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Capítulo 7

Chikungunya fever and pregnancy

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SUMMARY

Chikungunya fever, an acute infectious disease caused by the Chikungunya virus (CHIKV), is transmitted mainly by the bite of the *Aedes aegypti* mosquito. The epidemic spread from Africa to southern Asia and the islands of the Indian Ocean, and it is known to have been introduced to the American continent by 2013. In its epidemiological alert of February 13, 2023, the PAHO reported that in 2022, a significant

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increase in the number of cases and deaths from chikungunya compared to previous years were reported in the Americas. The frequent clinical manifestations suggesting chikungunya are the presence of arthralgia and fever. In general, mortality from CHIKV is very low, except in patients with atypical disease. The symptoms in pregnant are like those in their nonpregnant counterparts. In addition to the warning signs when present, the criteria for hospitalization for pregnant with CHIKV include decompensated underlying disease, atypical chikungunya, home away from a hospital and the last month of pregnancy. The main vulnerability in pregnant women is related to the affectation of the newborn when the mother acquires the disease 4 days before delivery or in the intrapartum period. Cesarean section does not have a protective effect on vertical transmission. Newborns of mothers who experience symptoms of chikungunya infection near the time of delivery require admission and observation for signs of vertical transmission for at least 7 days after delivery; transmission by breastfeeding has not been demonstrated**.** There is no specific treatment for the disease; its management focuses on the use of analgesics to mitigate pain, preferably with antipyretic activity to reduce fever**.** Prevention consists of the use of mosquito nets to avoid the bite of the Aedes mosquito and the use of skin repellants allowed during pregnancy. There is currently no vaccine available.

Keywords: Pregnancy complications, chikungunya fever, vertical transmission, breastfeeding, atypical disease.

RESUMEN

La fiebre chikungunya, una enfermedad infecciosa aguda causada por el virus Chikungunya (CHIKV), se transmite principalmente por la picadura del mosquito *Aedes aegypti*. La epidemia se extendió desde África hasta el sur de Asia y las islas del Océano Índico, y se sabe que se introdujo en el continente americano en 2013. En su alerta epidemiológica del 13 de febrero de 2023, la OPS informó que en 2022, hubo un importante aumento en el número de casos y

muertes por chikungunya en comparación con años anteriores. Las manifestaciones clínicas frecuentes que sugieren chikungunya son la presencia de artralgias y fiebre. En general, la mortalidad por CHIKV es muy baja, excepto en pacientes con enfermedad atípica. Los síntomas en las mujeres embarazadas son similares a los de sus contrapartes no embarazadas. Además de las señales de alerta cuando estén presentes, los criterios de hospitalización para embarazadas con CHIKV incluyen enfermedad subyacente descompensada, estar lejos del hospital y el último mes de embarazo. La principal vulnerabilidad en las mujeres embarazadas está relacionada con la afectación del recién nacido cuando la madre adquiere la enfermedad 4 días antes del parto o en el período intraparto. La cesárea no tiene un efecto protector sobre la transmisión vertical. Los recién nacidos de madres que experimentan síntomas de infección por chikungunya cerca del momento del parto requieren ingreso y observación para detectar signos de transmisión vertical durante al menos 7 días después del parto. No se ha demostrado la transmisión por lactancia materna. No existe un tratamiento específico para la enfermedad; su manejo se centra en el uso de analgésicos para mitigar el dolor, preferiblemente con actividad antipirética para reducir la fiebre. La prevención consiste en el uso de mosquiteros para evitar la picadura del mosquito Aedes y el uso de repelentes cutáneos permitidos durante el embarazo. Actualmente no hay ninguna vacuna disponible.

Palabras clave: Complicaciones del embarazo, fiebre chikungunya, transmisión vertical, lactancia materna, enfermedad atípica.

INTRODUCTION

Chikungunya fever, an acute infectious disease caused by the Chikungunya virus (CHIKV), genus alphavirus, family Togaviridae, is transmitted mainly by the bite of the *Aedes aegypti* mosquito. The first outbreak of chikungunya fever occurred in Tanzania, Africa, in 1952, and the virus was isolated in 1953. The epidemic spread from

Africa to southern Asia and the islands of the Indian Ocean, and it is known to have been introduced to the American continent by 2013. The disease is present in more than 100 countries and territories, and it is estimated that it causes 1 million infections per year worldwide (1). It is considered a reemerging disease, undoubtedly due to the impact of climate change on the vectors that cause arboviruses (2).

