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The impact of chikungunya fever on pregnancy: a systematic review

Impactos da febre da *chikungunya* na gestação: uma revisão sistemática da literatura

Symara Abrantes Albuquerque de Oliveira Cabral [1], Ricardo Queiroz Gurgel [2], Eitan Naaman Berezin [3]

Abstract

Introduction*: Chikungunya virus (CHIKV) was introduced in Brazil in 2015, with occasional occurrences that soon spread in a large part of the country. The disease, in view of its long-standing consequences for the affected individuals, brought intense public health concerns. Pregnancy is a period of intense organic changes and may be affected in the case of CHIKV infection. However, the maternal and fetal impacts of CHIKV virus infection during pregnancy are not fully understood.* ***Objective:*** *To describe the maternal and fetal impacts following a CHIKV infection during pregnancy.* ***Method:*** *A systematic narrative review of the literature was performed in order to establish a compendium of information about the impacts of CHIKV infection during pregnancy.* ***Results:*** *is a potential for placental transfer of infection from the pregnant woman to the fetus, especially when it occurs close to delivery, as well as fetal manifestations, including with imminent severity. No complications were reported for pregnant women after CHIKV infection.* ***Conclusion:*** *Potential severity for the fetus precedes a need for preventive investments, especially in prenatal care.*

Keywords*: Chikungunya virus, CHIKV, Pregnancy, Chikungunya fever*

Resumo

Introdução: *o vírus da chikungunya (CHIKV) foi introduzido no Brasil em 2015, com ocorrências pontuais que logo se disseminaram em grande parte do país. A doença, diante de suas consequências para o indivíduo acometido, sobretudo à longo prazo, trouxe intensas complicações para saúde pública. É consenso a ocorrência de morbimortalidade decorrente da doença e, sendo a gestação um período de intensas mudanças orgânicas, importante se faz considerar o questionamento: quais os impactos maternos e fetais da infecção pelo vírus da chikungunya na gestação?* ***Objetivo:*** *descrever os impactos maternos e fetais decorrentes da infecção pelo CHIKV.* ***Método:*** *revisão sistemática da literatura de modo a estabelecer um compêndio de informações acerca dos impactos da CHIKV na gravidez.* ***Resultados:*** *observou-se potencial de transferência placentária da gestante para o feto, sobretudo quando a infecção ocorre próximo ao parto, bem como manifestações fetais, inclusive com gravidade. Não foram descritas complicações à mulher grávida infectada pelo CHIKV.* ***Conclusões****: potencial de gravidade para o feto precede uma necessidade de investimentos preventivos, sobretudo no pré-natal.*

Palavras chave: *Vírus chikungunya, CHIKV, Gravidez, Febre de chikungunya*

Introduction

Chikungunya virus (CHIKV) is transmitted by infected female mosquitoes, the most frequent *Aedes aegypti*. Since no specific drug therapy or vaccine is available, the only effective infection control method involves controlling the vector. A recent study highlighted the potential for a viral genetic mutation in order to draw attention to new outbreaks[1].

CHIKV is an Alphavirus belonging to the Togaviridae family, with a genome composed of a positive-sense RNA molecule that encodes four non-structural proteins and five structural proteins. Such characteristics impact the diagnosis and are not hampered by cross-infection with other arboviruses. The diagnosis is made based on positive RT-PCR (between 4 and 7.5 days), specific IgM detection (increases from the fifth day onwards, persisting for up to 18 months), or IgG seroconversion[2].

1. Universidade Federal de Campina Grande. Centro de Formação de Professores. Campina Grande – PB – Brazil
2. Universidade Federal de Sergipe. Programa de Pós-graduação em Ciências da Saúde. Aracajú – SE – Brazil
3. Santa Casa de Sao Paulo School of Medical Sciences. Department of Pediatrics. São Paulo – SP – Brazil
Institution: *Santa Casa de Sao Paulo School of Medical Sciences. Sao Paulo - SP- Brazil*
Correspondence address: *Symara Abrantes Albuquerque de Oliveira Cabral. Rua Pedro Carlos de Moraes - Lot. Jose Bonifacio de Moura – 58900-000 - Cajazeiras – PB – Brasil. E-mail: symara_abrantes@hotmail.com*

Data from the last epidemiological reports issued by the Brazilian Ministry of Health confirmed 95 deaths in 2019 due to CHIKV in Brazil with a greater predominance in the Midwest, Southeast, and Northeast regions and a higher lethality rate among the elderly aged over 60 years, with greater predominance in those over 80 years old[3]. Between 2014 and 2015, there was a considerable epidemic of CHIKV of the Asian genotype in the Americas presenting about 1.5 million notified cases spread over about 20 countries[1].

