Original Article

Characteristics of the first cases of microcephaly possibly related to Zika virus reported in the Metropolitan Region of Recife, Pernambuco State, Brazil

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Abstract

Objective: to describe the first cases of microcephaly possibly related to Zika virus in live born babies reported in the Metropolitan Region of Recife, Pernambuco State, Brazil. **Methods**: this was a descriptive case series study (cases reported between August 1st and October 31st 2015), using medical record data and data from a questionnaire answered by the mothers of the babies. **Results**: 40 microcephaly cases were confirmed, distributed in eight municipalities within the Metropolitan Region, with Recife itself having the highest concentration of cases (n=12); median head circumference was 29 cm, median chest girth was 31 cm and median weight was 2,628 grams; 21/25 cases had brain calcification, ventriculomegaly or lissencephaly; 27 of the 40 mothers reported rash during pregnancy, 20 in the first trimester and 7 in the second trimester, as well as itching, headache, myalgia and absence of fever. **Conclusion**: the majority of the cases bore the characteristics of congenital infection; the clinical condition of the majority of mothers suggested Zika virus infection during pregnancy.

Key words: Microcephaly; Zika Virus; Congenital Abnormalities; Epidemiology, Descriptive; Brazil.

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Introduction

The Zika virus in an arbovirus which was first isolated in Uganda, in 1947,[1] and was identified in Brazil through the method of molecular biology in May 2015.[2] Since then, its circulation has been confirmed in 18 Brazilian states, initially in the Northeast region of the country.[3] Zika virus fever can present rash with pruritus, associated or not with mild fever and other unspecified symptoms, such as myalgia, headache, arthralgia and conjunctival hyperemia.[4-6]

Until the epidemic of Zika virus in Brazil, the knowledge on its natural history was limited to the sporadic occurrence of outbreaks, and the largest one registered so far occurred in French Polynesia.[7] At first, researchers believed that the Zika virus fever was benign and self-limited;[4-6] however, in that outbreak, there were some reports of post-infection neurologic problems, such as Guillain-Barre syndrome (GBS).[7]

> *Microcephaly is a congenital malformation in which the brain does not have a proper development: the newborns' head circumference is two standard-deviations under the average for the given age and sex.*

In Brazil, after the circulation of Zika virus was confirmed, there was a growth in the number of hospitalizations due to a range of neurological problems. Some descriptive studies conducted in the states of Pernambuco and Bahia identified that most (~51%) patients with GBS presented, between May and August 2015, a clinical picture that is compatible with arbovirus, such as the presence of rash, arthralgia and fever.[8,9] In Pernambuco, one of the cases of GBS presented positive results for Zika virus in the cerebrospinal fluid (CSF), using the molecular biology technique.[9]

The State Health Department of Pernambuco (SES/PE) detected an unexpected raise in the number of live births with microcephaly in October, 2015. Microcephaly is a congenital malformation in which the brain does not have a proper development: the newborns' head circumference is two standard-deviations under the average for the given age and sex, which may lead to brain damage and to neurological development problems.[10]

Microcephaly can be related to genetic and chromosomal factors, to the mother's exposition to environmental factors during prenatal or perinatal period, such as alcohol consumption, use of illicit or teratogenic drugs, contact with chemical substances or ionizing radiation, metabolic disorders, and the following infectious diseases: toxoplasmosis, rubella, cytomegalovirus, herpes and syphilis (TORCHS).[11]

On October 22nd, 2015, SES/PE notified to the Ministry of Health the occurrence of 54 live births with microcephaly. Besides microcephaly, the cases presented imaging exams with a pattern consistent with congenital infection and the mothers reported rash during pregnancy. This scenario made the local specialists wonder about a possible relation between the increasing number of microcephaly cases and the occurrence of Zika virus in Pernambuco. On October 26, technicians of the Secretariat of Health Surveillance of the Ministry of Health (SVS/MS) joined the local team to help with the epidemiological investigation.[12]

