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Congenital and perinatal complications of chikungunya fever: a Latin American experience



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SUMMARY

Background: During the years 2014 and 2015, the Region of the Americas underwent a devastating epidemic of chikungunya virus (CHIKV) of the Asian genotype, resulting in millions of affected individuals. However, epidemiological and clinical information on this experience is scarce. Prior knowledge of congenital and neonatal illness caused by CHIKV is limited and almost exclusively based on data obtained from a single outbreak of the East/Central/South African (ECSA) genotype. The effect of chikungunya fever (CHIKF) on pregnancy outcomes and its consequences for infants born to infected mothers at the peak of the epidemic wave in Latin America are reviewed herein. Epidemiological and clinical data on maternal and neonatal infections were collected prospectively and analyzed.

Methods: One hundred sixty-nine symptomatic newborns with CHIKF seen at four large regional maternity hospitals in three different Central and South American countries were evaluated prospectively. The outcomes of pregnancies in symptomatic infected mothers at two of these clinical centers were also analyzed.

Results: The observed vertical transmission rate ranged between 27.7% and 48.29%. The incidence of congenital disease was unrelated to the use of cesarean section or natural delivery. The case fatality rate (CFR) at the only center that reported deaths was 5.3%. The most common clinical manifestations included fever, irritability, rash, hyperalgesia syndrome, diffuse limb edema, meningoencephalitis, and bullous dermatitis. Severe complications included meningoencephalitis, myocarditis, seizures, and acute respiratory failure. Leukocytosis with neutrophilia and normal or increased platelets was a common finding, and in those with signs of meningeal involvement, moderate lymphocytic pleocytosis with normal glucose and protein levels was typical.

Conclusions: This study presents the largest number of symptomatic neonates with CHIKF analyzed so far in any region and is the first involving infection with the Asian genotype of CHIKV. Although the clinical manifestations found were similar to those reported previously, the percentage of neurological complications was lower. The CFR was comparatively high. Chikungunya represented a substantial risk for neonates born to symptomatic parturients during the chikungunya outbreak in the Americas Region, with important clinical and public health implications.

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1. Introduction

Little is known of the risk and impact of mother-to-child transmission of chikungunya virus (CHIKV). Most of our present knowledge is derived from the experience of the large outbreak caused by the East/Central/South African (ECSA) genotype in La Réunion Island, where perinatal infection, as well as the clinical

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manifestations and several complications of neonatal illness, were described for the first time.^{1–3}

Since December 2013, a large epidemic of chikungunya fever (CHIKF) caused by the Asian genotype of CHIKV has affected the Caribbean and Central and South America, with over 1.5 million cases of the disease reported from more than 20 countries.⁴ A recent report by Villamil-Gómez et al., emphasizes the threat to maternal and child health in the Americas, describing a case series of eight severely ill newborns with documented congenital CHIKF seen at a private health facility in the city of Sincelejo, Sucre Department, Colombia.⁵

The aim of this study was to determine the effect of CHIKF on pregnancy outcomes and its consequences for infants born to infected mothers in the Americas. Information was collected from four large regional maternity hospitals in three countries of the region. The epidemiological and clinical data pertaining to maternal and neonatal infections observed at the peak of the epidemic wave are analyzed herein.

2. Materials and methods

Prospective clinical and epidemiological data collected from all symptomatic pregnant women and newborns with a confirmed diagnosis of CHIKF, seen at two large reference hospitals in El Salvador from August to October 2014, were reviewed. All patients had either one CHIKV end-point conventional PCR or reverse transcriptase (RT)-PCR confirmatory result, or else a CHIKV monoclonal antibody-based IgM capture ELISA test performed at a diagnostic reference laboratory. Relevant information was supplemented by data collected from the Epidemiological Surveillance System of the Ministry of Health of El Salvador (VIGEPES), as well as through personal communication with Dr Julio Armero of the Pediatric Department of Zacamil National Hospital and “Hospital Nacional de la Mujer”, San Salvador, El Salvador.

