SPECIAL ARTICLE

Oropouche fever and pregnancy

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Abstract

The Oropouche virus (OROV), the etiologic agent of Oropouche fever, has been circulating in several South American and Central American countries since 1955. In Brazil, the disease spent many years restricted to the North region, but since 2023 it has been confirmed in almost all Brazilian States. The aim of this article was to update the state of the art and warn about the risk of vertical transmission of OROV. The virus is an arbovirus transmitted mainly by the Culicoides paraenses mosquito, popularly known as the maruim or gunpowder mosquito. Recently, the possibility of vertical transmission from the pregnant woman to the fetus has been observed, with reports of confirmed cases of miscarriage, fetal death or congenital malformations such as microcephaly. Few studies suggest vertical transmission of OROV, and research with a larger number of pregnant women is needed to prove this association. However, the current evidence, although considered weak, is sufficient to suggest that health professionals and pregnant women should be informed of this possibility and try to prevent contact with the transmitting mosquito, in addition to the need for health authorities to combat breeding sites.

Key words *Oropouche fever, Pregnancy, Vertical transmission*

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Introduction

The Oropouche virus (OROV), responsible for the arbovirus disease known as Oropouche fever, was described in 1955, from a single patient who presented the disease in the Vega de Oropouche community in Trinidad and Tobago, in the Caribbean.[1] It is a ribonucleic acid (RNA) virus belonging to the *Peribunyaviridae* family, *Orthobunyavirus* genus, Simbu serological group.[2] In Brazil, the virus was isolated for the first time in 1960 in the blood of a sloth of the *Bradypus trydactilus* species.[3]

Oropouche fever is considered a zoonotic disease transmitted mainly by mosquitoes of the *Culicoides paraenses* species, popularly called *maruim* or mosquito-powder. *Culicoides paraensis* is possibly a native insect to America, which was first described in Pará in 1905.[4] The mosquito is found in most of South and Central America and can be found in all Brazilian States. In general, this mosquito lives in forests and rural areas, but can also be found in urban areas due to their proximity.[4]

Mosquitoes are active during the morning, with peak activity in the early and late afternoon. They breed in tree holes, leaf litter and damp soil. In the area modified by humans, they look for places with a high content of organic matter and high humidity, especially in banana and cocoa plantations. Adult male and female *maruins* feed on plant nectar. However, the females bite because they need blood to mature their eggs.[4]

In its wild cycle, animals such as monkeys, sloths, rodents and even birds are reservoirs of the virus. Insects become infected when they bite an infected animal and transmit the virus to other animals through the bite or to humans when they enter the forest.[5] In the urban cycle, humans are the reservoirs of the virus.[5] The *maruim* is the main vector in this environment, but *Culex quinquefasciatus*, popularly called the mosquito, can act as a secondary vector.[3] It has been observed that the *maruim* can become infected from a low viral load in the blood, while the mosquito needs a high viral load to become infected.[5]

The mosquito species *Coquilletidia venezuelensis* and *Aedes serratus* have been proposed as vectors of the wild cycle of Oropouche virus in Trinidad and Tobago and Brazil, respectively.[3] However, their role as competent vectors and their participation in outbreaks require further investigation.

Oropouche fever is a neglected human disease and the number of cases and distribution of the disease may be underestimated. Outbreaks of Oropouche fever apparently have a seasonal pattern, with most events occurring during the rainy seasons.[6] There is contradiction in the literature as to whether the disease is more prevalent in males or females, or whether the affected age groups are young or old.[6]

In regard to epidemics and outbreaks, OROV has only caused epidemics in South and Central American countries. In 1961, the first urban epidemic of Oropouche was registered in Belém do Pará, which affected 11,000 human cases. It is believed that the disease spread in the State as a result of the construction of the Belém-Brasília highway, which cleared forest areas. Workers entered the forest, where the disease circulated in the wild, and became infected.[3] Since then, several outbreaks of Oropouche fever in urban settlements have been reported in Brazil. From the 1980s onwards, epidemics began to occur in other South and Central American countries, such as Peru, Panama, Colombia, Ecuador and French Guiana.[7]

The virus is currently spreading in Brazil, Bolivia, Colombia, Cuba and Peru. Brazil concentrates more than 90% of Oropouche fever cases in the Americas, according to the World Health Organization (WHO).[8] Between 1961 and 2023, more than 30 Oropouche fever epidemics were registered in Brazil, in the States of Acre, Amapá, Amazonas, Goiás, Maranhão, Pará, Rondônia and Tocantins.[9]