Few studies address CHIKV during pregnancy. Considering this scenario we have performed the following research question: "What are the maternal and fetal impacts following CHIKV infection during pregnancy?". To answer it we have carried out a narrative review of the manuscript published to date, presented in chronological order.

Methods

We have performed a systematic review, which elaborates assumptions based on PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyzes)[6]. The search for the articles took place between the months of January 2019 and December 2020 and included articles published between 2000 and 2020.

The following databases were used: Scielo (Scientific Electronic Library Online), MEDLINE (Medical Literature Analysis and Retrieval System Online / PubMed), EMBASE (Elsevier) and CENTRAL (The Cochrane Central Register of Controlled Trials The Cochrane Library), and LILACS (Scientific and technical literature from Latin America and the Caribbean / VHL - Virtual Health Library). The search strategy combined descriptors (MeSH - medical subject headings) for the Pubmed database and Decs descriptors (Health Sciences Descriptors), using the search strategies: 1) Chikungunya Virus (OR) Chikungunya Fever (AND) Vertical Transmission Infectious Disease; 2) Chikungunya Virus (OR) Chikungunya Fever (AND) Pregnancy; and their respective MeSH translations: 3) Chikungunya Virus Infection (OR) Chikungunya Fever (AND) Infectious Disease Transmission, Vertical; 4) Chikungunya Virus Infection (OR) Chikungunya Fever (AND) Pregnant Women.

For the analysis of the compiled data, the content analysis methodology proposed by Bardin[7] was used in order to allow the systematic analysis of the communications, thus allowing possible inferences. As inclusion criteria, all original articles were defined and elaborated with a methodological rigor that presented guidance with the research question, whereas the exclusion criteria are review articles, with the presentation of secondary data and those that do not fit in with the proposed direction for the study.

Results

The article selection proceeded with the reading and correlation with the research question so that in view of the small number of articles found proceeded with the snowball technique so that the references cited in the articles from the search were also analyzed.

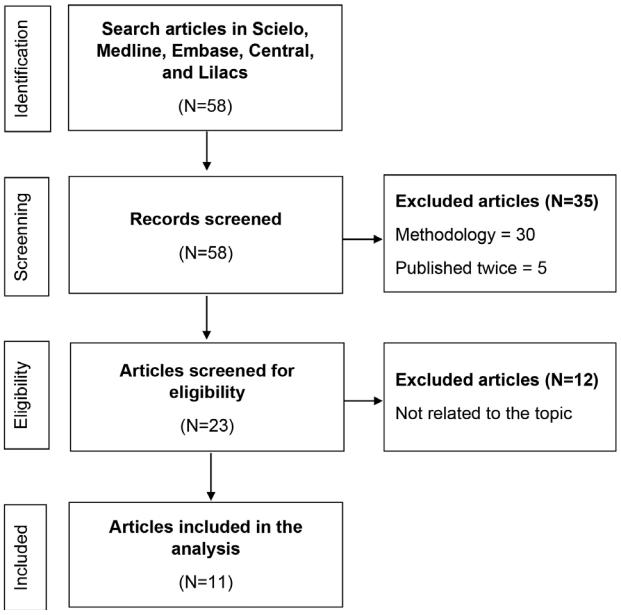

Figure 1 – Flowchart for the selection process. Source: Prepared by the authors, 2020.

Individuals infected with CHIKV have on average 3 to 7 days incubation period, with the viremia period that can last up to ten days starting about 2 days before the onset of symptoms. Approximately 70% of people with CHIKV are symptomatic, and the disease may develop in an acute phase (lasts until the tenth day), subacute (up to three months with the presence of symptoms), or chronic (persistence of symptoms after three months). The mortality rates are lower than in dengue and it is more present in the association with comorbidities or in extremes of age [8]. Following the established objectives, the studies described in table 1 were selected.

The first country in South America to report a CHIKV infection case was French Guiana, which registered an outbreak between 2014 and 2015, presenting several atypical cases and two deaths. Serious cases involved neurological complications, cardiorespiratory failure, acute heart failure, and digestive and hepatic disorders, in addition to kidney disorders and muscle impairment[9].

Regarding the presentation of symptoms, there is a well-defined clinical characterization with rash, vomiting, bleeding and oral ulcers being the symptoms most associated with female individuals. Joint pain, edema, and a longer du-

Table 1

Articles selected.

