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Fetal and Neonatal Deaths Resulting from Chikungunya Virus Infection During Pregnancy: A Case Series

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Purpose: We report maternal outcomes, fetal and neonatal deaths resulting from chikungunya virus (CHIKV) infection during pregnancy, addressing clinical manifestations, complications and laboratory changes.

Patients and Methods: This case series included four pregnant women infected with the chikungunya virus during gestation, three fetal deaths, and two neonatal deaths confirmed as resulting from maternal-fetal transmission, during an epidemic in 2015 and 2016, in the state of Pernambuco, Northeastern Brazil. Laboratory and clinical-epidemiological criteria were applied to confirm the infection.

Results: All the pregnant women were symptomatic with an onset of symptoms from the first trimester of pregnancy until 4 days after birth, with the infection confirmed by laboratory and clinical-epidemiological criteria. Among the fetal deaths, changes in the brain were the most prominent (softening and autolysis). In the neonatal deaths, there were signs of acute suffering, and low Apgar, in addition to the manifestation of severe disease with skin hyperpigmentation, limb edema, and encephalitis.

Conclusion: We demonstrate the rare, although possible, occurrence of fetal death due to maternal CHIKV infection at any stage of pregnancy, as well as the risk of vertical transmission during birth, resulting in neonatal mortality. We would suggest that during epidemics this diagnosis should be considered in fetal and neonatal deaths of mothers with symptoms suggestive of chikungunya.

Keywords: chikungunya virus, vertical transmission, fetal death, infant mortality

Introduction

Chikungunya is the second most widely distributed arboviral disease, transmitted by *Aedes aegypti* and *Aedes albopictus*, worldwide.[1] In Latin America and the Caribbean, the arboviruses chikungunya (CHIKV), dengue (DENV), and zika (ZIKV) represent an important public health concern.[2] In Brazil, the first autochthonous cases were confirmed in 2014, followed by spread and epidemics in subsequent years.[3] Severe cases and neonatal deaths due to CHIKV acquired in the perinatal period were described in sequence.[4,5] Pernambuco was the most affected state between 2015 and 2016, with an excess of 4505 deaths (47.9 per 100,000 people) and 707 reported cases of pregnant women.[6,7]

The CHIKV may pass vertically from mother to child with an intrapartum transmission rate of 50%. The impact on fetuses and newborns of maternal CHIKV infections is very uncommon but may present the severe involvement of multiple organs and, rarely, death.[8] The pathogenesis is uncertain, but the severity of the infection is related to high exposure to the maternal viral load and compromised antiviral immune response, thereby facilitating inflammation and damage to the placenta.[9,10]

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Methods

This case series included four pregnant women infected with the chikungunya virus during pregnancy, resulting in three fetal deaths and two neonatal deaths due to maternal-fetal transmission during the 2015–2016 epidemic in the state of Pernambuco, northeastern Brazil.

Laboratory confirmation of CHIKV infection followed the guidelines of the Brazilian Ministry of Health and the Pan American Health Organization, based on a reactive/positive result for CHIKV genome detection through viral RNA detection by Reverse Transcriptase Polymerase Chain Reaction (RT-PCR) and/or detection of Immunoglobulin M (IgM) antibodies via serological tests (Enzyme-Linked Immunosorbent Assay - ELISA).[11,12] Blood, serum, cerebrospinal fluid, tissue and/or organ samples collected during the first week of symptom onset were tested.

In an epidemiological context, the use of clinical-epidemiological criteria for diagnosis is recommended by the Brazilian Ministry of Health and is applied when there is an epidemiological link between patients, with one having laboratory confirmation, alongside compatible clinical signs and symptoms, and the area of residence showing other confirmed cases,[11] as conducted in this study.

All deaths were discussed and confirmed as being caused by CHIKV after investigation using the protocols of epidemiological surveillance services with systematic collection of clinical, laboratory, and epidemiological data, interviews with family members, home visits, and discussion in the State Committee for the Investigation of Dengue Deaths, Chikungunya and Zika Virus.[13]

Results

The infection was confirmed in all four mothers: three by laboratory criteria with reactive IgM chikungunya serology and one through the clinical-epidemiological linkage with the newborn. They were symptomatic, and all of them presented with fever and severe arthralgia, in addition to headache, edema, and rash. The onset of symptoms related to childbirth occurred from the first trimester of pregnancy to 4 days after birth. They received prenatal monitoring, with ultrasound examinations revealing the normal fetal development, with no comorbidities. All births were performed in a hospital obstetric center. They presented negative serology for other infectious diseases (Table 1).