In Brazil, in the period from 2010 to 2014, an average of 156 microcephaly cases was annually registered on the Information System on Live Births (Sinasc). However, by December 1st 2015, 1,247 live births had been registered with this malformation, and the state with the highest number of cases was Pernambuco, with 646, whilst the annual average of that state by then – for the period from 1999 to 2014 – was of nine cases.[13] The growth in the number of microcephaly cases was also observed in other Brazilian states.[12]

On November 11th, 2015, due to the change in the pattern of microcephaly cases in Brazil, Pernambuco and other states, the Ministry of Health declared microcephaly as a Public Health Emergency of National Concern.[12]

This health event was evaluated according to Attachment II of the International Sanitary Regulations (ISR), classified as potential Public Health Emergency of International Concern (PHEIC) for presenting serious impact on Public Health and for being an uncommon/unexpected event. On November 29th, the national representative for ISR notified the regional representative of the World Health Organization for ISR.

The objective of this study was to describe the first cases of live births with microcephaly possibly related to Zika virus, reported to SES/PE and the epidemiological profile of their mothers, resident in the Metropolitan Region of Recife, Pernambuco State, Brazil.

Methods

A descriptive cases series study was conducted with live births with microcephaly among the residents in the Metropolitan Region of Recife (MRR), which is composed by 14 municipalities: Recife, Olinda, Jaboatão dos Guararapes, Paulista, Igarassu, Abreu e Lima, Camaragibe, Cabo de Santo Agostinho, São Lourenço da Mata, Araçoiaba, Ilha de Itamaracá, Ipojuca, Moreno and Itapissuma. In 2014, the MRR had approximately 3,914,317 inhabitants, which corresponded to 42% of the total population of Pernambuco State.[14]

All the cases reported to SES/PE in the period from August 1st to October 31st, 2015 were included in the study. The investigation occurred from October 26th to November 19th, 2015.

Initially, the live births with microcephaly were reported to SES/PE by the doctors who assisted the cases in state maternity wards and noticed, still subjectively, a growth in the number of cases when comparing to the routine of the services. There were several means used to detect suspect cases, which included both informal means, such as e-mail, telephone and SMS, and the Sinasc records, classified as microcephaly by the Q02 code of the International Statistical Classification of Diseases and Related Health Problems 10th Revision (ICD-10), besides an electronic form – FormSUS –, developed by SES/PE for notifying new cases after October 27th, 2015.

The following definitions were used for searching the cases:

a) Suspect case of microcephaly: Live birth, in the period between August 1st and October 31st, 2015, whose mother was resident in the Metropolitan Region of Recife, and was notified to SES/PE as microcephaly or registered on Sinasc with the code Q02 of the ICD-10.
b) Confirmed case of microcephaly: Suspect case of microcephaly live birth at term (gestational age between 37 and 42 weeks) with head circumference (HC) smaller than 33 cm or live preterm birth (gestational age <37 weeks) with HC two standard deviations below the average, according to the given gestational age and sex, as stated in Fenton[15] or diagnosis of microcephaly by the assistant doctor.
c) Discarded case: Live birth suspect case of microcephaly with absence of microcephaly diagnosis by the doctor during the physical exam and whose HC was in accordance with the expected for the given gestational age and sex.

From the cases notified to SES/PE, the investigation team searched for extra information in the medical records and other health care records on the pregnant women and the live births in the facility where the childbirth took place. Besides that, interviews were conducted with the mothers, using a semi-structured questionnaire which covered sociodemographic variables, epidemiological antecedents, tests they had undergone, information on their obstetric and gynecological history, prenatal and perinatal period, infectious disease during pregnancy, among others.

The cases in which the mothers were not found for the interview after at least to attempts were considered as loss.

The statistical analysis of the data was conducted with the frequencies, measures of central tendency and dispersion, among the quartile distribution (Q). The softwares used were Epi Info TM 7, Microsoft Office Excel® 2010 and QGIS 2.6.1. Georeferencing of cases was performed with the residence addresses located by Google Maps application (http://batchgeo.com/).