According to a report by the Pan American Health Organization (PAHO), from the beginning of the epidemic in December 2013 to epidemiological week 30 of 2015, in the Americas, more than 1.6 million suspected or confirmed cases of chikungunya and at least 253 associated deaths were reported (3). The countries that reported the most cases were Brazil, Bolivia and Colombia. In Brazil, the CHIKV outbreak was aggravated by the concomitant circulation of other arboviruses, such as dengue and Zika, and many patients experienced a dual infection (4).

CURRENT EVENTS IN THE AMERICAS

Since 2017, there have been cases of chikungunya on a smaller scale throughout the Americas. In its epidemiological alert (5) of February 13, 2023, the PAHO reported that in 2022, a significant increase in the number of cases and deaths from chikungunya compared to previous years were reported in the Americas. Specifically, a total of 271 176 cases of chikungunya were reported, including 95 deaths in 13 of the countries and territories of the Americas, while during the first four epidemiological weeks of 2023, 30 707 cases and 14 deaths from the disease were reported.

In the first months of 2023, Paraguay faced an unprecedented epidemic of chikungunya (6), with 11 467 cases reported (epidemiological weeks 7-9 of 2023), including 226 pregnant women; individuals aged 20 to 39 years are the most affected (29 %), followed by those older than 60 years of age (24 %). Most of the affected were female (58 %). Additionally, 43 deaths were reported (from week 51 of 2022 onward), 35 in those over 30 years of age, and all presented some type of comorbidity, with hypertension being the most frequent.

CLINICAL MANIFESTATIONS

The incubation period of the disease is 2 to 12 days, generally 2 to 7 days, and frequent clinical manifestations suggesting chikungunya are the presence of arthralgia (with or without synovitis/arthritis) and fever. The symptoms in the acute stage include arthralgias of variable severity, and the intensity of the pain can be very important on the first day of the infection, even limiting daily activities. The pain forces people to adopt a semi stooped position, hence the name "chikungunya" (stooped or folded). Arthralgias and arthritis occur mainly in small joints of the hands, feet and wrists, but the knees, shoulders, elbows and spine can also be affected (2,4).

Arthralgia and/or arthritis are generally symmetrical, and the involvement of several joints is typical. Approximately 50 % of patients present with maculopapular eruption. In the acute phase, weakness, headache, asthenia, loss of appetite and insomnia also usually appear. Most patients recover in 7 to 10 days, with a variable proportion progressing to the subacute and chronic forms of the disease.

Chronicity manifests as the persistence of joint symptoms for a period greater than 3 months, especially in elderly individuals, people who experience previous rheumatological diseases and patients who present with a strong inflammatory response in the acute stage.

The warning signs (4) can be seen in Table 1.

Atypical disease occurs in a very low percentage of individuals, with a predilection, although not exclusive, in the groups mentioned above. The clinical manifestations are usually serious, the most frequent of which include encephalitis, seizures, myocarditis, pericarditis, heart failure, kidney failure, respiratory failure, various ocular manifestations (episcleritis, granulomatous and no granulomatous uveitis and more), hyperpigmentation and bullous eruption (7). Atypical chikungunya can have an aggressive behavior, with septic shock, multiorgan failure and acronecrosis (8).

Manifestations in the nervous system appear to be the most common serious complications of chikungunya infection. Studies have shown that among the manifestations of chikungunya in patients requiring intensive care, neurological disorders are the main problem (9).

Table1.

Chikungunya fever warning signs

Fever lasting more than 5 days.	Postural dizziness
Intense joint pain lasting more than 5 days.	Cold extremities.
Intense and continuous abdominal pain.	Decreased urine output.
Persistent vomiting and intolerance to oral nutrition.	Bleeding from any orifice.
Petechiae, subcutaneous hemorrhage, or mucosal bleeding.	Newborn of a mother with viremia at the time of delivery with signs and symptoms.
Alteration of the state of consciousness.	

Ref. 4.

Risk groups for atypical disease include neonates (with or without symptoms) of mothers with viremia during childbirth or in the last 4 days before delivery, children under 1 year of age, adults over 65 years of age, people with comorbidities (diabetes, arterial hypertension, chronic kidney failure, cardiovascular diseases, HIV-AIDS, tuberculosis, cancer, and hematological diseases, among others) (7-9).