All newborns admitted to the University Hospital “Hernando Moncaleano Perdomo”, in Neiva, Colombia, whose mothers had documented or suspected clinical CHIKF from January 1 to March 31, 2015, after the official declaration of the chikungunya outbreak situation in the municipality, were evaluated prospectively. The clinical information obtained for 35 newborns with characteristic clinical manifestations suspected of having CHIKF, as well as for two severely ill patients with laboratory confirmation of CHIKV infection by CHIKV RT-PCR, were analyzed.

Prospective and retrospective clinico-epidemiological data from symptomatic pregnant women and newborns seen at the Maternity Hospital “Nuestra Señora de La Altagracia”, Santo Domingo, Dominican Republic, from May to August 2014, were provided by Dr Luis Rivera Mejía. Standard Pan American Health Organization chikungunya fever case definitions and clinical classification were used.⁶ A suspected case was any symptomatic newborn from a mother with acute onset of fever $>38.5^{\circ}\text{C}$ and severe arthralgia/arthritis during the previous 2 weeks, not explained by other medical conditions, residing or having visited epidemic areas with reported transmission within 15 days prior to the onset of symptoms. No confirmatory tests for CHIKV infection were widely available in the country during the study period.

In general, CHIKF was considered as a vertical mother-to-child transmission when symptoms occurred during the first week of life, in the absence of evidence of a mosquito bite.

Fisher's exact test was used to determine non-random associations between two categorical variables when applicable.

3. Results

One hundred ninety-one symptomatic pregnant women with CHIKV infection confirmed by specific serology or PCR were followed prospectively and their pregnancy outcomes assessed at two different public medical centers in San Salvador, El Salvador (Hospital Nacional de la Mujer, and Hospital Nacional Zacamil). A total of 53 CHIKV-infected newborns, confirmed by either conventional end-point PCR or RT-PCR, were identified and clinically followed in the Pediatric Department of Zacamil National Hospital and “Hospital Nacional de la Mujer”, located in the same city.

All women were in the third trimester of pregnancy (mean gestational age 38.2 weeks, range 35–40 weeks). Maternal age ranged from 14 to 30 years (mean 22.8 years). A total of 53 newborns developed a congenital infection confirmed by specific CHIKV RT-PCR (vertical transmission rate 27.7%). Premature delivery occurred in 17 cases (8.9%), but no miscarriages were observed. The average weight of affected newborns was 3.1 kg.

The predominant clinical manifestations in symptomatic newborns were fever (100%), irritability (90%), rash (84%), generalized edema (86%), hyperalgesia (94%), stiff neck or pain on mobilization (38%), and hemodynamic instability (52%). Relevant abnormal hematological parameters included hemoglobin (median 15.8 g/dl, range 12.0–20.1 g/dl), leukocytes (median $18.24 \times 10^9/l$, range $3.53\text{--}37.29 \times 10^9/l$), neutrophils (mean $13.27 \times 10^9/l$, range $2.27\text{--}27.69 \times 10^9/l$), percentage of bands (median 4%, range 0–30%), and platelets (median $242.0 \times 10^9/l$, range $88\text{--}372 \times 10^9/l$). Moderate thrombocytopenia was observed in two patients.

Thirty-seven symptomatic neonates (24 male, 13 female) born to mothers with documented (20 patients) or suspected (17 patients) clinical CHIKF, were evaluated at the service of Neonatal Basic Care and/or Neonatal Intensive Care Unit of the University Hospital “Hernando Moncaleano Perdomo”, in Neiva, Colombia. Other confounding acute viral and bacterial infections were excluded in all newborns, either by conventional serology or by culture. Rapid tests for dengue (Ad-bio Rapid Ag dengue CE and Duo IgG/IgM rapid test CE; CTK Biotech, San Diego, CA, USA) were routinely performed, and all cases were negative. Zika serology was not included, as circulation of the virus was not known to be occurring on the continent at that time.