With regard to ethical aspects, the interviewed women orally agreed to participate after reading the Informed Term of Consent, and the privacy and confidentiality of the individuals and data involved were assured according to the Resolution of the National Health Council (CNS) No. 466, dated December 12, 2012. The data analyzed was obtained within the epidemiological surveillance actions, so the present study was exempted from appreciation by an Ethics Research Committee.

Results

During the studied period, 60 suspect cases of microcephaly were registered. There were 13 losses and no refusals, and 47 investigations were concluded. From those cases, microcephaly was confirmed in 40. We observed a peak of live births with confirmed cases on the epidemiological week 42 (n=12), from October 18 to 24, 2015 (Figure 1).

The confirmed cases were distributed in eight municipalities of the MRR, being Recife the municipality with the highest number of cases (n=12), followed by Jaboatão dos Guararapes, Paulista and Olinda (Figure 2).

The type of delivery was vaginal for the majority of confirmed cases (n=27) and they were born at term (n=31), being the median of the gestational age for the childbirth equals to 38 weeks of pregnancy (range:

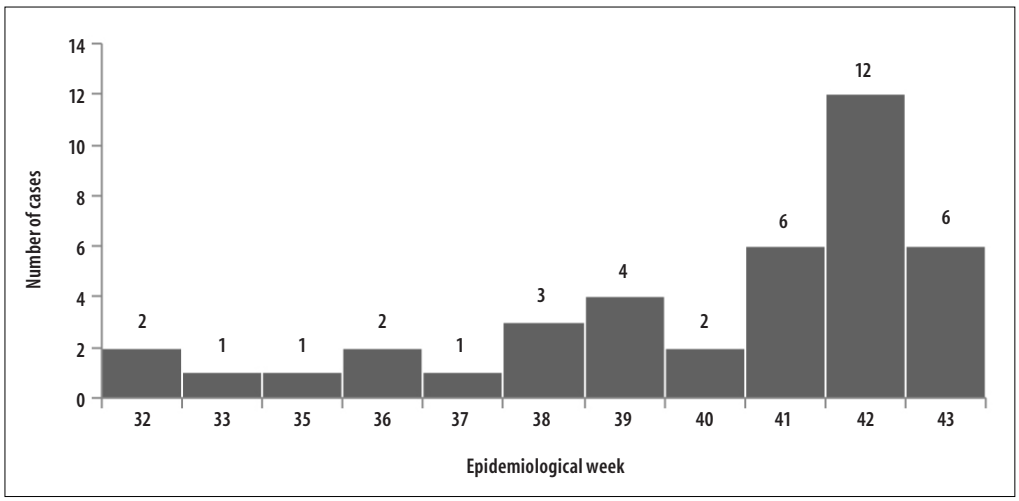


Figure 1 – Distribution of the cases confirmed of microcephaly (N=40) according to epidemiological week of birth, Metropolitan Region of Recife, August-October 2015

31 to 41.5). The median of the Apgar score of preterm and at term live births was nine in the 1st minute and 10 in the 5th minute after birth. For three individuals the value of Apgar score was dissonant; one of them, who was born at preterm, evolved to death (Figure 3 – A). In the first physical examination, the median of the head circumference was of 29 cm (range: 23 to 33 cm), of the chest girth, 31 cm (range: 21 to 35.5 cm), of the height, 46 cm (range: 23 to 49.5 cm), and of weight, 2,628 grams (range: 810 to 3,450 grams) (Figure 3 – B).

With regard to sex, there were 20 boys and 19 girls, and one of them had ambiguous external genitalia, i.e., undefined. Six cases were born with other congenital malformations, among them: hydrocephalus (n=2), musculoskeletal alterations (n=3), external genitalia (n=2) and cardiovascular (n=1).

Throughout the hospitalization period, which presented a median of eight days (Q1: 3.5/Q3: 18), other clinical findings were observed, such as jaundice (n=12), petechiae (n=2), convulsions (n=2), bacterial conjunctivitis (n=2), sepsis (n=1) and apnea (n=1).