CHIKUNGUNYA IN PREGNANCY

The symptoms of CHIKV in pregnant women are similar to those in their nonpregnant counterparts, with joint and dermatological

manifestations observed in some series in greater proportion than fever. A large study (10) including 658 pregnant women infected with CHIKV revealed that the infection occurred during the first trimester in 99 women (15 %), in the second trimester in 387 patients (59 %), and in the third trimester in 172 patients (26 %). The most frequent maternal signs and symptoms were fever (62 %), arthralgia (93 %), headache (54 %), edema (54 %), diarrhea (12 %), canker sores (9.6 %), epistaxis or gingivorrhagia (9.0 %) and skin rash (76 %). In total, 137 (21 %) were hospitalized with a median duration of 2 days (range 1-75 days). Signs of infection began at a median of 108 days before delivery (range 1-263 days), and only 4 infected women (0.6 %) had symptoms in the 7 days before delivery (10). The pregnancy outcomes included 656 live births. Of the 4 children born to mothers infected with CHIKV during the last week of pregnancy, only one newborn had signs of infection on the third day of life according to a positive RT-PCR and IgM test. The mother had chikungunya symptoms one day before delivery. Cesarean section had no protective effect.

Atypical chikungunya in pregnant women is not frequent, although it has been reported, resulting in admission to the intensive care unit and presenting with an adverse evolution of pregnancy, miscarriage, prematurity and neonatal death (11).

In general, mortality from CHIKV is very low, except in patients with atypical disease; in some cases, mortality can reach 10 % and increases with age (7).

The differential diagnosis of chikungunya fever in pregnant women includes dengue, Zika, rubella, infection by cytomegalovirus and Epstein-Barr virus, and Mayaro fever, among others (12,13).

A photograph of a pregnant woman with a clinical diagnosis compatible with chikungunya fever (fever, joint pain, synovitis, rash) is shown Figure 1.

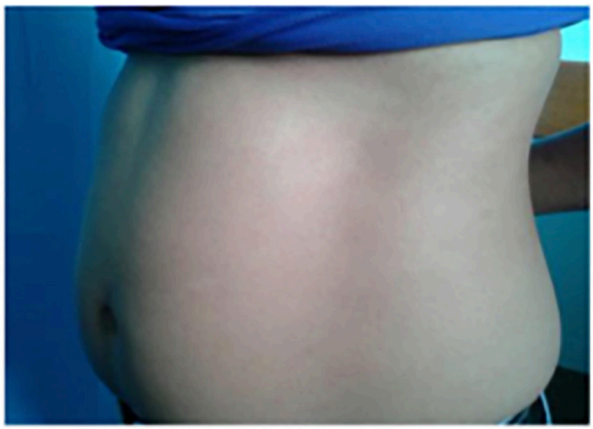

Figure 1. Maculopapular eruption in a woman with symptoms compatible with CHIKV. The patient presented with arthralgia, synovitis, fever and this eruption at 15 weeks of pregnancy. Courtesy of Ana Carvajal de Carvajal. Caracas. Venezuela. Year 2014.

HOSPITALIZATION CRITERIA IN PREGNANT WOMEN

In addition to the warning signs when present, the criteria for hospitalization for pregnant women with CHIKV include: atypical disease, decompensated underlying disease, home away from a hospital and the last month of pregnancy or date close to its end. If the pregnant woman is not hospitalized, regular control should be performed within 24 to 48 hours. It is important to rule out dengue, Zika and other diseases that cause rash and fever. Patients with CHIKV can be coinfected with dengue and other viruses. A good epidemiological surveillance system is essential to sensitize primary care and emergency physicians to identify suspected cases of CHIKV that merit referral to a more complex level of care. In this sense, it is recommended that all pregnant women with chikungunya be evaluated by their obstetrician before deciding if they should be treated with outpatient care or if they should be hospitalized.

CHIKUNGUNYA VERTICAL TRANSMISSION (VT)

CHIKV VT was demonstrated for the first time in the epidemic on the French island of Reunion in 2005-2006. The main vulnerability in pregnant women is related to the affectation of the newborn when the mother acquires the disease 7-3 days before delivery or in the intrapartum period. All studies have shown that chikungunya is severe in infected neonates.

