Case Report: Recrudescence of *Plasmodium falciparum* in a Primigravida after Nearly 3 Years of Latency

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Abstract. We present a case of a primigravid woman who presented with *Plasmodium falciparum* nearly 3 years after she last visited a malaria-endemic region. We review the literature to identify case reports of recrudescence *P. falciparum* malaria during pregnancy, including those with prolonged latency. Reports of recrudescence of *P. falciparum* during pregnancy are limited. *Plasmodium falciparum* infection can persist for years. Recrudescence can occur with waning of immunity following departure from endemic areas. Pregnancy, particularly the primigravid state, is a risk factor for severe infection.

CASE REPORT

A 29-year-old primigravid woman presented with fever and thrombocytopenia during her third trimester of pregnancy. Originally from Ghana, she permanently relocated to the United States 5 years ago. She visited Ghana 2¾ years ago for 1 month, but otherwise denies travel outside the United States. She says that she previously had malaria more than 10 times, including during her most recent trip to Ghana for which she did not take chemoprophylaxis and recalls being treated with a several-day course of chloroquine.

At 29 weeks into an otherwise uncomplicated pregnancy, she developed headache, back pain, dark urine, and fever and was admitted to Saint Vincent Hospital in Worcester, MA, for further evaluation. Physical examination revealed a temperature of 101.4°F, blood pressure of 97/57 mmHg, and heart rate of 114 per minute. She was awake, alert, and oriented and her sclerae were anicteric. Heart examination showed tachycardia with no murmurs. Her respiratory examination was normal and her abdomen was soft and protuberant, corresponding with her gestational age, with no tenderness or splenomegaly noted. Results of the back examination and neurological examination were unremarkable. Laboratory evaluation revealed low hemoglobin and platelets of 9.1 g/dL and 36,000/μL, respectively, which were considerably decreased from 11.2 g/dL and 149,000/μL 3 months prior. Other pertinent laboratory values included a total bilirubin of 2.1 mg/dL, direct bilirubin 1.0 mg/dL, and haptoglobin < 15 mg/dL. Her serum glucose, liver enzymes, and creatinine were within normal limits. Both disseminated intravascular coagulation work up and human immunodeficiency virus serology were negative. Thick and thin blood smears revealed 3% parasitemia (~90,000/μL) with *Plasmodium falciparum* with small ring forms and appliqué cells (Figure 1). Chest radiograph was normal.

She was given intravenous quinidine (640 mg loading dose followed by 20 mcg/kg/minute), plus intravenous clindamycin 600 mg every 8 hours, then was transferred to the University of Massachusetts Memorial Medical Center in Worcester for more intensive monitoring for high-risk pregnancy. She received betamethasone for fetal lung maturation due to concerns of possible uteroplacental insufficiency in the

setting of *P. falciparum* malaria. Her parasitemia cleared within 72 hours and laboratory abnormalities, including thrombocytopenia, gradually resolved. As she was able to tolerate oral intake by 48 hours, she was switched to oral quinine and clindamycin to complete a 7-day course of antimalarial treatment as an outpatient in accordance with Centers for Disease Control and Prevention (CDC) treatment guidelines.¹

The remaining course of her pregnancy was unremarkable. At 38 weeks and 6 days gestation, she had a spontaneous vaginal delivery. Pathology revealed a normal mature placenta and umbilical cord with no signs of malaria burden on microscopic examination. Blood tests that had been collected 5 days after her initial presentation and subsequently processed by the CDC included a *P. falciparum* indirect fluorescent antibody titer of 1:16,384 (≥ 1:64 is considered elevated) and a polymerase chain reaction (PCR) test that confirmed *P. falciparum*.