Authors and year of publication	*Title*	*Periodical*
Bonifay et al (2018)[9]	Atypical and severe manifestations of chikungunya virus infection in French Guiana: A hospital-based study	PLoS ONE
Touret Y et al (2006)[10]	Early maternal-fetal transmission of the Chikungunya virus	Presse Med.
Watanaveeradej, et al (2006)[11]	Transplacental Chikungunya Virus Antibody Kinetics, Thailand	Emerg Infect Dis.
Ramful et al, (2007)[12]	Mother-to-child transmission of Chikungunya virus infection	Pediatr Infect Dis J.
Shenoy, Pradeep (2012)[13]	Neurodevelopmental outcome of neonates with vertically transmitted Chikungunya fever with encephalopathy	Indian Pediatr.
Gérardin et al (2014)[14]	Neurocognitive outcome of children exposed to perinatal mother-to-child Chikungunya virus infection: the CHIMERE cohort study on Reunion Island.	PLoS Negl Trop Dis.
Alvarado-Socarras et al (2016)[15]	Congenital and Neonatal Chikungunya in Colombia	J Pediatric Infect Dis Soc.
Laoprasopwattana et al (2016)[16]	Chikungunya and dengue virus infections during pregnancy: seroprevalence, seroincidence, and maternal-fetal transmission, southern Thailand, 2009-2010.	Epidemiol Infect.
Evans-Gilbert (2017)[17]	Chikungunya and Neonatal Immunity: Fatal Vertically Transmitted Chikungunya Infection.	Am J Trop Med Hyg.
Contopoulos-Ioannidis et al (2018)[18]	Mother-to-child transmission of Chikungunya virus: A systematic review and meta-analysis.	PLoS Negl Trop Dis.
Duarte et al (2019)[19]	Maternal and congenital infections arising from Zika, dengue, and Chikungunya arboviruses in Salvador, Brazil	Transactions of the Royal Society of Tropical Medicine and Hygiene Source: Prepared by the authors, 2020.

ration of fever are more frequent in proportion in older age. Cutaneous manifestations are described in about half of the infections and characterized by macular or maculopapular rash appearing between the second and the fifth day after the onset of fever[8].

The first study was published in 2005, reporting the first cases of CHIKV maternal-fetal transmission in France. The three pregnancies resulted in fetal deaths shortly after maternal infections. Vertical transmission was confirmed by positive findings for specific anti-CHIKV IgM and positive RT-PCR in amniotic fluid and by ruling out other viral and bacterial infections[10].

In Thailand, a study published in 2016 evaluated the serological characteristics for CHIKV, using two thousand pregnant women who did not present complications in their pregnancies and childbirth, with material collected between 1998 and 1999. One-third of the women were positive, and blood samples from umbilical cord serum were analyzed by inhibiting hemagglutination (IH): 81% were positive, indicating possible vertical transmission. It was observed that 58% of the samples had the same titles between mother and children, 31% higher and 11% lower, defining an active placental transport mechanism [11]. In a 2006 study with 84 French women, 88% of the cases had asymptomatic babies at birth, one hundred newborns (NB) had severe outcomes, of which had encephalitis, three had disseminated intravascular coagulation, and six needed neonatal resuscitation and required assisted ventilation. For all cases, specific IgM serology was performed on mothers and newborns[9].

The other [15] was evaluated on the twenty-third postpartum day when she presented fever for 4 days, followed by a maculopapular rash associated with irritability that persisted for 3 days, with no mosquito bites referred or documented. The baby presented generalized seizures and

cardiopulmonary involvement, and laboratory tests revealed severe thrombocytopenia and lymphopenia. Magnetic resonance was performed and identified several changes that corresponded to encephalitis and mild hearing impairment and evidence of decreased muscle tone were documented at 13 months of life [15]. CHIKV was confirmed by IgM[15]

A study performed in Latin America and published in 2016 described an assessment carried out with 169 symptomatic NB with CHIKV. The vertical transmission rate varied between 27.7% and 48.29%, and the mortality rate was 5.3%. The most frequent clinical manifestations included fever, irritability, skin rashes, diffuse edema of the limbs, meningoencephalitis, and bullous dermatitis. Regarding complications, it describes meningoencephalitis, myocarditis, convulsions, and acute complications such as cardiorespiratory arrest[10].

In Thailand, a study published in 2016 shows discordant results, and no differences were observed regarding congenital anomalies when comparing positive and negative newborns for CHIKV infection. In addition, none of the NBs from CHIKV positive mothers showed IgM positivity[16]. A study published in 2017 shows two cases of vertical transmission in Jamaica, one confirmed by RT-PCR and the other by clinical-epidemiological criteria. The NB presented abdominal distension, reduced perfusion pressure, and hypotension on the third day of life, in addition to breathing difficulties. Both died 24 and 48 hours after the onset of symptoms[17].