The mean duration of fever was 3 days (range 1–5 days), and the average length of hospital stay was 3.9 days (range 1–11 days). The most common clinical findings were exanthema (97.2%), lower extremity edema (27%), diffuse hyperalgesia syndrome (13.5%), diarrhea (19%), distal cyanosis (8.1%), diffuse abdominal pain (8.1%), and bullous dermatosis (5.4%). Two of these babies developed severe myocarditis, with echocardiographic evidence of ventricular dysfunction. Both recovered uneventfully. In both cases, conventional CHIKV RT-PCR performed on serum obtained early in the course of the illness was positive. Another newborn had a generalized seizure, with normal cerebrospinal fluid results and no evidence of neurological sequelae.

At “Nuestra Señora de La Altagracia” Maternity Hospital in Santo Domingo, Dominican Republic, 205 pregnant women with symptoms of CHIKF, classified as suspected cases, as defined previously (see above), were evaluated. A total of 99 newborns developed symptoms suggestive of the condition. All of them had fever, poor feeding, and irritability, in combination with any of the following: rash, hyperalgesia/allodynia, diffuse lower limb edema, dermatosis bullosa/skin scaling, meningoencephalitis, respiratory failure, hyperpigmentation, or myocarditis. Of note, 85 (85.85%) of them became ill on the fifth day after birth. Although confirmatory tests for CHIKV infection were not available, other confounding acute viral infections including dengue, as well as bacterial

infections, were excluded in all cases by either conventional serology or by culture. Zika virus was not present in the population during the period of observation. The vertical transmission rate was 48.29% (99 symptomatic neonatal infections out of 205 mothers). Caesarean sections were performed in 59 of the 99 symptomatic mothers (74.6%). The incidence of congenital disease in newborns was statistically unrelated to cesarean delivery (Fisher's exact test, $p > 0.05$).

Seventy-nine infected newborns with typical signs of acute CHIKF could be evaluated prospectively in detail. The onset of symptoms in all of these children occurred between days 3 and 9 after birth (median day 5). Fever, difficulty in feeding, and irritability were documented in all patients. A rash was seen in 43.0% of cases, diffuse edema of the extremities in 41.8%, bullous dermatosis and/or intense skin scaling in 8.9%, and hyperpigmentation in 5.1%. Other relevant clinical findings included diffuse hyperalgesia syndrome in 57.0%, acute respiratory failure in 10.1%, meningoencephalitis in 1.2%, and myocarditis in 1.2%. In none of the newborns were congenital malformations identified.

Four out of 79 newborns died (including a pair of twins), giving a case fatality rate (CFR) of 5.1%. The cause of death was extreme low birth weight and acute respiratory distress syndrome in two newborns, meconium aspiration with congenital pneumonia in one, and extreme low birth weight with intraventricular hemorrhage in the other.

The comparative and combined results of the clinical findings observed in these 169 neonates with confirmed (55 cases) or suspected (114 cases) CHIKV infection, seen at four medical institutions in three different Latin American countries, are shown in Table 1. Rash, hyperalgesia or allodynia, and meningoencephalitis were the only clinical findings observed significantly less often in the unconfirmed suspected cases at Nuestra Señora de Altigracia Maternity Hospital, as compared to those confirmed at the other clinical centers studied (Fisher's exact test p -value of < 0.0001).

Twenty-two neonates with a confirmed infection underwent lumbar puncture. Results were abnormal in 10 of them, with cytochemical analysis of the cerebrospinal fluid (CSF) revealing consistently normal levels of glucose, elevated leukocytes (median $158 \times 10^6/l$, range $32\text{--}376 \times 10^6/l$) with a predominance of lymphocytes (median 64%, range 38–89%), and normal proteins (median 68 mg/dl, range 38–69 mg/dl). The specific CHIKV RT-PCR test of CSF was positive in two cases (Table 2).