Twenty-five cases were submitted to imaging exams – transfontanelar ultrasound, CT scan or MRI; 21 of them presented calcification, ventriculomegaly and/or lissencephaly.

Ophthalmic (n=15) and audiological (n=8) exams were also performed. Two cases presented eye problems in the ophthalmoscopy – alteration of macula and optic disc –, and two cases presented alteration on the otoacoustic emissions.

Of all the etiologic tests conducted, three were positive for syphilis, whilst one was inconclusive (4/16) for this disease, one had IgM serology positive for herpes (1/10), one had IgM serology positive for cytomegalovirus (1/19) and three resulted inconclusive for polymerase chain reaction (PCR). The other agents tested for TORCHS resulted negative.

The median of mothers' age was 25 years (range: 16 to 41). Most of them were brown or black-skinned (n=28), had complete high school (n=25), lived in cohabitation or were married (n=24) and were housewives (n=16). The median of the per capita family income was of BRL 400.00 (range from BRL 80.00 to BRL 2,466.00 – Q1: BRL 212.5/Q3: BRL 533.00).

All the mothers attended at least one prenatal care appointment, and the median of appointments was seven (Q1: 06/Q3: 08), and the higher number of appointments was 16. In the first prenatal care appointment the median for gestational age was of 12 weeks (range: 3 to 35). Before the pregnancy, the median of the body mass index was 24.1 kg/m^2 (Q1: 20.8/Q3: 27.0) and, by the end of pregnancy it was 28.7 kg/m^2 (Q1: 25.1/Q3: 30.9).

Of the total of 40 mothers, 16 were nulliparous. Of the 24 multiparous, the median was of one previous pregnancy (Q1: 01/Q3: 02), and the highest number was 13. Among the women with previous pregnancies, seven had had at least one abortion. Of the children from previous pregnancies, only two presented congenital malformation, both of cardiac etiology.

