

Congenital malaria by *Plasmodium falciparum*

Malaria congénita por *Plasmodium falciparum*

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What do we know about the subject matter of this study?

Congenital malaria is a *Plasmodium* infection transmitted from the mother to the fetus during gestation or birth. This infection increases the risk of intrauterine growth retardation and preterm delivery and can cause serious illness in the newborn.

What does this study contribute to what is already known?

This article points out to consider congenital malaria as a differential diagnosis of neonatal sepsis in children of women living in non-endemic areas who migrate or visit malaria-endemic areas.

Abstract

Congenital malaria (CM) is a *Plasmodium spp* infection acquired *in utero* or during delivery with nonspecific clinical manifestations. *Plasmodium falciparum* can cause severe illness in pregnant women and newborns. **Objective:** to describe two cases of CM caused by *Plasmodium falciparum*, differential diagnosis of sepsis in newborns of pregnant women who live in or have visited endemic malaria zones. **Clinical Cases:** Female neonates born in a non-endemic malaria area, diagnosed with neonatal sepsis and treated with antibiotics without clinical response. After the first week of life, the peripheral blood smear identified trophozoites of *Plasmodium falciparum* thus the newborns were treated with intravenous quinine, improving their condition. The mothers of the two newborns who had malaria in pregnancy, one of them received treatment and she was asymptomatic, and the other one had severe malaria at the time of delivery. **Conclusions:** CM can cause severe neonatal disease with non-specific, sepsis-like clinical manifestations in which early treatment decreases the risk of complicated malaria. It is a differential diagnosis in newborns of women with a history of malaria during pregnancy or pregnant women visiting or living in endemic malaria areas.

Keywords:

Malaria;
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Introduction

In Colombia in 2019, 74,409 cases of malaria were reported, 455 of them in pregnant women (0.6%)¹. Since 2015, the Americas have seen an increase in cases in Venezuela, outbreaks in countries moving toward elimination such as Costa Rica, the Dominican Republic, and Ecuador, and increased transmission in endemic areas (Brazil, Colombia, Guyana, Nicaragua, and Panama). Paraguay and Argentina were certified malaria-free in 2018 and 2019, respectively². *Plasmodium vivax* causes 74.1% of cases³.

Congenital malaria (CM) occurs by an infection in utero or during birth and is defined by the identification of asexual forms of the parasite in the peripheral blood of the newborn between the first 24 hours and the next seven days of life⁴. Its incidence is variable in endemic and non-endemic areas, ranging from 0.3 to 37%⁵. The signs and symptoms are nonspecific, the diagnosis requires a suspicion index, thorough physical examination, thick blood film, and it can be confused with neonatal sepsis and STORCH (syphilis, toxoplasmosis, rubella, cytomegalovirus, herpes virus)⁶.

Untreated, severe malaria is fatal, causing coma, metabolic acidosis, severe anemia, jaundice, hypoglycemia, acute renal failure, pulmonary edema, coagulopathy, shock, or hyperparasitemia⁷.

The thick blood film identifies trophozoites of *Plasmodium spp* and consists of obtaining a drop of blood that is arranged on a slide, is stained with Romanowsky dyes, and observed under a light microscope⁸. The gold standard for the diagnosis of CM is the identification of the parasite in neonatal peripheral blood⁹, the presence of parasites in cord blood may not represent active infection¹⁰.

When reviewing the literature, we found less than 20 cases of CM reported in Colombia and one case caused by *Plasmodium falciparum* (*P. falciparum*)¹¹. The objective of this paper is to describe two cases of CM caused by this *Plasmodium* species, differential diagnosis in newborns of pregnant women visiting or residing in malaria-endemic areas.