In another study from La Réunion and published in 2018 analyzed 7.629 viable newborns, 9% of them were infected during delivery and 0.8% in the pre or intrapartum, being diagnosed by RT-PCR or IgM. The prevalence rate in the vertical transmission was 48.7%, with all neonates being asymptomatic a priori, average onset of the disease on the fourth day of life, and 100% cases referring pain, prostration, and fever on all of them, thrombocytopenia in 89% and complications in 52.6%, including encephalopathy, with four of them progressing to persistent disabilities [18].

A study carried out in the state of Bahia, Brazil, and involving 101 parturients and 102 newborns aimed to assess the potential for congenital transmission of dengue (DENV), Zika virus (ZIKV), and CHIKV: 6.9% of the parturients were positive for ZIKV, 11.9% for DENV and 22.8% for CHIKV. Congenital infection for CHIKV was found in 13% of positive mothers with all of them being healthy and showing no relevant symptoms at birth[19].

In 2007, a study carried out between 2005 and 2006 in Réunion Island, a French department in the Indian Ocean, screened 38 neonates, of which only two were from asymptomatic mothers and were included in the study because they showed signs in the first days of life[9]. To confirm the diagnosis, RT-PCR was performed in cerebrospinal fluid, which was positive for 22 cases. In the study, the symptomatologic presentation of newborns between the third and seventh day of life was observed, with an average of 4, when they presented the clinical signs of fever (79%), pain (100%), rash (82%) and peripheral edema (58%). It was also observed: thrombocytopenia, lymphopenia, decreased prothrombin value, and increased aspartate aminotransferase. As for complications, it was found cases of convulsions, hemorrhagic syndrome, and hemodynamic disorders. There were also abnormal findings in the brain magnetic resonance imaging with lesions in the white matter or intraparenchymal hemorrhages or both, myocardial hypertrophy on echocardiography, ventricular dysfunction, pericarditis, and coronary artery dilation. One of the newborns died from necrotizing Enterocolitis[12].

In India, a study published in 2012 described the follow-up of two newborns affected by encephalopathy, both being diagnosed with CHIKV by RT-PCR. One of them presented convulsive apnea on the fifth day of life and his mother had a history of fever and arthralgia a few days before delivery. In the first week of life, hyperpigmentation was observed in the nose, face and groin that lasted for two months and gradually disappeared. RN had hypertonia, spastic diplegia and seizure disorder. It also presented language, non-significant memory, conceptual thinking, non-verbal and numerical reasoning that were inadequate in long-term evaluation[13].

The other newborn described in the study had convulsive apnea and repeated lethargy after two days of life, the mother had fever and arthralgia in the peripartum. The newborn had hypoproteinemia and lymphedema. On the tenth day of life, he presented perioral, limb and abdominal hyperpigmentation, in addition to hypotonic. At six months of age, he had visual impairment. At the time of the study, the child, at the age of three, had hypotonic cerebral palsy with mental retardation[13].

A study published in 2014 proceeded with a comparative retrospective cohort of 33 children vertically infected with CHIKV with an average of two years of age, with uninfected pairs. For analysis, the revised Brunet-Lezine scale was used for movement and posture, coordination, language, sociability skills as criteria, and Poisson multivariate regression modeling to predict global developmental delay. The results considered the neurocognitive outcome of children exposed to perinatal CHIKV infection from mother to child to also considering neonatal CHIKV encephalopathy as the worst outcome found[14].

In Colombia, a study published in 2016 presented two cases of neonatal CHIKV infection, highlighting

the potential neurological impact and sequelae. In the case presented, the mother presented fever, edema, pelvic pain and rash shortly before delivery. At three days of age, the newborn had fever for 74 hours, erythematous maculopapular rash in the trunk in concomitance with jaundice 24 hours after the fever had ceased, in addition to distal cyanosis and exacerbated irritability, with neonatal sepsis being initially suspected in order to proceed with blood and urine culture, which were negative. He presented thrombocytopenia, hyperbilirubinemia, increased aspartate and alanine aminotransferase and C-reactive protein. The diagnosis of CHIKV was confirmed by positive IgM. The child was followed up after discharging due to remission of the clinical condition, and in the 12-month follow-up period he presented normal psychomotor development[15].

Conclusion

There is consistency in the data, which clearly indicates that vertical transmission is present in maternal CHIKV infections, without evidence of complications to the neonates' health. No studies have been reported with consequences for women during pregnancy beyond the characteristic symptoms of the disease itself, with no evidence of worsening. There is a need for a better understanding of the factors involved in the placental transfer of the virus, as well as the search for the establishment of effective preventive strategies for applicability in prenatal care.

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