegypti* is the main urban vector of yellow fever, dengue, chikungunya, and *Zika* diseases[2].

The human disease caused by ZIKV was first recognized in Nigeria in 1953. In 2007, a virus outbreak occurred in several islands in Yap, which resulted in about 5,000 cases. Subsequently, it is estimated that an outbreak in French Polynesia in 2013 and 2014 involved 32,000 cases[1].

In the Americas, ZIKV was first identified in March 2015, when an outbreak of exanthematous disease occurred in Bahia, Brazil[3]. In October 2015, the virus spread to at least 14 Brazilian states and in December 2015, the Brazilian Ministry of Health (MoH) estimated the occurrence of 1.3 million suspected cases. In March 2016, the virus spread to at least 33 countries and territories in the Americas[1].

Vertical transmission, certainly the greatest concern, due to the risk of damaging the embryo, is already well established by some studies that detected the virus in the amniotic fluid. This demonstrates that the virus is able to cross the placental barrier and even more obviously cause fetal malformations[4]. In addition, less frequently, ZIKV transmission can occur through sexual intercourse, and by blood transfusion.

In this scenario, in 2015, the MoH recognized the relationship between increased number of newborns with microcephaly and ZIKV infection during pregnancy[5]. In the same year, in December, the Pan American Health Organization announced that the virus RNA had been identified by reverse transcriptase polymerase chain reaction (RT-PCR) in samples of amniotic fluid from two pregnant women[6].

The spread of the disease throughout Brazil and the world was quickly perceived. ZIKV circulation was confirmed by means of laboratory tests in several units of the federation and

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in other countries[1]. Given this scenario, the event was classified as a public health emergency of international concern[5].

In the state of São Paulo, cases of microcephaly had been monitored through the Information System on Live Births (Sistema de Informações sobre Nascidos Vivos). As from November 2015, cases began to be monitored through the Public Health Event Registry (Registro de Evento de Saúde Pública[5] [RESP]), an electronic form created by the MoH for mandatory reporting of cases that met criteria for microcephaly and / or central nervous system alteration.

In addition, the state of São Paulo monitors and investigates pregnant women at any gestational age with acute rash. This surveillance of pregnant women was based on a specific form to investigate cases of pregnant women with exanthema through the Public Health Emergency Surveillance System (CeVeSP), which is a dynamic web-based platform for notification of emergency events and grievances that provides surveillance agents with the opportunity of issuing real-time reports in case of risk situations. The Center for Strategic Information in Health Surveillance (CIEVS) in partnership with the Division of Dengue, Chikungunya and Zika, developed this instrument to characterize and follow up any pregnant woman with an exanthema. Of note, the form fields were designed to report time, place and person, laboratory tests for infectious diagnosis, PCR results for Zika and the outcome of the conceptus.

This follow-up allows the laboratory diagnosis of ZIKV as well as the clinical and epidemiological characterization of the cases and follow-up of the pregnancy outcome (stillbirth, abortion, neonatal death, healthy newborn, congenital microcephaly and / or other central nervous system anomalies).

The objective of this article is to characterize pregnant women with rash reported through the CeVeSP of the State of São Paulo and the outcome of their pregnancies.

This is a descriptive study conducted in the state of São Paulo and its 27 Epidemiological Surveillance Groups. The state is divided into 645 municipalities, distributed in an area of 248,221,996 km^2 with an estimated population of 44,749,699 inhabitants, in 2016[7].

All pregnant women with exanthematous disease at any gestational age, notified to the epidemiological surveillance system of the State of São Paulo in the year 2016 through the CeVeSP, were included in this study.

We used the following case definitions in this study:

Pregnant woman confirmed by laboratorial criteria: pregnant women with rash who tested positive for ZIKV in RT-PCR.

Pregnant women confirmed by clinical epidemiological criteria: pregnant woman who presented with clinical manifestations compatible with the disease (pruritic maculopapular rash accompanied by two or more of the following signs and symptoms: fever, or conjunctival hyperemia without secretion and pruritus, or polyarthralgia, or periarticular edema), who lived in municipalities with virus circulation, and that did not undergo sample collection for specific research for ZIKV or who underwent sample collection at an inopportune time, resulting in a negative result.