Clinical Case

Case 1

25-day-old female newborn presenting with a two-day history of jaundice, fever, irritability, and decreased appetite. First child of a 20-year-old female, born in a non-endemic area for malaria (Pasto, located at 2,527 m asl) at 38 weeks of gestation via cesarean section due to oligohydramnios, and low birth weight (2,115 g). She was pale, jaundiced, and febrile, had petechiae and

hepatosplenomegaly. Then she was diagnosed with neonatal sepsis and suspected STORCH infection and was treated with antibiotics. Complete Blood Count showed leukopenia (3600/mm³) and thrombocytopenia (66,000/mm³), no anemia (11 g/dL); reticulocytosis (6%); high C-reactive protein (18 mg/dL); hyperbilirubinemia (total bilirubin 13.9 mg/dL, direct 0.9 mg/dL); normal capillary blood glucose. Cultures were negative as well as IgM antibody studies for STORCH, nontreponemal tests, and human immunodeficiency virus (HIV). Later, the mother reported traveling to a malaria-endemic area (Urabá) at 22 weeks of gestation and having *P. falciparum* infection treated with quinine. She was asymptomatic at delivery. The rapid antibody test of the newborn was positive for *P. falciparum* and the thick blood film identified 5400 trophozoites / μ L (Figure 1), thus intravenous (IV) quinine administration was started 10 mg/kg every 8 hours for 3 days. The control thick blood film (at 48 hours, 72 hours, and 7 days) were negative. The patient was discharged with no complications and was asymptomatic 8 days after discharge.

Case 2

Female neonate, first child of an 18-year-old female with severe malaria and obstetric sepsis at delivery, born at 36 weeks of gestation in a non-endemic area for malaria (Pasto), via emergency C-section due to unsatisfactory fetal status and severe oligohydramnios. She had a low birth weight (2,410 g), was impregnated with meconium, hypotonic, hypothermic, and cyanotic, then she was admitted to neonatal intensive care due to respiratory distress and sepsis. Antibiotic treatment was initiated, the CBC showed leukocytosis (26,000/mm³), without anemia or thrombocytopenia (hemoglobin 14.4 g/dL and platelets 190,000/mm³), Capillary blood glucose 47 mg/dL. HIV tests and cultures were negative. On the seventh day of life, the patient continued with ventilatory support, the CBC showed pancytopenia (leukocytes 4,800/mm³, hemoglobin 8.3 g/dL, platelets 13,000/mm³), and the thick blood film identified 83 trophozoites/ μ L of *P. falciparum*. IV quinine was administered at an initial dose of 20 mg/kg followed by 10 mg/kg/dose every 8 hours for 3 days with improvement and negative control thick blood film (at 48 hours, 72 hours, and 7 days). She was discharged without complications.

Discussion

We described two infants with CM due to *P. falciparum*, born in a non-endemic area for malaria and affected by oligohydramnios and low birth weight,

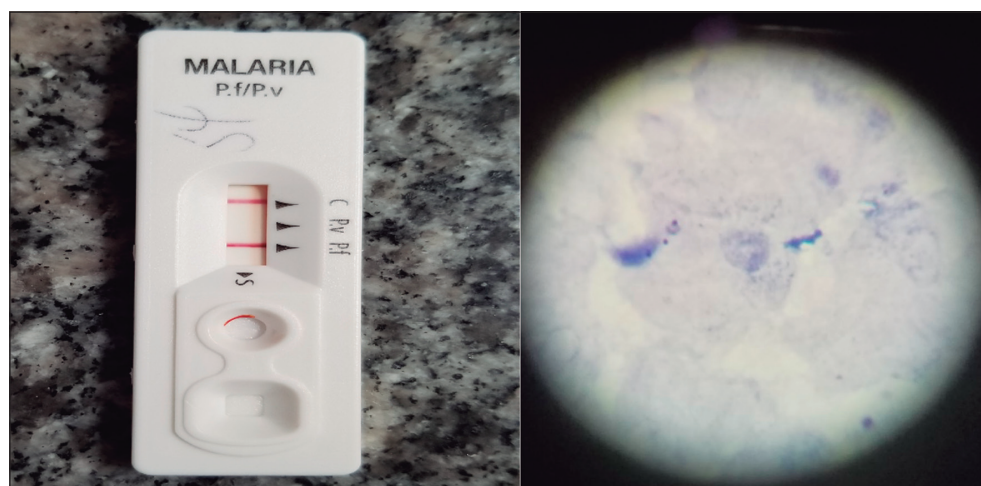


Figure 1. A. Rapid antibody test for *Plasmodium* infection. B. Peripheral blood smear with evidence of *P. falciparum* trophozoites.

who were diagnosed through thick blood film and were treated with IV quinine. New mothers, one of them was asymptomatic and the other one presented severe malaria at the time of delivery. The areas of malaria transmission are below 1,700 m asl in Colombia; the newborns were born and remained in Pasto that is located at 2,527 m asl, which rules out neonatal infection.