In a systematic review of CHIKV VT (14), out of a total of 266 CHIKV-infected neonates confirmed by serological and/or molecular tests, the vertical transmission rate was 50 % in the outbreak of Reunion Island (which was the subject of most studies and where VT of the virus was demonstrated for the first time (years 2005-2006)), premature birth was reported in 45.2 % of studies; the fetal distress rate was 19.6 % of infected babies, and fetal loss occurred in 2 % of cases. Approximately 68.7 % of perinatally infected newborns were diagnosed with encephalopathy or encephalitis. Most infected newborns were born healthy and developed the clinical syndrome of CHIKV sepsis in the first week of life.

In a study carried out in three Latin American countries (Colombia, El Salvador and the Dominican Republic) (15), 160 neonates with congenital chikungunya were studied; the most frequent clinical manifestations included fever, irritability, rash, hyperalgesia syndrome, diffuse edema of the extremities, meningoencephalitis and bullous dermatitis. Serious complications included meningoencephalitis, myocarditis, seizures, and acute respiratory failure. A case fatality rate of 5.3 % was reported by only one of the included hospitals.

FINDINGS IN THE PLACENTA

Pathogens can access the intra-amniotic compartment through multiple mechanisms that can be observed from transplacental transmission, including ultrastructural alterations, thinning of the basal endothelium and even fetal and maternal hemorrhages, patterns that support vertical transmission (1,7).

Given the increase in the incidence of chikungunya, histopathological examination of the placentas of pregnant patients infected by this virus has been made mandatory to minimize injury to the mother-child pair and to prevent possible perinatal complications.

Among the initial studies of this disease, such as those in 2005, cases of vertical transmission of the chikungunya virus were suspected in asymptomatic mothers without observable effects on the newborn (1,7); however, later studies found that the newborns of mothers with symptoms in their third trimesters of pregnancy also developed symptoms (16).

Deciduitis, a frequent complication of chikungunya infection, presents as an absence of remodeling in the decidual segments, an increase in fibrinoid material and necrosis of the placental bed. CHIKV infection seems to disrupt placental homeostasis leading to histopathological alterations in addition to increase in cellularity and cytokines overproduction ($CD8^+$ and $CD163^+$), evidencing an altered and harmful environment to the pregnant woman and fetus (17). Histopathological analyses of the placental beds from deciduitis and edema to chorioamnionitis and the structural changes of the syncytiotrophoblast demonstrate the viral infection, and its complexity explains the complications observed in the infected pregnant woman.

These changes and their consequences in the maternal-fetal sphere urge us to continue the detailed observation of vertical transmission for better management of viral diseases from the perspective of prenatal management and in the product.

METHOD OF DELIVERY

Cesarean section does not have a protective effect on VT, the indication for which is made according to obstetric conditions and the clinical condition of the patient. In pregnant women for whom cesarean section has been planned and who present with symptoms suggestive of the disease, the recommendation is to delay delivery as much as possible to avoid congenital transmission of CHIKV.

Newborns of mothers who experience symptoms of chikungunya infection near the time of delivery require admission and observation

for signs of vertical transmission for at least 7 days after delivery, as they may be asymptomatic during the first days of life (14).

Newborns of mothers infected outside the peripartum period are generally unaffected by the chikungunya virus. The neurocognitive evolution of children exposed perinatally to CHIKV is poor; if the neonate has encephalopathy, the cognitive disorder is even worse (16).

Newborns infected with chikungunya should be followed for at least 2 years, regardless of symptoms in the first week of life, as they may present severe neurological sequelae (18).

CHIKUNGUNYA IN NEONATES

Chikungunya fever can present asymptomatically in 3 % to 28 % of patients, particularly in the oldest and youngest patients, including neonates.

The first reports of neonatal infection were described during the 2005-2006 epidemic on the island of Reunion, France. The main transmission mechanism is mosquito bites; however, there are less frequent forms, such as maternal-neonatal transmission (vertical). If the mother is infected during the first trimester of pregnancy, it can cause miscarriage, and during the peripartum period, there may be variable degrees of clinical presentations that range from infection in up to 45.2 % of preterm newborns or infected term neonates that will develop chikungunya in the first week of life, with clinical manifestations that can simulate neonatal sepsis or neuroinfection. Therefore, surveillance should be carried out on all pregnant women with chikungunya in endemic areas (14,15).