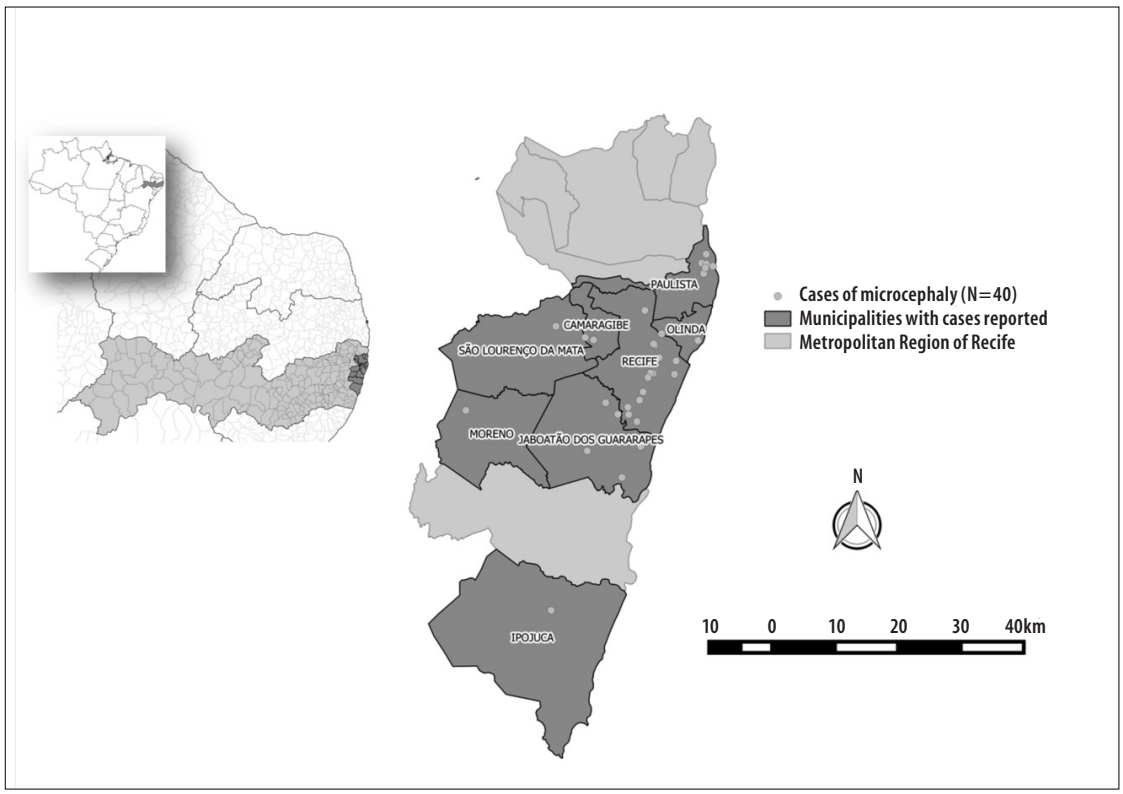


Figure 2 – Distribution of the cases confirmed of microcephaly (N=40) according to the mother's municipality of residence, Metropolitan Region of Recife, August-October 2015

The third trimester ultrasound was performed in 33/40 of the women, and 13 of them received the diagnosis of intrauterine microcephaly.

Concerning the mothers' history, none of them reported consanguinity, exposition to pesticides or ionizing radiation, nor any congenital malformation or history of microcephaly in the family. The use of alcoholic drinks and smoking during pregnancy were reported, respectively, by six and five mothers; two of them used crack and marijuana. Three women were exposed to chemical agents – hair-smoothing products, product to sterilize medical equipment – and only one was exposed to a product used for recycling plastic. Two of them reported contact with insecticide: one with aerosol and the other, during disinsectization.

Among those with pre-existing conditions (n=6), two reported lung diseases, two reported metabolic disorders and two, hemoglobinopathies. With regard to previous use of continuous medication, 11 of them used contraceptive pills and one used salbutamol.

Most of the mothers reported rash during pregnancy (n=27): 20 in the first trimester – between February and May – and seven in the second trimester – between April and July (Figure 4). In addition to the rash, they also reported, most frequently, other symptoms, such as pruritus, headache, myalgia and absence of fever (Figure 5). Of the mothers who presented rash during pregnancy, one of them underwent serology for dengue, and it resulted negative. None of them were tested for other arbovirus during pregnancy.

Discussion

Forty cases of live births with microcephaly were confirmed in the Metropolitan Region of Recife, among the cases reported to the State Health Department of Pernambuco in the period from August 1st to October 31st, 2015. The majority of cases presented an imaging pattern that suggested congenital infection – cerebral calcification, ventriculomegaly and lissencephaly – and their mothers presented clinical conditions that suggested infection by Zika virus, with rash and pruritus during the months of fetus development.

The intrauterine period is known to be a critical phase for the growing and development of the fetus' organs