Table 1 Clinical and Laboratory Aspects of Four Pregnant Women Infected by Chikungunya Virus During Pregnancy, State of Pernambuco, Brazil, 2015 and 2016

Maternal Variables	Case 1	Case 2	Case 3	Case 4
Age (years)	20	30	18	23
Clinical signs and symptoms	Fever, headache, arthralgia, vomit, pelvic pain, edema on limbs	Fever, joint pain, itching and rash	Fever, severe arthralgia, rash	Fever, generalized skin rash, headache, joint pain, pain in the lower limbs and hands
Hematological and/or biochemical laboratory changes	Neutrophilia, monocytosis, hyperuricemia	Plateletopenia, low hemoglobin, and hematocrit, lymphopenia	Not recorded	Not recorded

(*Continued*)

Table 1 (Continued).

Maternal Variables	Case 1	Case 2	Case 3	Case 4
Chikungunya, dengue and Zika test results	RT-PCR - chikungunya: detected; dengue: not detected; Zika: not detected. chikungunya IgM serology: positive	IgM serology -chikungunya: reactive positive, dengue: non-reactive; Zika: non-reactive	IgM serology - chikungunya: reactive, dengue: non-reactive; Zika: non-reactive	Not performed
Other tests	Serology IgM Herpes Virus: non-reactive; IgM Rubella: non-reactive; IgM Toxoplasmosis: non-reactive; IgM Parvovirus B19: non-reactive	Serology IgM Cytomegalovirus: non-reactive; IgM Toxoplasmosis: non-reactive; IgM Rubella: non-reactive; HIV and VDRL: negative	IgM Rubella serology: non-reactive; Cytomegalovirus IgM: non-reactive; IgM Toxoplasmosis: non-reactive	HIV and VDRL: negative
Gestational age at birth (weeks and days)	38w and 4d	39w and 2d	37w and 3d	Not recorded
Period of onset of symptoms in relation to childbirth (months and days)	1st gestational trimester	4 days before birth	7 days before birth	Days after birth

Abbreviations: IgM, Immunoglobulin M; HIV, Human Immunodeficiency Virus; VDRL, Venereal Disease Research Laboratory.

Case 1

Twin pregnancy, CHIKV infection between the 5th and 8th gestational week, reactive IgM chikungunya serology, and detectable RT-PCR. This was a full-term vaginal birth at 38 weeks and 4 days, with the presence of two dead fetuses, both male, weighing 2725 grams and 1995 grams. Fetal necropsy revealed a good nutritional status, one of the fetuses was meconium stained, with cerebral softening and autolysis, and the other fetus with macerated skin, congested lungs, and liver, with cerebral softening and congestion (Table 2).

Table 2 Clinical and Laboratory Aspects of Five Fetal and Neonatal Deaths Related to Maternal Infection with the Chikungunya Virus During Pregnancy, State of Pernambuco, Brazil, 2015 and 2016

Variables of Fetuses and Newborns	Case 1		Case 2	Case 3	Case 4
	Fetus Twin A	Fetus Twin B			
Neonatal assessment	Term, HC: 34cm; CC: 30cm; Length: 49 cm; Foot measurement: 7cm, no malformations	Term, HC: 32.5 cm; CC: 30 cm; Length: 45cm; Foot measurement: 7cm, no malformations	Term, no malformations, presence of hydrocele, desquamation of the epidermis of the scrotum	Apgar 3/4/6 did not cry at birth, intubated, cyanosis, hypoactive	–

(*Continued*)

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Table 2 (Continued).