Table 2

Lumbar puncture results for 22 neonates with chikungunya fever and clinical findings of meningoencephalitis, seen at the Pediatric Department of Zacamil National Hospital and "Hospital Nacional de la Mujer", San Salvador, El Salvador

CSF cytochemical parameter	Mean value	Range
Glucose, mg/dl	57	45–80
WBC count, $\times 10^6$ cells/l	158	32–376
Percentage of lymphocytes	64%	38–89%
Proteins, mg/dl	68	38–69

CSF, cerebrospinal fluid; WBC, white blood cell count.

4. Discussion

Mother-to-child transmission of CHIKV was reported during the large 2005–2006 outbreak on La Réunion Island, France.⁷ Maternal–fetal transmission almost invariably occurs in the setting of maternal viremia concomitant with delivery. As shown in the present series of patients, a cesarean section does not appear to prevent vertical transmission of CHIKV; therefore, the systematic performance of cesarean sections for infected mothers in order to reduce the risk of viral transmission should not be recommended.^{8–10} Close monitoring of viremic parturients and delivery in maternity facilities with adequate obstetric and neonatal care is advised.

Early maternal–fetal transmission of CHIKV, before 16 weeks of gestation, has resulted in fetal deaths with no malformations, with the presence of viral genome in the amniotic fluid, placenta, and/or brain of the fetuses.⁹

When maternal infection occurs at the end of pregnancy, about 12% of newborns are expected to be symptomatic and most of them will develop severe manifestations such as meningoencephalitis and intravascular coagulation, requiring a prolonged neonatal hospitalization and/or intensive care.^{10–12} This may be due in part to the higher viral concentrations observed in this age group.^{10–12}

Of note, conjunctivitis – a common finding in adults and older children – was not observed in any of the newborns in this series of cases. Furthermore, thrombocytopenia, which has been reported in up to 89% of infected neonates,¹³ was a very unusual finding (1.2%) in the patients in this study.

In the context of outbreaks, CHIKV may represent a significant cause of central nervous system disease in children. Indeed, a cumulative incidence rate (CIR) per 100 000 persons of 187 in

Table 1

Clinical characteristics of 169 neonates with chikungunya fever seen at the Maternity Hospital "Nuestra Señora de La Altigracia" in Santo Domingo, Dominican Republic, the University Hospital "Hernando Moncaleano Perdomo" in Neiva, Colombia, and the Pediatric Department of Zacamil National Hospital and "Hospital Nacional de la Mujer" in San Salvador, El Salvador

	Zacamil National Hospital and "Hospital Nacional de la Mujer", El Salvador $n = 53$	"Nuestra Señora de La Altigracia" Maternity Hospital, Dominican Republic $n = 79$	University Hospital "Hernando Moncaleano Perdomo", Colombia $n = 37$	Total All institutions combined $n = 169$
Clinical finding	n (%)	n (%)	n (%)	n (%)
Fever	53 (100%)	79 (100%)	37 (100%)	169 (100.0%)
Poor feeding	52 (98.1%)	79 (100%)	36 (97.3%)	167 (98.8%)
Irritability	48 (90.6%)	79 (100%)	37 (100%)	164 (98.2%)
Rash ^a	45 (84.9%)	34 (43.0%)	36 (97.3%)	115 (68.0%)
Hyperalgesia/allodynia ^a	50 (94.3%)	45 (57.0%)	5 (13.5%)	97 (57.4%)
Diffuse lower limb edema	46 (86.8%)	33 (41.8%)	10 (27.0%)	89 (52.7%)
Hemodynamic instability	28 (52.8%)	-	1 (2.7%)	29 (17.2%)
Dermatosis bullosa/skin scaling	8 (15.1%)	7 (8.9%)	2 (5.4%)	17 (10.1%)
Respiratory failure	4 (7.5%)	8 (10.1%)	1(2.7%)	13 (7.7%)
Meningoencephalitis ^a	10 (18.86%)	1 (1.2%)	1 (2.7%)	12 (7.1%)
Hyperpigmentation	-	4 (5.1%)	-	4 (2.4%)
Myocarditis	-	1 (1.2%)	2 (5.4%)	3 (1.8%)