DISCUSSION

Plasmodium falciparum malaria is a major cause of morbidity and mortality worldwide. Although the incubation period is usually between 2 and 4 weeks, asymptomatic *P. falciparum* infection may persist for many years despite the absence of the hypnozoite stage. Although cases of late occurrence of *P. falciparum* malaria have been reported between 2 and 9 years after departure from endemic areas,^{2–5} the maximum confirmed duration of infection is 13 years.⁶ Prolonged infection is especially common in highly endemic areas where persistent exposure to malarial antigens may prevent severe disease, but may not completely protect against malaria.⁷ The appearance of symptoms years after infection may be due to waning of host immunity in semi-immune hosts. A case-control study identified both pregnancy and being an immigrant who never returned to malaria-endemic regions as independent risk factors associated with prolonged *P. falciparum* infection.⁸

Pregnant women are at increased risk of malaria infection independent of previously acquired immunity. This is in part due to immune modulation during pregnancy, when a shift toward Th2 responses occurs.⁹ In addition, *P. falciparum*-infected erythrocytes can accumulate in the placenta through expression of specific membrane proteins such as VAR2CSA; such variant parasites are unique to pregnancy and render pregnant women highly susceptible to malaria disease and complications.¹⁰ Immunoglobulins against VAR2CSA are pregnancy specific and increase with parity, as primigravidae

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FIGURE 1. The patient's peripheral blood smear shows small ring forms as well as appliqué cells, consistent with *Plasmodium falciparum*.

lack antibodies to placental-type parasites but can develop such antibodies during the course of pregnancy if exposed to *P. falciparum*.¹¹ This provides an explanation for why women pregnant for the first time in a malaria-transmission area are highly susceptible to malaria infection. Pregnant women with malaria infection are particularly prone to developing severe anemia, acute kidney injury, disseminated intravascular coagulation, shock, seizures, and hypoglycemia, whereas obstetric complications include miscarriage, intrauterine death, preterm labor, and low birth weight.¹²

This case illustrates recrudescence of *P. falciparum* after a prolonged period of apparent latency during pregnancy. Walters in 1960 and Mahmood in 1966 reported cases of imported *P. falciparum* in the United Kingdom in Nigerian women after prolonged quiescence, specifically at 17 and 19 months.^{13,14} In each case, the patient was in the second trimester of pregnancy and presented with anemia. Following diagnosis and treatment, no complications ensued. Giobbia and others described a pregnant patient diagnosed with *P. falciparum* 4 years after her last stay in an endemic area.¹⁵ In their case-control study, D'Ortenzio and others described four pregnant immigrant women who developed clinical malaria more than 3 years after their arrival in Paris, but no additional travel information was provided.⁷ Of all these cases, only Mahmood described a multigravid patient.¹⁴

Limited information has been reported on imported *P. falciparum* malaria of any duration of recrudescence during pregnancy. In the United States, Subramanian and others described three Nigerian national women each diagnosed with *P. falciparum*, two during the third trimester and one during the second trimester.¹⁶ All had been in Nigeria within 2 months of presentation. Although two had a favorable outcome, one woman who presented with 14% parasitemia expired despite eventual clearance of parasitemia. Jiménez and others in Madrid retrospectively reviewed 19 cases of pregnant women each diagnosed with *P. falciparum* by microscopy, rapid antigen detection, and/or PCR test for *Plasmodium* nucleic acid.¹⁷ Eighteen patients were multigravid and 53% presented in the third trimester. Nine of 15 symptomatic patients reported symptoms between 7 and 69 days after leaving sub-Saharan endemic areas. About 84% were treated with quinine and clindamycin; no severe

complications or deaths were reported, but two had premature abortions. Finally, Käser and others performed a retrospective analysis on 632 pregnant women, who presented with travel-associated malaria in eight non-endemic countries including the United States.¹⁸ More than 70% of the cases were *P. falciparum* malaria. Of all the malaria cases, no maternal deaths were reported, but several fetal abortions occurred; no data were made available on the interval between travel and time of presentation. Of particular note, in all cases, very few women had taken chemoprophylaxis.

CONCLUSIONS

Although *P. falciparum* malaria can be relatively asymptomatic in individuals with high levels of immunity, women such as our patient who reside in non-endemic areas for years have likely lost immunity to malaria and are at increased risk of symptomatic malarial infections after return to endemic areas. Additionally, our patient was at increased risk for malaria given her pregnancy, in particular since she was a primigravida.

Travel to malaria-endemic areas during pregnancy should be avoided or delayed. When unavoidable, chemoprophylaxis should be considered. For pregnant women even with a remote history of travel to malaria-endemic regions, early diagnosis and correct treatment are of paramount importance.

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