Excluded pregnant women: pregnant women with rash, with non-reactive result for ZIKV in RT-PCR and that did not fit the definition of pregnant woman confirmed by clinical epidemiological criteria.

The cases were classified by age, municipality and epidemiological surveillance of the area of residence, signs and symptoms, classification of cases and outcome of the pregnancy. To describe the cases, we used absolute and relative frequencies, measures of central tendency and dispersion. For data storage and analysis, the software Microsoft Excel 2010 andEpi-Info 7.2 from CDCwas used.

From January 1 to December 31, 2016, 2,698 cases of pregnant women with exanthema were notified through the CeVeSP of the state of São Paulo; of these, 2,209 investigations had been completed (91.7%). Among these, 1,401 (63.4%) were ruled out for ZIKV, 808 (36.6%) confirmed: 780 (96.5%) confirmed by laboratory tests and 28 (3.5%) confirmed by clinical epidemiological criteria. Most cases were reported in the first months of the year (**Figure 1**).

The mean age of pregnant women reported through the CeVeSP with a positive result for ZIKV in 2016 was 27.4 (standard deviation = 6.3) years, and the median was 28.0 (range, 14–44) years, whereas for those with negative results the mean was 27.2 (standard deviation = 6.5) years, and the median was 27.0 (range, 13–44) years (**Table 1**).

Most pregnant women with confirmed ZIKV infection had symptoms in the 2nd and 3rd trimesters of pregnancy (**Table 1**). The main signs and symptoms noted in the pregnant women were rash, followed by headache, myalgia and pruritus. However, we observed that fever was not a frequent symptom (**Table 1**).

Of the pregnant women who tested positive for ZIKV, 52 (6.4%) did not have a favorable outcome, i.e., 18 infants (34.6%) presented with microcephaly and / or central nervous system (CNS) abnormalities; there were 27 (51.9%) abortions, and 7 (13.5%) stillbirths (**Table 1**).

Of the 18 conceptuses born to mothers testing positive for ZIKV, who were born with microcephaly and / or CNS abnormality, only one was not reported through the RESP. Nevertheless, this case was a newborn small for gestational age (SGA), according to the CeVeSP information. The other 17 cases were reported through RESP, of which 15 were confirmed by means of Zika positive samples, 1 confirmed as suggestive of congenital STORCH infection (syphilis, toxoplasmosis, other, rubella, cytomegalovirus, and herpes) and 1 ruled out for microcephaly due to a congenital infection.

Of the 15 cases of infants born with microcephaly to mothers with a confirmed diagnosis for ZIKV, 9 (60.0%) infection cases due to the virus occurred in the 1st trimester (infection rate = 6.3%; 9/143), 5 (33.3%) in the 2nd (infection rate = 1.6%; 5/309) and only 1 (6.6%) occurred in the third trimester (infection rate = 0.3%; 1/342). The proportion of newborns with microcephaly born to women positive for ZIKV in 2016 was 1.85% (15/808).

Most cases of pregnant women with positive results for ZIKV were concentrated in the northwest region of the state of