CHIKV infection in neonates can present with typical and atypical clinical manifestations (in approximately 0.3 % of cases for the latter). The typical manifestations are sudden onset fever, lasting 3 to 10 days, hyperalgesia (86 %), arthralgias, myalgias, systemic manifestations such as nausea, vomiting, generalized rash-erythema (52 %), and skin hyperpigmentation (5 %), which evolve into vesicle or blister-like lesions (bullous dermatitis) that can denude, expose the dermis of the skin (exfoliative dermatitis) and ulcerate (15). Edema can

be evidenced at the facial and genital levels (25 %). Direct, atypical manifestations of the virus include neurological, cardiovascular, and renal manifestations. The severe forms of the disease can present with meningoencephalitis, myocarditis, necrotizing enterocolitis, and sepsis (15). From the laboratory perspective, normal leukocytes can be observed with leukopenia, normal platelets with thrombocytopenia, slight elevation of transaminases and inflammatory reactants such as elevated C-reactive protein. In histopathology in patients with skin lesions, necrosis of the epidermis and the superficial dermis can be evidenced with acute vasculitis, blisters and ulcers.

Diagnostic methods for CHIKV neonatal infection include the following:

1. Viral isolation.
2. Real-time polymerase chain reaction (RT-PCR): sample in serum or plasma.
3. Determination of IgM CHIKV antibodies in serum during the acute or convalescent phase.

Regarding treatment, all neonates born to a mother with a CHIKV infection four days prior to or during delivery, regardless of symptoms, should be hospitalized for surveillance. There is no specific antiviral for the disease. The treatment is supportive, guaranteeing adequate hydro electrolyte, metabolic and acid-base balance and adequate comfort for the newborn and the use of antipyretics and analgesia to relieve pain. The use of antimicrobials is intended for cases of super aggregated bacterial infection, and anticonvulsants can be used in cases with neurological manifestations. With regard to prognosis, studies such as CHIMERE (20) carried out in children with a history of perinatal mother-child infection with CHIKV compared their neurocognitive development with that of uninfected children around the age of 2 years (16). Some studies have shown that neonatal Chikungunya infection is associated with poor neurodevelopmental outcome at 1 year of age. Other research showed that among neonatal infections; long-term neurodevelopmental delays occurred in 50 % of symptomatic

Figure 2a. Figure 2b.

Figure 2a y Figure 2b. Maculopapular eruption in a newborn with congenital chikungunya fever and bullous dermatitis.
Courtesy of Rafael Navas. Hospital Central de Maracay, Venezuela. Year 2014.

neonatal infections (21). Neurodevelopmental follow-up is required for identification and management of sequelae.

BREASTFEEDING

Transmission of CHIKV by breastfeeding has not been demonstrated. Although CHIKV is similar to other alphaviruses, breastfeeding could be a potential VT pathway. The WHO recommends that mothers with CHIKV disease breastfeed their children (Table 2).

DIAGNOSIS

When the CHIKV epidemic has just entered a country, it is convenient to carry out an etiological diagnosis to identify geographic location, affectation of vulnerable groups and the most affected age

Table 2. Maternal and newborn characteristics of chikungunya fever.

Adverse pregnancy evaluation	Method of delivery	Vertical transmission (VT)	Breast-feeding	Disease in the neonate	Congenital malformation (CM)
Miscarriage and premature delivery possible Maternal mortality in atypical presentations	Cesarean section according to obstetric indications and severity of the disease in the pregnant woman Cesarean section has no protective effect	Rare during pregnancy Occurs in 48.5 % of cases if there is acute disease in the peripartum period	Allowed Transmission of the disease by this route in humans has not been documented	50 % of infected neonates may have severe disease Neonate should be admitted and observed for signs of VTa for at least 7 days postpartum; may be asymptomatic during the first days of life.	Has not been associated with CMb Cognitive disorders are possible Newborns infected with chikungunya should be followed-up for at least 2 years, regardless of symptoms in the first week of life There may be alterations in the neurodevelopment of those without clinical encephalopathy at birth

VT: vertical transmission CM: Congenital malformations Ref: own elaboration

group. In an already established epidemic, the etiological diagnosis is made in hospitalized patients, pregnant women, newborns, the elderly population and people with underlying disease or comorbidities.

Diagnostic methods for CHIKV infection include the following (22,24).