^a Fisher's exact test $p < 0.0001$ for differences between "Nuestra Señora de La Altigracia" Maternity Hospital suspected chikungunya fever cases and confirmed cases at the other three clinical centers.

patients under 1 year of age (which is far greater than those of cumulated causes of encephalitis in the USA in this age category), with a CFR of 16.6%, has been reported recently based on the experience of the large epidemic observed in La Réunion Island. The proportion of children discharged with persistent disabilities was estimated at between 30% and 45%.¹¹

Vertical transmission rates in the present series (27.2% to 48.29%) were similar to those reported previously in the literature (47%). Nonetheless, the CFR observed (5.3%) is significantly greater than reported previously in La Réunion Island in 2006 (ranging from 0.8% (5/658) to 2.6% (1/38)) and in Colombo, Sri Lanka in 2007 in which no deaths were described.^{12–15}

A recent study in Colombia aimed at characterizing CHIKF in children and detecting differences in presentation and severity between neonates and other age groups, showed that both hemoglobin and hematocrit levels were significantly lower in the group of neonates with confirmed CHIKV infection, and platelet counts were abnormally low ($<100 \times 10^9/l$) in 20% of them ($p = 0.040$). Rash was significantly more frequent in neonates than in other children with confirmed CHIKF, and the interquartile range (IQR) of viral load was also higher ($p = 0.030$). Neonates had an adjusted relative risk of being admitted to critical care of 7.77 (95% confidence interval 1.37–43.79), as compared to the other age groups. Some of the results of this study have been published recently.¹⁶

Recent estimates, also from Colombia, suggest a high economic impact of pediatric infection in this region. Indeed, the average cost per uncomplicated CHIKF case was US\$ 517.5 for children ≥ 1 year of age and US\$ 375.1 for children < 1 year old. The average length of stay was 2.7 days per patient.¹⁷

The prognosis of uninfected children born to mothers infected by CHIKV during pregnancy is identical to that of children exposed in utero to maternal fever, for which there is currently no convincing evidence of subsequent neurocognitive impairment. However, in neonates diagnosed with CHIKF, long-term follow-up is needed, given the implications of potential long-term sequelae, such as neurocognitive impairment, microcephaly, and cerebral palsy.¹¹

One obvious limitation of this series is the lack of confirmatory results in a large proportion of the cases. However, all patients were seen during the peak of a well-documented epidemic of CHIKV, and many of them showed characteristic clinical findings such as a distinct rash, hyperalgesia syndrome, diffuse inflammatory lower limb edema, and bullous dermatosis, all of these considered hallmarks of neonatal CHIKF.^{13,14} Moreover, confounding factors like dengue fever were routinely excluded in all mothers and newborns, and Zika virus was not present in the Western Hemisphere at that time.

It must be highlighted that with few exceptions, the frequency of clinical findings seen in suspected cases was similar to that of confirmed patients in this series. Although rash and meningoencephalitis were clearly significantly less common in the former, it can be argued that hyperalgesia or allodynia, also seen less often in suspected cases, may easily be missed or underestimated by a less meticulous clinician.

These results may help public health officials, obstetricians, pediatricians, and infectious disease specialists who provide care for pregnant women or newborns in the region. In countries experiencing epidemics of CHIKF, clinicians must be familiar with the possibility of mother-to-child transmission and its consequences, as such knowledge may help to improve its future management and strengthen mitigation strategies.

Conflict of interest: No conflict of interest/funding to declare.