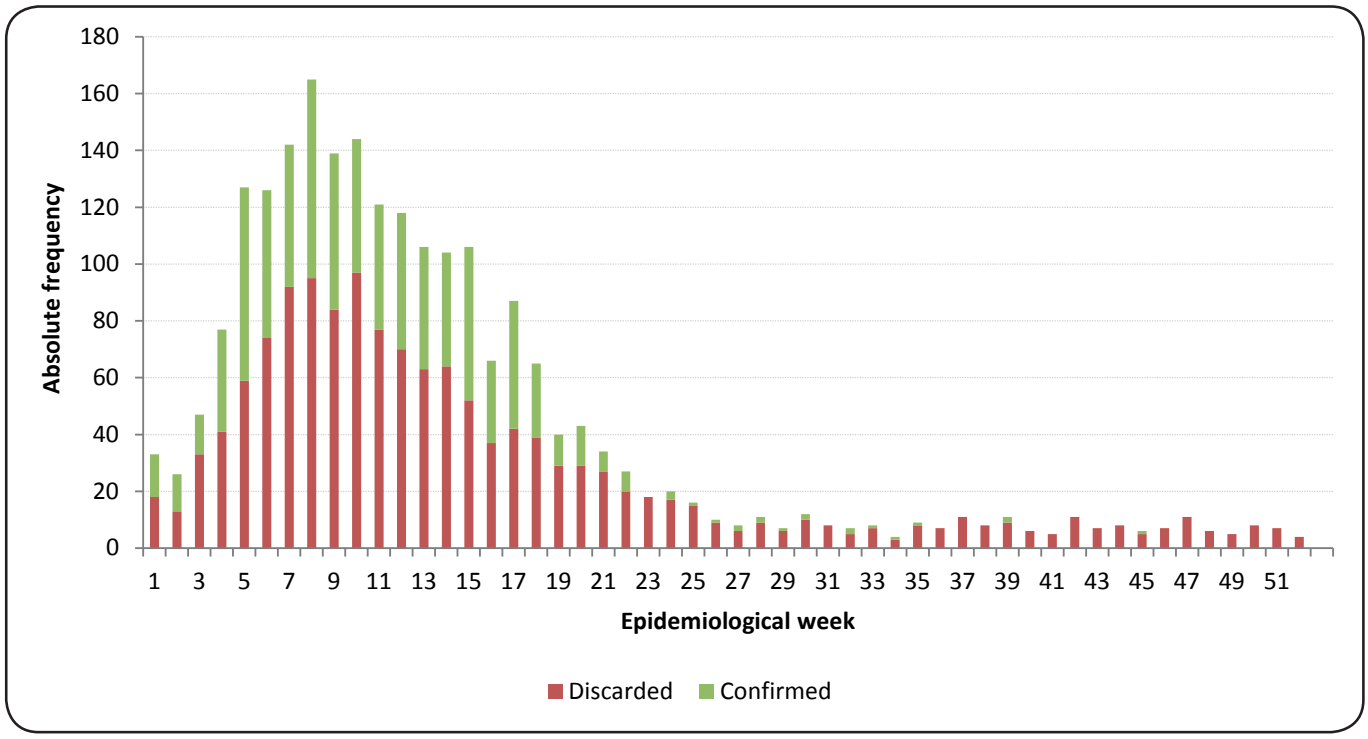

FIGURE 1: Distribution of positive and negative cases of pregnant women with exanthema according to epidemiological week, State of São Paulo, 2016.

São Paulo, mainly in the municipality of Ribeirão Preto (404) followed by Jardinópolis (59) and São José do Rio Preto (57) (**Figure 2**).

Of the confirmed cases for ZIKV infection, more than 95% presented specific laboratory confirmation for ZIKV, pointing to the importance of timely investigation, which involves collecting samples from pregnant women possibly exposed to ZIKV in the acute phase of the disease[5].

Most cases occurred in the first months of the year, and the peak of incidence was from the second half of February onwards, probably because this is the month with the highest yearly temperatures, compatible with the seasonal pattern of infections transmitted by *Aedes aegypti*, such as dengue fever, which occurs in the first half of the year[8].

The median age of pregnant women reported through the CeVeSP with a positive result for ZIKV in 2016 was 28.0 years. The main sign observed in these pregnant women was rash and the most common symptoms were myalgia, headache and pruritus. On the other hand, fever was not a frequent symptom, revealing a similar profile to national[9] and international studies[10].

The majority of confirmed cases of ZIKV occurred in the second and third trimesters of gestation. However, when analyzing the trimester of ZIKV infection in children born with microcephaly, we noticed that most of them became infected in the first trimester of pregnancy, which is compatible with the literature, since pregnant women with infection in the first trimester have the most severe cases, as well as an increased risk of microcephaly in their conceptuses[11,12,13].