Variables of Fetuses and Newborns	Case 1		Case 2	Case 3	Case 4
	Fetus Twin A	Fetus Twin B			
Clinical signs and symptoms	–		–	Respiratory depression, hypoventilated lung, petechiae in the abdominal region, syndromic facies	Fever, irritation, refusal to eat, body and face with hyperpigmented lesions, bilateral eyelid edema, edema in the left hand, tremors, pain in the lower limbs, encephalitis, cerebral edema
Result of the anatomopathological examination	Good nutritional status, covered with meconium, softened brain and autolysis, light red lungs, rubbery, and with no air	Regular nutritional status, skin maceration, brownish red umbilical stump, congested lungs and liver, softened and congested brain	Regular nutritional status, hyperinflated lungs with purulent exudate in bronchi, fluid in pleural spaces, kidneys with cortical pallor and median congestion	–	–
Test results for chikungunya, dengue and Zika	RT-PCR dengue, chikungunya, and Zika virus: not detected; Zika virus immunohistochemistry: inconclusive		Not performed	Not performed	RT-PCR chikungunya: detected
Confirmation criteria for CHIKV infection	Clinical-epidemiological with the mother		Clinical-epidemiological with the mother	Clinical-epidemiological with the mother	Laboratory
Causes of death recorded on the Death Certificate	Intrauterine anoxia	Intrauterine anoxia; maternal infection with Zika virus; twin pregnancy	Intrauterine anoxia, respiratory infection, bilateral pleural effusion, unspecified maternal viral syndrome	Unspecified bacterial septicemia and fetus and newborn affected by infectious and parasitic diseases of the mother	Unspecified bacterial septicemia; other congenital viral diseases; Fetus and newborn affected by infectious and parasitic diseases of the mother

Abbreviations: RT-PCR, Reverse-Transcription Polymerase Chain Reaction; HC, head circumference; CC, chest circumference; APGAR, Appearance, Pulse, Grimace, Activity, Respiration.

Case 2

At 38 weeks and 6 days, the mother was presented with fever, intense joint pain, skin rash, no cramping and/or vaginal leaks, auscultation of 144 fetal heartbeats per minute, closed cervix, and a positive IgM chikungunya serology test. She remained hospitalized for 3 days, evolving with itching, decreased movement, and absence of fetal heartbeats. Cesarean surgery was performed, and the fetus was dead, male, weighing 3130g, without malformations, presence of a mild hydrocele, and desquamation of the scrotum epidermis (Table 2). Fetal necropsy revealed a regular nutritional status, hyperinflated lungs, with purulent exudate in main and segmental bronchi, a large volume of fluid in both pleural spaces, kidneys with cortical pallor, and median congestion.

Case 3

Seven days before giving birth, at 36 weeks and 4 days, the mother began with a fever, rash, and severe arthralgia, with positive IgM chikungunya serology. At 37 weeks and 3 days, after fluid loss, a cesarean section was performed, male, weighing 2020g, identifying ruptured membranes, clear fluid, and placenta with vesicles. The Newborn was born depressed, did not cry, had central cyanosis, hypoventilated lungs, ambu ventilation, petechiae in the abdominal region, Apgar 3/4/6, and presented syndromic facies. Diagnostic hypothesis of Newborn, Small for Gestational Age, sepsis, pulmonary hypoplasia, and genetic syndrome (Table 2). Intubated, he presented progressive worsening and after 6 hours of life, early neonatal death was recorded.

Case 4

Gestational course occurred within normal limits. Surgical cesarean delivery, female, weighing 2700g, with no recorded complications or abnormalities. Both received hospital discharge. Four days after birth, the mother and newborn presented symptoms: mother with fever, diffuse skin rash, headache, joint pain, and pain in lower limbs and hands. The medical assessment indicated chikungunya. No tests were collected, and medication was prescribed and discharged. The newborn was presented with a fever (39°C), a blood count demonstrating lymphopenia, and increased C-reactive protein (CRP). Newborn remained hospitalized for seven days, progressing until late neonatal death was confirmed at 11 days of life. Upon admission, the patient was hypoactive, bradycardic, and breathless, with hyperpigmented lesions on the body and face, bilateral eyelid edema, edema in the left hand, tremors, and pain in the lower limbs. Cerebrospinal fluid (CSF) examination revealed hemorrhagic appearance, pleocytosis (Leukocytes 19 cells/mm³, 75% Polymorphonuclear), the presence of red blood cells (5280 red blood cells/mm²), increased protein (proteins 191 mg/dL), and reduced glucose (glucose 28 mg/dL). Transfontanelle ultrasound: signs of intracranial hypertension and effacement of sulci. Abdominal ultrasound: hepatomegaly, ascites, and a small amount of free fluid. A head CT scan: diffuse cerebral edema. Hematological tests revealed leukocytosis and thrombocytopenia. RT-PCR test detected chikungunya (Table 2).

Discussion

The present report describes five deaths related to maternal-fetal transmission of the Chikungunya virus (CHIKV), three of which were identified as antepartum fetal deaths (APFD) and two as neonatal deaths.