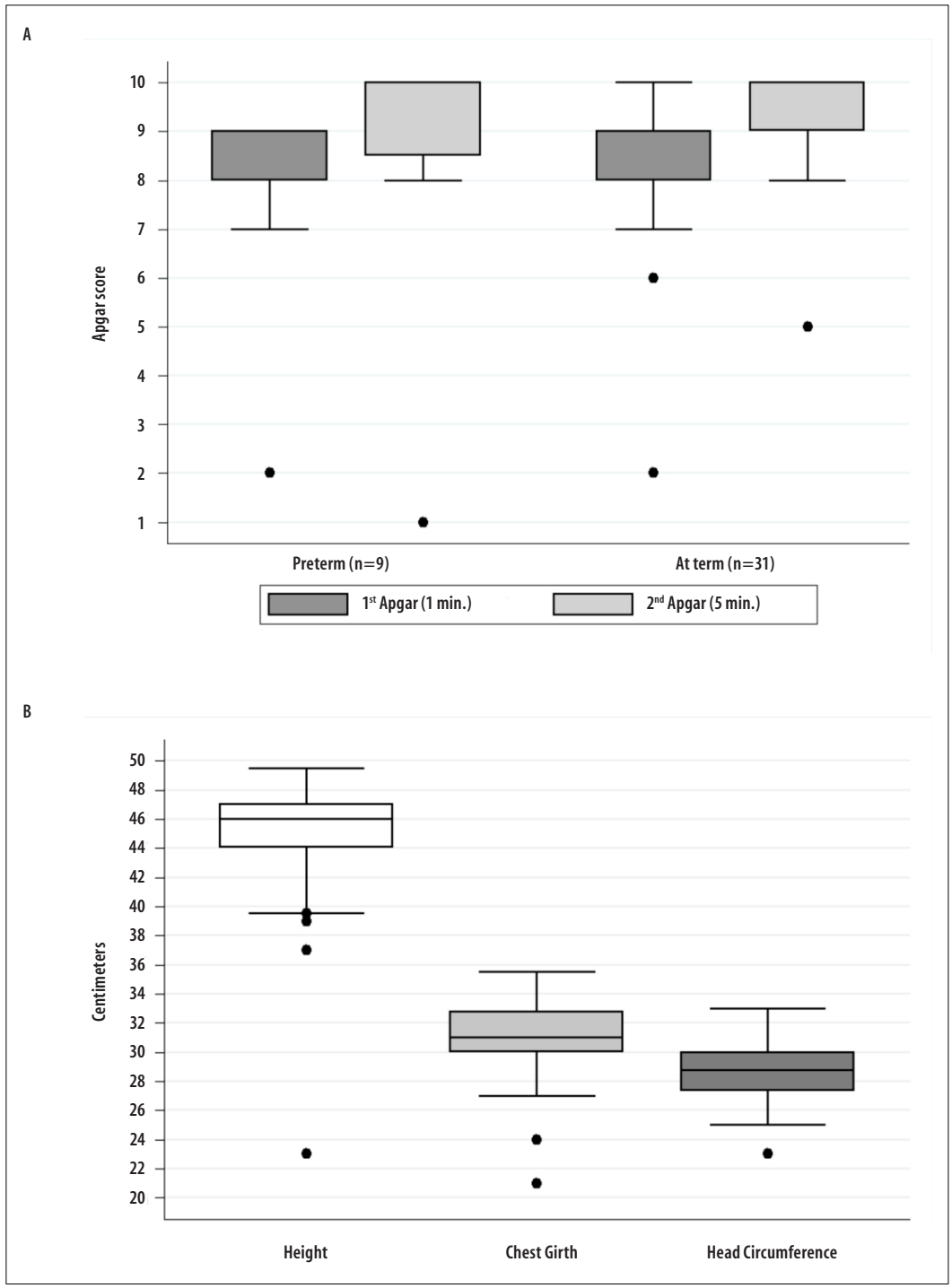
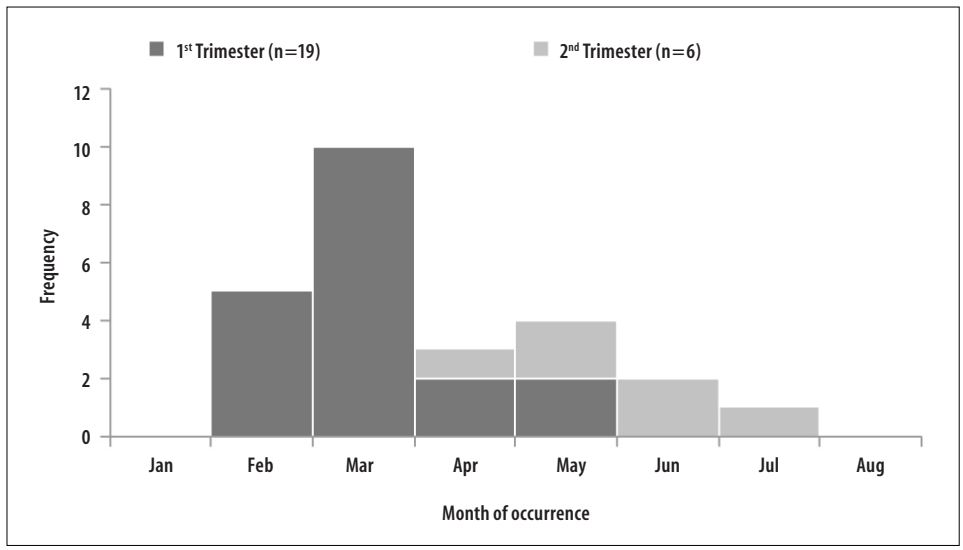