Of the conceptuses of pregnant women positive for ZIKV, 6.4% did not have a favorable outcome, that is, they presented with microcephaly and/or CNS alteration or died (abortion, stillbirth). Almost all of these cases were reported through the national public health emergency response system (RESP), showing how accurate the notification system of pregnant women with rash of the state of São Paulo was.

Regarding the outcome abortion and stillbirth, there was no significant difference in absolute numbers in the groups of pregnant women who had confirmed Zika infection and those that were excluded. A significant difference in the rate of fetal loss between mothers who tested positive and negative for ZIKV (7.2% and 6.6%, respectively, p = 1.0) was not observed in a control group[9].

In this study, the proportion of microcephaly in infants born to pregnant women positive for ZIKV was 1.85%, similar to that found by Brasil et al[9].

A study by Johansson et al. showed that different rates of Zika virus infection in the population, as well as rates of underreporting of microcephaly and the gestational trimester in which the infection occurred are relevant factors to determine different prevalences of microcephaly, ranging from 2 to 12 cases per 10,000 births[11].

The confirmed cases were concentrated in the Southeast and Northeast of the state, regions where there was a greater number of ZIKV infections in the year 2016[14].

The prevalence of microcephaly in the state of São Paulo increased three-fold in the period 2015-2016, from 3.46 cases

TABLE 1: Distribution of confirmed and discarded cases for zika Zika virus infection in pregnant women with exanthema, according to signs and symptoms, State of São Paulo, 2016.

Variables	Confirmed n=808		Excluded n=1,401	
	n	%	n	%
Age				
Mean	27.4	***	27.2	***
Standard Deviation	6.3	***	6.5	***
Median	28.0	***	27.0	***
Range	14-44	***	13-44	***
Gestational trimester				
1st trimester	143	17.7	360	25.7
2nd trimester	309	38.2	482	34.4
3rd trimester	342	42.4	532	38.0
Not known	14	1.7	27	1.9
Signs and symptoms				
Exanthema	739	91.5	1118	79.8
Headache	320	39.6	604	43.1
Pruritus	285	35.3	572	40.8
Myalgia	296	36.6	520	37.1
Fever	249	30.8	557	39.8
Edema	261	32.3	365	26.1
Ocular manifestation	187	23.1	182	13.0
Diarrhea	83	10.3	153	10.9
Nausea	50	6.2	172	12.3
Ocular pruritus	113	14.0	75	5.4
Cough	52	6.4	125	8.9
Vomit	26	3.2	116	8.3
Neurological status	19	2.4	63	4.5
Abdominal pain	20	2.5	63	4.5
Petechiae	20	2.5	68	4.9
Hemorrhage	8	1.0	28	2.0
Vesicle	1	0.1	11	0.8
Progression of the conceptus				
Healthy	611	75.7	824	58.8
Microcephaly and/or CNS abnormalities	18	2.2	9	0.6
Abortion	27	3.3	26	1.9
Stillborn	7	0.9	4	0.3
Information not provided	145	17.9	538	38.4