Malaria can cause severe illness in pregnant women with no or little prior immunity and women from non-endemic areas traveling to endemic areas¹⁰. In areas of high transmission, new mothers produce antibodies and are partially protected in subsequent pregnancies, which does not occur in areas of low transmission¹².

P. falciparum invades erythrocytes of all ages, presents high parasitemias¹³, and there is placental sequestration by parasitized erythrocytes due to the interaction of chondroitin sulfate A and VAR2CSA protein (Variant Surface antigen 2-CSA)¹⁴. This activates inflammation, monocyte migration and release of humoral factors that could favor preterm delivery.

Placental thickening, decreased transplacental nutrient transport and hormone production, altered angiogenesis, changes in villous mucosa, and uterine and placental blood flow deteriorate fetal growth^{12,13}.

The risk of vertical transmission is from 1 to 4%¹³. The transplacental transmission of IgG antibodies, fetal hemoglobin, and low partial pressures of oxygen in the fetal circulation are defense mechanisms¹⁵.

The World Health Organization (WHO) recommends quinine and clindamycin for the treatment of uncomplicated malaria due to *P. falciparum* in the first trimester of pregnancy and artemisinin-based combination therapy in later trimesters⁷. In case 1, the pregnant woman received quinine at 22 weeks of pregnancy, which has shown less efficacy than artemisinin

derivatives¹⁶ and, although it penetrates the placenta, is not therapeutic for the fetus¹⁷.

The nonspecific symptoms and signs in Case 1 can be attributed to late infection during pregnancy and the need for several erythrocytic cycle to cause disease¹⁰. The clinical manifestations occur between 10 and 28 days after birth, 80% of the patients have fever, anemia, and splenomegaly, and a one third present jaundice and hyperbilirubinemia¹⁸.

In case 2, the infection occurred in the last trimester of pregnancy, the pregnant woman had severe malaria, and the newborn was premature, with low birth weight, respiratory distress, and hypoglycemia. The erythrocyte life cycle of asexual replication of *P. falciparum* occurs in the fetal circulation releasing merozoites every 48 hours¹⁹, and there may be mild or late symptoms or not at all since the antimalarial antibodies prevent or reduce the replication of the parasite¹⁰.

The WHO recommendation for treatment of uncomplicated malaria due to *P. falciparum* in children < 5 kg is artemisinin-based combination therapy with doses equal to those of children > 5 kg. Artesunate, artemether, or quinine are indicated for the treatment of severe malaria⁷.

National guidelines recommend artemether plus lumefantrine for treatment in children > 5 kg and quinine and clindamycin in children < 5 kg, however, in neonates, they suggest not using clindamycin^{20,21}. Artemether is available in tablet form and artesunate was not available in the country at the time of case presentation. The neonates were treated according to local guidelines; case 2 was classified as severe malaria and therefore quinine doses were administered.

The prognosis depends on the species of *Plasmodium*, the region, the immunity of the pregnant woman, and the parasitemia⁹.

Conclusion

CM can cause severe neonatal disease with nonspecific and sepsis-like clinical manifestations. Early treatment decreases the risk of severe malaria. CM is a differential diagnosis in newborns of women with malaria during pregnancy or pregnant women visiting or residing in endemic areas.

Ethical Responsibilities

Human Beings and animals protection: Disclosure the authors state that the procedures were followed according to the Declaration of Helsinki and the World Medical Association regarding human experimentation developed for the medical community.

Data confidentiality: The authors state that they have followed the protocols of their Center and Local regulations on the publication of patient data.

Rights to privacy and informed consent: The authors

have obtained the informed consent of the patients and/or subjects referred to in the article. This document is in the possession of the correspondence author.

Conflicts of Interest

Authors declare no conflict of interest regarding the present study.

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