Figure 3 – Distribution of the cases confirmed of microcephaly (N=40) (A) according to Apgar score at the 1st and 5th minutes after birth and (B) according to the anthropometric measurements (height, head circumference and chest girth) in the first physical examination, Metropolitan Region of Recife, August-October 2015



a) Two mothers informe the month of initial symptoms, but could not inform the day.

Figure 4 – Distribution of frequency of mothers who presented rash (n=25[a]) among the cases confirmed of microcephaly according to the month of occurrence of the rash and trimester of pregnancy, Metropolitan Region of Recife, August-October 2015

and tissues, and injuries suffered during this process may interfere in this process. Pregnant women, when infected by teratogenic agents, such as toxoplasmosis, rubella, cytomegalovirus, herpes and syphilis may vertically transmit them.[16] In Brazil, the fact that the microcephaly epidemic appeared at the same time as the circulation of Zika virus brought up the discussion about a possible causal association between an arbovirus and congenital malformations, which was later confirmed.[17]

In French Polynesia, where an important outbreak of Zika virus occurred between 2014 and 2015, 17 microcephaly cases, with malformation in the central nervous system and others, were reported. Of those 17 cases of microcephaly, 12 consisted of brain malformations or syndromes of multiple malformations, including brain damages, brain stem dysfunction and absent swallowing. In a study published by the European Centre for Disease Prevention and Control, none of the pregnant women reported clinical signs of infection by the Zika virus during pregnancy, but four of them resulted positive for IgG serology for Flavivirus, which suggests possible asymptomatic infection.[18]

In the present study, most of the live births with microcephaly were discarded for TORCHS and, although there was positive result for syphilis, cytomegalovirus and herpes in five cases, we cannot conclude that they led to microcephaly, because these conditions can be transmitted during pregnancy, childbirth or breastfeeding, and those mothers also presented rash history during pregnancy.

Many factors likely to lead to microcephaly were described in the literature. After the exclusion of the most common causes of microcephaly, the rash associated with pruritus, headache or myalgia, which are characteristics of the Zika virus fever, and was presented by most of the mothers emerged as an important evidence. Diseases such as measles, rubella, parvovirus, dengue, roseola, rickettsiosis[19] and Zika virus fever may present rash,[20] and from those agents, dengue and Zika virus were epidemic in the region and period studied.[3]

The distribution of cases according to the mothers' municipality of residence showed a higher number of cases in Recife, followed by Jaboatão dos Guararapes, Paulista and Olinda. Although this distribution reflects the population density of the municipality, the achieved places were the same that had the highest incidence of dengue in than past six years in the state of Pernambuco.[3]

It is important to highlight that the months from February to July, mentioned by the mothers as the initial period of the rash correspond to the period of higher incidence of the urban arbovirus and introduction of