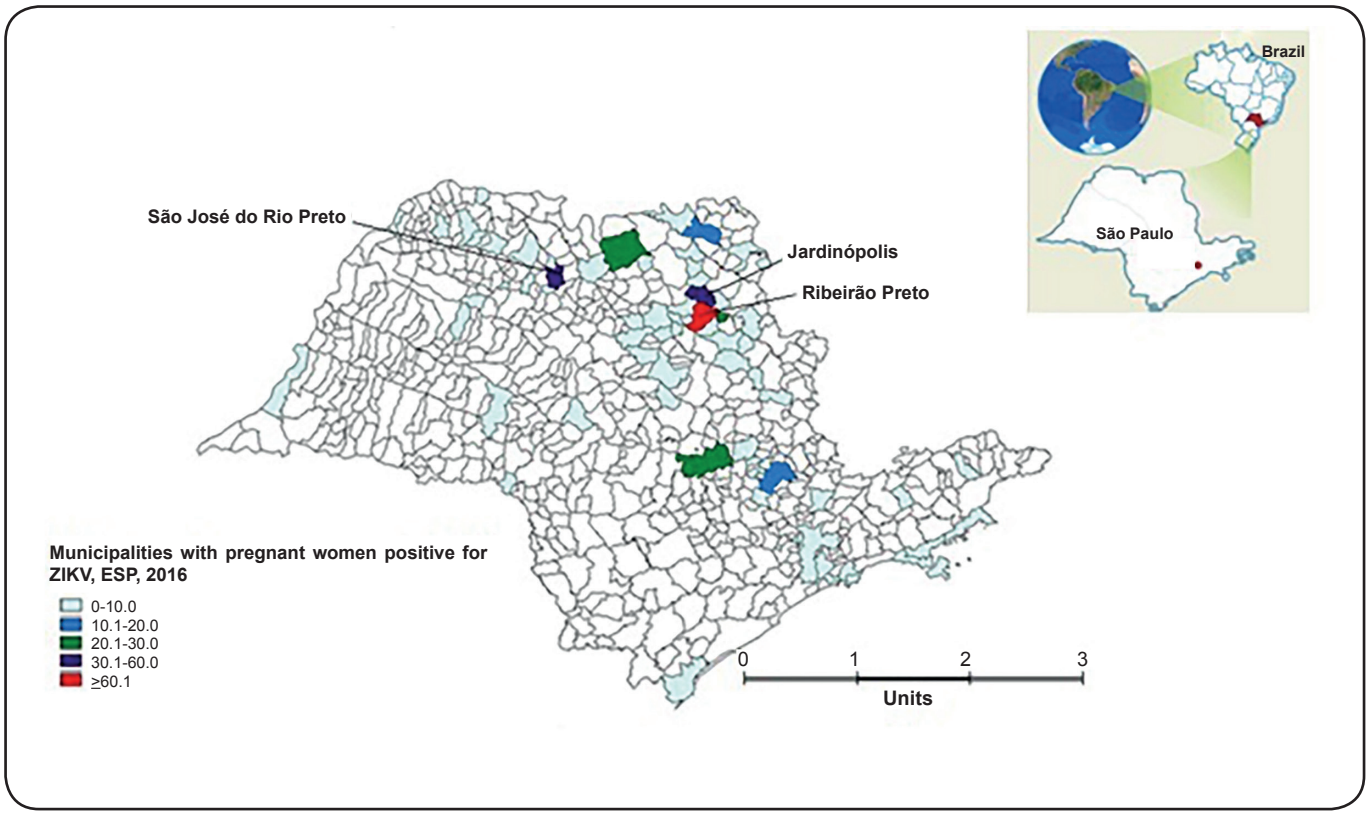

FIGURE 2: Spatial distribution of pregnant women with rash with confirmed results for Zika virus, State of São Paulo, 2016.

per 10,000 live births to 9.52 cases per 10,000 live births, similar to other studies[15].

Among the methodological limitations of the present study, we can mention the incomplete documentation inherent to the routine of surveillance systems, which may compromise the accuracy of the data of descriptive studies. Another limitation observed was the use of RT-PCR, which is a highly specific laboratory test, for the diagnosis of ZIKV in pregnant women, as serological tests were unavailable at the time of the investigation.

Our results allowed the clinical and epidemiological characterization of pregnant women possibly exposed to ZIKV. They also enable us to describe the outcome of their pregnancy, whether it resulted in abortion and/or stillbirth or the characterization of the clinical conditions of the newborn exposed to ZIKV (microcephaly, CNS changes, healthy). Furthermore, the results hereby presented also made it possible to identify the regions with greater occurrence and circulation of the virus within the state of São Paulo, thus acting as a sentinel surveillance of the ZKV.

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Conflict of Interest: The authors declare that there is no conflict of interest.

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