Between 2023 and 2024, autochthonous transmission was documented in some States that had not previously reported cases, such as Bahia, Espírito Santo, Santa Catarina, Minas Gerais, Mato Grosso, Rio de Janeiro, Piauí, Pernambuco and Maranhão.[10] According to the Ministry of Health, 831 cases were confirmed in Brazil in 2023. In 2024, as of August 18, 7,767 cases of OROV had been confirmed in the country. The majority of cases were registered in cities in the North States and only four States such as: Goiás, Paraná, Rio Grande do Norte and Rio Grande do Sul and Brasilia, the Federal District have not registered any cases of the disease.[11]

After an incubation period of four to eight days, symptoms appear which include fever (~39ºC), headache, myalgia, arthralgia, chills, photophobia, dizziness, nausea and vomiting, similar to those of other arboviruses. Less frequent are patients presenting a rash, anorexia, retro-orbital pain and general malaise. Hemorrhagic phenomena such as epistaxis, bleeding gums or petechiae have also been described. More severe conditions have been reported, such as aseptic meningitis.[6]

The acute phase of the disease usually lasts from two to seven days, although some patients have experienced symptoms such as myalgia and asthenia for up to a month.[12] Some patients relapse within two weeks of recovery, with a symptomatic picture similar to that at the start of the disease or sometimes more severe.This may be due to increased circulation of the virus in the infected person or reinfections in areas with constant circulation of infected vectors.[12]

As of 2023, the Brazilian Ministry of Health (MS) began distributing the Oropouche test to all Brazilian States for the entire national network of *Laboratórios*

Centrais de Saúde Pública (LACEN) (Central Public Health Laboratories), due to the presence of many cases with symptoms compatible with Dengue, Zika and Chikungunya, but which were negative for these diseases.[13]

To date, there are no commercial tests available for serological diagnosis. Among laboratorial methods, there are virological (direct) methods, by amplifying the virus genome or viral isolation, and serological (indirect) methods to detect antibodies produced against the virus.[14]The combination of compatible symptoms plus an IgM-positive serum sample detected with an enzyme-linked immunosorbent assay (ELISA) should be considered positive for an acute case of Oropouche fever, until virus detection can be established by identifying S or M RNA segments using reverse transcription polymerase chain reaction (RT-PCR).It should be noted that serological testing requires five days after the onset of the symptoms in order to detect circulating antibodies.[12]

The disease was described as self-limiting and with low potential for complications. However, in 2024, the Ministry of Health validated the confirmation of two deaths from Oropouche fever registered by the Bahia State Health Department in two women who presented an abrupt onset of fever, headache, retro-orbital pain and myalgia, which quickly evolved into severe symptoms, including severe abdominal pain, bleeding and hypotension. Both women had no comorbidities and were not pregnant.[15,16] To date, there have been no reports of deaths from the disease in the scientific literature worldwidely. Another death in the State of Santa Catarina is still under investigation.[15]

Regarding the risk of vertical transmission, until a few years ago, studies pointed to the lack of data on the potential effect of OROV on fetal development, reporting only abortions and teratogenic effects in animals caused by other viruses of the Simbu group, such as the Akabane (AKAV) and Schmallenberg (SBV) viruses.[17,18] Thus, the possibility of transmission of OROV from the infected mother to the fetus during pregnancy has existed since the first outbreaks identified in Brazil, but without consistent scientific evidence.

In the literature, there is a report of possible vertical transmission in 1982, where nine cases of OROV infection in pregnant women were reported. Of these, two, who were in the second month of pregnancy, resulted in miscarriage. The technique used for diagnosis was a serological test (due to the unavailability of molecular tests at the time).[10]

Recently, in 2024, investigations began in some cases of possible vertical transmission of Oropouche fever infection in the States of Pernambuco and Acre. The pregnant women suffered fetal death, miscarriage and malformations such as microcephaly.[19] On July 11, 2024, the Ministry of Health issued a technical note to the States and cities recommending intensified health surveillance following confirmation of vertical transmission of the Oropouche virus, which identified the presence of the virus genome in a case of miscarriage in the 8th week of pregnancy and in a case of fetal death in the 30th week of pregnancy.The presence of antibodies was also reported in samples from four newborns with microcephaly, negative for other arboviruses.[15,10]