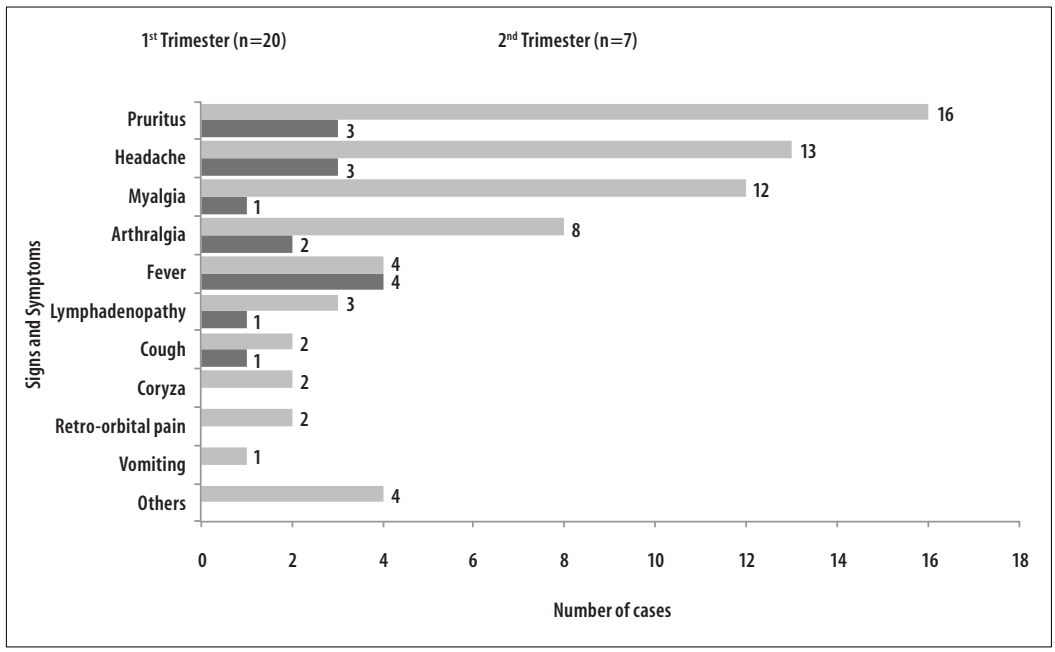


Figure 5 – Frequency of signs and symptoms in mothers who presented rash (n=27) during the 1st and 2nd trimesters of pregnancy among the cases confirmed of microcephaly, Metropolitan Region of Recife, August-October 2015

the Zika virus in Pernambuco.[2] These findings reinforce the hypothesis of a time relation between the infection by the Zika virus in pregnancy and the occurrence of microcephaly at birth.

As limitations in this study, we can mention the (i) possibility of recall bias, due to the difficulty of the mothers to report the probable exposition to signs and symptoms during pregnancy, the (ii) high proportion of loss, the (iii) lack of opportunity for laboratory diagnosis, because of the time after the probable infection, and the (iv) unavailability of imaging exams and serology tests results for TORCHS for all the cases.

It is important to inform that after the conduction of the present research, there were two changes concerning definition of suspect cases for live births with microcephaly; these changes aimed to increase the specificity for cases notification. In the first change, for live births at term, the HC size was reduced to ≤32 cm, regardless of sex.[21] In the second change – adopted so far – for preterm live births, the reference for standard-deviation was adjusted to InterGrowth, and for at term live births, the HC for girls changed to ≤31.5 cm and for boys, ≤31,9.[22]

Taking into consideration all the suggestive evidence of a causal relation between the infection by the Zika virus during pregnancy and the occurrence of microcephaly, more studies – analytical and laboratorial – are necessary to better understand the phenomena related to this Public Health emergency, and also support strategies for tackling it.

Authors' contributions

Vargas A and Percio J contributed to the conception and design of the study, data collection, analysis and interpretation, literature review, typing the questionnaires and discussion of results and manuscript's drafting.

Percio J guided the conduction of the study.

Saad E, Wada MY, Dimech GS, Santos RH, Sivini MAVC, Albuquerque LC, Assunção RS, Lima PMS, Frutuoso LCV, Oliveira WK, Souza PB,Carmo GMI, Henriques CMP, Barreto IC, Andrade ME, Lima PMS, Carvalho PI, Azevedo RSA and Vasconcelos RCO contributed to the conception and design of the study, data analysis and interpretation, discussion of the results and critical review of the intellectual content of the manuscript.

Barreto IC, Andrade ME, Lima PMS, Carvalho PI, Azevedo RSA and Vasconcelos RCO collected the data.

All the authors contributed to the development and final review of the manuscript and declared to be responsible for all aspects of the work, ensuring its accuracy and integrity.

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