Data from 8 cohorts on infections that brought together 1203 pregnant women, their fetuses, and newborns, demonstrated a 1.7% risk of APFD (20 cases). Deaths occurred with maternal infections in all trimesters, including during the beginning of pregnancy,[8] as in Case 1, where the maternal infection was confirmed by IgM chikungunya serology during the first trimester, while in Case 2 infection occurred at 38 weeks.

Determining the status of CHIKV infection in APFDs is rarely undertaken,[8] and was confirmed in just three cases in a Reunion Island outbreak, following maternal infections between 12 and 15 gestational weeks, reducing a confirmed diagnosis of the risk of APFD to 0.3%.[14]

In our Case 1, fetal death was suspected secondary to ZIKV complications. However, similar to another report,[14] extensive research for viral material in the fetal tissues was negative for any virus, and the only infection documented throughout the pregnancy was due to CHIKV, through a positive IgM and RT-PCR chikungunya result in the mother. The case was confirmed by clinical-epidemiological criteria supported by the literature.[15] What stands out in this case is the full-term birth and, the presence of brain changes in both twins, one of whom presented brain softening and autolysis.

In Case 2 there was no viral research in the fetal tissues, a limitation of our study, and was diagnosed through an epidemiological link with the mother. Simultaneous viral detection or serological conversion in the mother-child pair is difficult, and confirmation by clinical-epidemiological criteria is common.[15] During epidemics, laboratory diagnosis can be challenging in resource-limited settings where serological tests are not routinely available.[7] In this case, the normal weight for a full-term fetus is also of note, suggesting the event was late and probably of an acute nature, resulting in fetal death.

Case 3 was the early death of a newborn whose mother presented symptoms of CHIKV seven days before birth, classified as a pre-partum infection, a critical moment for transmission to the newborn.[16] The newborn was born with signs of acute suffering, low Apgar, hypoactive and cyanotic, and died within a few hours, as presented in another report.[5] He showed signs of a genetic syndromic disease possibly unrelated to the CHIKV infection, reaching term during pregnancy. Maternal infection may have worsened the baby's general condition at birth and contributed to death. Studies have shown the significant mortality associated with CHIKV, whether due to the worsening of pre-existing comorbidities or complications directly caused by CHIKV.[17,18]

In Case 4, the mother and newborn were asymptomatic at the time of birth, four days after birth, both presented with typical symptoms of the infection, leading to the assumption that viremia and intrapartum mother-fetal transmission had occurred, even though the mother presented no symptoms at birth. Investigations of both the hospital and home environments ruled out the hypothesis that the mother and infant were bitten by an infected mosquito in the days following childbirth. The incubation period of the disease, which includes viremia, occurs between two and four days before the onset of symptoms, hence, it is likely that the baby's infection occurred during intrapartum, a period in which the overall transmission risk from mother to child reaches 50%.[8]

Also in Case 4, the newborn presented a serious illness with skin hyperpigmentation, limb edema, and neurological impairment, represented by encephalitis, typical occurrences of vertically transmitted chikungunya.[19,20] Neurological impairment was documented through pleocytosis, the presence of red blood cells, and elevated protein levels in the cerebrospinal fluid, in addition to transfontanelle ultrasound and head CT revealing cerebral edema. Findings reported in the literature.[21]

The cases described suggest a link between maternal CHIKV infection and adverse fetal/neonatal outcomes; however, we emphasize the possibility of other contributing factors to these outcomes, as highlighted in the description of case 3.

Conclusion

This report demonstrates that, although it is rare in the early trimesters, fetal death related to maternal CHIKV infection can occur at any time during pregnancy, plus the risk of vertical transmission in the peri-partum and intrapartum periods resulting in neonatal mortality.

During epidemic years, when CHIKV proliferation is intense, many health services and professionals fail to recognize the possibility of a link between clinical signs, complications, maternal infection, and adverse effects, including fetal and neonatal deaths. We alert health professionals to monitor sick pregnant women, as well as the importance of preventing the disease in this population.

In epidemics, laboratory diagnosis is challenging, particularly in resource-limited settings where serological and molecular tests are not routinely available.

Ethical Approval

The study was approved by the Research Ethics Committee of the Federal University of Pernambuco (CAAE: 66317022.2.0000.5208). No identifiable patient information was disclosed. Appropriate ethical procedures were followed to ensure patient privacy.

Consent for Publication

All patients or their durable power of attorney included in this case series provided written informed consent to publish the data presented in this manuscript. A copy of the written consent is available for review by the editor-in-chief of this journal upon request. Institutional approval was not required to publish the case details.

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Disclosure

The authors report no conflicts of interest in this work.

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