The newborns were diagnosed by a retrospective analysis of serum and cerebrospinal fluid (CSF) samples that had tested negative for Dengue, Chikungunya, Zika and West Nile virus.In this study, four newborns with microcephaly were detected with IgM class antibodies to the Oropouche virus in their serum and CSF. This is evidence that vertical transmission of OROV occurs, but the limitations of the study at the time meant that it was not possible to establish a causal relationship between OROV infection during intrauterine life and neurological malformations in babies.[10]

Another case of vertical transmission was reported in a more recent technical note from the Ministry of Health.In the first week of August 2024, a case of congenital anomaly associated with OROV was confirmed in the State of Acre in a 33-year-old pregnant woman who presented symptoms compatible with arboviruses in the second month of pregnancy. At the 33rd week of pregnancy, ultrasound and fetal magnetic resonance imaging confirmed some alterations, such as oligoamnion, fetal hydrops, microcephaly, diffuse thinning of the brain parenchyma, absent corpus callosum with a possible interhemispheric cyst and severe supratentorial ventriculomegaly.[19]

The pregnant woman's blood sample tested positive for Oropouche IgM (ELISA) on the 1st postpartum day. In the newborn, serological tests on day 2 were negative for toxoplasmosis, rubella, cytomegalovirus, herpes and syphilis (TORCHS), ZIKV, DENV and CHIKV, and positive for Oropouche IgM in CSF and serum samples. This newborn died at 47 days of age and post-mortem analysis by real-time RT-qPCR identified the OROV genome in the brain, lung, kidney, cerebrospinal fluid and pleural fluid. These findings supported the association between exposure to OROV during pregnancy and the occurrence of congenital anomalies.[19]

In this sense, since the sudden increase in the number of OROV cases in the Amazon region, the Pan American Health Organization (PAHO) has released some recommendations for laboratorial surveillance of OROV in pregnant women, stillbirths indicative of congenital infection and healthy neonates or those with evidence of neurological complications/malformations.[10] Among the recommendations, as vertical transmission is being studied for OROV, a sample of amniotic fluid should be collected under medical indication and can be used for

molecular detection of viral genetic material (RT-PCR) or for detection of IgM antibodies.A positive result indicates possible transplacental transmission of OROV.[20]

In cases of spontaneous abortion and stillbirth indicating congenital infection, a serum sample should be obtained for the detection of IgM antibodies and a tissue sample, preferably from the nervous system. In addition, it is recommended that serum samples from the mother be analyzed in parallel for IgM antibodies.If an amniotic fluid sample is available, it can be used for molecular detection by RT-PCR.It should be noted that, depending on gestational age, it is also recommended to use CSF for molecular detection of viral genetic material by RT-PCR and for serology (IgM).[20]

For healthy neonates of infected mothers, it is recommended to perform OROV detection (molecular and serological) in placenta samples, umbilical cord fluid and serum of the newborn and the mother; and neonates with evidence of neurological complications or malformations, in addition to performing OROV detection (molecular and serological), detection of the virus in the CSF is also recommended.[20]

In terms of prevention, vector control measures are of great importance, through the identification and elimination of breeding and resting places. These measures include entomological surveillance to detect species with vector potential, mapping urban and rural areas with conditions for the development of potential vectors, encouraging good agricultural practices to avoid the accumulation of waste that can act as breeding sites, filling in or draining puddles, ponds or flooded areas that can serve as oviposition sites for females and eliminating undergrowth around buildings to reduce vector harborage sites.[21]

In addition, as protective measures, especially for pregnant women, it is recommended to avoid areas where there are many *maruins* and mosquitoes and try not to expose themselves during peak hours (late afternoon), use fine mesh screens on doors and windows, wear clothes that cover most of the body, keep the house clean, including cleaning the land and animal breeding sites and collecting leaves and fruit that fall to the ground. It should be noted that repellents and insecticides do not work against *Culicoides paraenses* (*maruim*), but they are effective against *Culex quinquefasciatus* (mosquito). In addition, the application of body oil can be a good alternative since, due to its low weight, the *maruim* adheres to the oil and prevents from biting.[22]

In view of the above, there are few studies suggesting vertical transmission of OROV, and research with a larger number of pregnant women is needed to confirm this association.The current evidence, although considered weak, is sufficient to suggest that health professionals and pregnant women should be aware of this possibility and try to prevent contact with the transmitting mosquito, in addition to the need for health authorities to combat breeding sites, especially in areas where the vector is frequent.

Authors' contribution

All the authors contributed equally to the design of the article and declared no conflict of interest.

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