References

- Robillard PY, Boumahni B, Gérardin P, Michault A, Fourmaintraux A, Schuffenecker I, et al. Transmission verticale materno-foetale du virus chikungunya. Dix cas observés sur l'île de la Réunion chez 84 femmes enceintes. *Presse Med* 2006;**35**:785–8.
- Ramful D, Carbonnier M, Pasquet M, Bouhmani B, Ghazouani J, Noormahomed T, et al. Mother-to-child transmission of chikungunya virus infection. *Pediatr Infect Dis J* 2007;**26**:811–5.
- Fritel X, Rollot O, Gérardin P, Gauzere BA, Bideault J, Lagarde L, et al. Chikungunya virus infection during pregnancy, Reunion, France, 2006. *Emerg Infect Dis* 2010;**16**:418–25.
- Pan American Health Organization. Chikungunya statistic data. PAHO; 2015. Available at: http://www.paho.org/hq/index.php?option=com_topics&view=readall&cid=5927&Itemid=40931&lang=en (accessed October 19, 2015)
- Villamil-Gómez W, Alba-Silvera L, Menco-Ramos A, Gonzalez-Vergara A, Molinères-Palacios T, Barrios-Corrales M, et al. Congenital chikungunya virus infection in Sincelejo, Colombia: a case series. *J Trop Pediatr* 2015;**61**:386–92.
- Pan American Health Organization. Preparedness and response for chikungunya virus: introduction in the Americas. Washington, DC: PAHO; 2011.
- Economopoulou A, Dominguez M, Helynck B, Sissoko D, Wichmann O, Quenel P, et al. Atypical Chikungunya virus infections: clinical manifestations, mortality and risk factors for severe disease during the 2005–2006 outbreak on Réunion. *Epidemiol Infect* 2009;**137**:534–41.
- Passi GR, Khan YZ, Chitnis DS. Chikungunya infection in neonates. *Indian Pediatr* 2008;**45**:240–2.
- Gérardin P, Sampéris S, Ramful D, Boumahni B, Bintner M, Alessandri JL, et al. Neurocognitive outcome of children exposed to perinatal mother-to-child chikungunya virus infection: the CHIMERE Cohort Study on Reunion Island. *PLoS Negl Trop Dis* 2014;**8**:e2996. <http://dx.doi.org/10.1371/journal.pntd.0002996>
- Lenglet Y, Barau G, Robillard PY, Randrianaivo H, Michault A, Bouveret A, et al. Chikungunya infection in pregnancy: Evidence for intrauterine infection in pregnant women and vertical transmission in the parturient. Survey of the Reunion Island outbreak. *J Gynecol Obstet Biol Reprod (Paris)* 2006;**35**:578–83.
- Gérardin P, Couderc T, Bintner M, Tournebise P, Renouil M, Lémant J, et al. Chikungunya virus-associated encephalitis: a cohort study on La Réunion Island, 2005–2009. *Neurology* 2016;**86**:94–102.
- Touret Y, Randrianaivo H, Michault A, Schuffenecker I, Kauffmann E, Lenglet Y, et al. Transmission materno-foetale précoce du virus chikungunya. *Presse Med* 2006;**35**:1656–8.
- Gérardin P, Barau G, Michault A, Bintner M, Randrianaivo H, Choker G, et al. Multidisciplinary prospective study of mother-to-child chikungunya virus infections on the Island of La Réunion. *PLoS Med* 2008;**5**:e60. <http://dx.doi.org/10.1371/journal.pmed.0050060>
- Boumahni B, Bintner B. Five-year outcome of mother-to-child transmission of chikungunya virus. *Med Trop (Mars)* 2012;**72**. Spec No: 94–6.
- Senanayake MP, Senanayake SM, Vidanage KK, Gunasena S, Lamabadusuriya SP. Vertical transmission in chikungunya infection. *Ceylon Med J* 2009;**54**:47–50.
- Pinzón-Redondo H, Paternina-Caicedo A, Barrios-Redondo K, Zarate-Vergara A, Tirado-Pérez I, Fortich R, et al. Risk factors for severity of chikungunya in children: a prospective assessment. *Pediatr Infect Dis J* 2016 Mar 15 [Epub ahead of print].
- Castañeda-Orjuela C, Díaz-Jiménez D, Rodríguez-Castillo L, Paternina-Caicedo A, Pinzón-Redondo H, Alvis-Guzman N, et al. Medical care costs of chikungunya virus infection in a pediatric population in Colombia. *Value in Health* 2015;**18**:A1–307.