1. Real-time polymerase chain reaction (RT-PCR): sample in serum or plasma samples obtained up to seven days after the onset of symptoms. It is the most recommended test; it can make the difference between arboviruses and flaviviruses. RT-PCR can also be performed in patients with neurological symptoms due to the chikungunya virus and in the amniotic fluid in pregnant women.
2. Serological detection: Indicated after the first 7 days of the disease, it is based on the detection of IgM and IgG antibodies, mainly by the ELISA method. ELISA in the acute phase has low sensitivity and specificity. There may be cross-reaction with other alphaviruses and with flaviviruses. Other tests have been used such as: immunofluorescence, complement binding and hemagglutination.
3. Cultivo: It is an expensive, laborious and limited access method; it must be performed when there is viremia.
4. Electron microscopy: detection of the virus or its particles in tissue samples (liver, placenta, lung, synovial membrane, among others) usually used in research studies.
5. Currently, newer technologies are being proposed such as: CRISPR-Cas, sequencing, and colorimetric or fluorometric biosensors. In general, there is a tendency towards the design of more simple, cost-effective, and portable techniques, independent of sophisticated equipment and capable of detecting different arboviruses

TREATMENT

There is no specific treatment for the disease; its management focuses on the use of analgesics to mitigate pain, preferably with

antipyretic activity to reduce fever. Paracetamol is safe for pregnant women, but liver function should be monitored. Similar to dengue, the use of acetylsalicylic acid is contraindicated in CHIKV (25). The control of fever in pregnant women is of particular importance because fever per se has been associated with congenital malformations.

Several compounds that have been shown to be effective at inhibiting CHIKV replication. However, owing to limited knowledge on CHIKV pathogenesis, the dynamics of viral mutations and the lack of studies carried out in animal and human models have proven to be insufficient to authorize antiviral therapy for CHIKV disease (26).

In severe and/or complicated illness, treatment will be carried out in conjunction with a multidisciplinary team. In the chronic phase of the disease, for selected patients, various treatment approaches, including steroids, have been used. At this stage, care by the rheumatologist and physiatrist is essential in pain mitigation and patient rehabilitation.

PREVENTION

Prevention consists of the use of mosquito nets to avoid the bite of the Aedes mosquito and the use of skin repellants allowed during pregnancy. There is currently no vaccine available, but studies are in progress (19).

CONCLUSIONS AND RECOMMENDATIONS

Chikungunya fever is a reemerging disease in the Americas, and it can cause serious illness in both pregnant women and their newborns. It is essential to document the epidemiological and clinical characteristics of pregnant women and newborns infected with CHIKV, in addition to evaluating the impact of the virus on the evolution of the pregnancy and the effects on the newborn, including cognitive disorders. Obstetricians and doctors in charge of the care of pregnant women, such as primary care and family medicine doctors, pediatricians and neonatologists, among others, should be aware of this disease, which can be potentially serious for both the mother and the newborn.

Pregnant women with chikungunya symptoms should be hospitalized, especially if they present with warning signs or atypical manifestations or are in the last month of pregnancy.

Given that newborns may present with severe forms of the disease, pregnant women with chikungunya should be reported to the neonatology service of the corresponding health institution.

Pregnant women with chikungunya should be evaluated jointly with infectious disease, internal medicine or other specialists according to the clinical manifestations and/or involvement of specific organs.

In the acute febrile phase, the use of mosquito nets should be implemented.

It is advisable to carry out research on cohorts of pregnant women with chikungunya fever to assess the severity of the disease, the potential incidence of miscarriage and VT, among others.

Faced with the chikungunya epidemic in a country, health institutions must guarantee personnel, resources and supplies for the care of infected pregnant women and their newborns.

DECLARATIONS SECTION

Ethics approval and consent for publication: The faces of people with chikungunya (pregnant and child) are not shown. Photos of the cases are published under consent

Conflict of interest: the authors declare that they have no conflict of interest in this publication.

Author Contribution

Conceptualization: Paulino Virgilio De Gracia (PVD), Ana Carvajal de Carvajal (ACC), Rafael José Navas Gómez (JRNG), Carlos Cabrera Lozada (CCL), contributed equally to conceive and design the study.

Data curation and formal analysis. PVD, ACC, JRNG and CCL were responsible for performed the search and analysis of relevant articles.

Supervision, validation, visualization: PVD and ACC were responsible.

Wrote the paper, review and editing: PVD, ACC, JRNG and CCL wrote the paper. All authors reviewed and approved the final manuscript.

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