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When Epidemiology Is the Clue to a Positive Outcome: A Case of Malaria During Pregnancy

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

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Patient: Female, 29
Final Diagnosis: Malaria
Symptoms: Fever
Medication: —
Clinical Procedure: —
Specialty: Infectious Diseases

Objective: Unusual setting of medical care

Background: Malaria infection during pregnancy is associated with increased perinatal and maternal morbidity and mortality.

Case Report: A 29-year-old primigravida at 37 weeks of gestation, with no significant medical history, presented complaining of fever, chills, and generalized body aches. She had been living in Malawi for 1 year and was on atovaquone/proguanil prophylaxis until she was found to be pregnant. Prophylaxis was changed to mefloquine and discontinued upon her return to the US. Six weeks prior to presentation, she traveled to Malawi for 1 month when she was off prophylaxis. On admission, vital signs and physical exam results were normal. Given epidemiologic findings, a malaria smear was performed and showed 4% parasitemia. She was treated with mefloquine and discharged. Two days after discharge, she again presented with fever, chills, and body aches. A malaria smear showed <0.01% parasitemia, with 2 ring forms. Serologies for dengue, chikungunya, leptospira, and blood cultures were negative. These symptoms were deemed secondary to early recrudescence. The species was later identified as *P. falciparum*. The patient was treated with quinine sulfate and clindamycin. She delivered at full term without complication.

Conclusions: Pregnant women are more susceptible to severe forms of malaria, such as *P. falciparum*. A high index of suspicion and early identification of malaria are vital to prevent deleterious outcomes.

MeSH Keywords: Malaria • Malawi • Pregnancy Complications, Parasitic

Full-text PDF: https://www.amjcaserep.com/abstract/index/idArt/905543

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Background

Malaria is a major public health problem, and according to the World Health Organization (WHO), in 2015 there were approximately 210 million malaria cases with nearly 429 000 deaths [1]. Pregnant women, young children (under 5 years of age), non-immune travelers, and immunocompromised individuals are the most affected. Malaria during pregnancy is associated with devastating maternal and fetal complications, including anemia, miscarriages, stillbirth, intrauterine growth retardation, low birth weight, congenital infection, and premature delivery [1–3].

Malaria is no longer endemic in the United States, but approximately 1700 cases of malaria are reported every year as a result of infections acquired by US civilians in areas with endemic malaria. Most of the cases are due to *P. falciparum* (66.1%) *and P. vivax* (13.3%), while *P. ovale* (5.2%), *P. malariae* (2.7%), and *P. knowlesi* are less frequent causes [4].

According to the Centers for Disease Control and Prevention (CDC) 2017 Morbidity and Mortality Weekly report (MMWR), in 2014 there were 32 cases of malaria during pregnancy reported in the United States in women who did not comply with chemoprophylaxis. Four of these patients had severe malaria. All of the infected patients recovered, but 2 miscarriages occurred and 1 infant had congenital malaria [4].

P falciparum and *P. vivax* are known to cause placental infection [5,6]. The pathophysiology of the placental infection in cases of *P. falciparum* occurs by the accumulation of the infected erythrocytes that express the VAR2CSA protein that adheres to the chondroitin sulfate proteoglycans (primarily), hyaluronic acid, and other receptors present in the syncytiotrophoblast, causing ischemia of the placental tissue [7,8]. *P. vivax* has not been confirmed to sequester in the placenta, but it has been proposed that involvement of ICAM-1 and CSA, as key receptors, mediate cytoadherence and pathology [9,10].

Pregnant women are 3 times more likely to develop severe disease than are non-pregnant women [11]. Pregnancy itself is an immunocompromised state in which cellular immunity is decreased; therefore, infections are cleared less effectively [12].

Worldwide, in areas of stable (endemic) transmission where there is an acquired immunity due to repeated infections, affected patients are typically asymptomatic; in these cases, women in their first or second pregnancies, young women, and immunocompromised people are more susceptible to malaria than are multigravida women, and these are, in turn, more susceptible than non-pregnant women. On the other hand, in areas of unstable (epidemic) transmission, malaria infection, independently of gravity (primigravid *vs.* multigravid), causes severe clinical illness, and is associated with poor birth outcomes, stillbirth, and premature delivery [1,5,12–14].

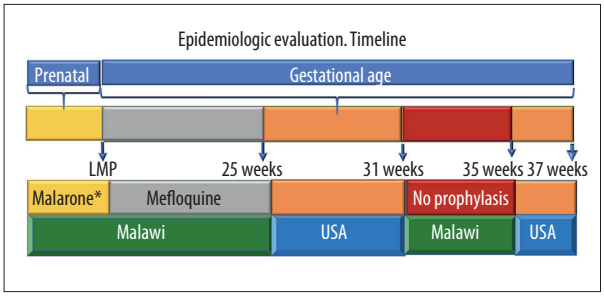

Figure 1. Epidemiological evaluation timeline. Timeline of events according to gestational age, chemoprophylaxis received, and country of residency. * Malarone: proguanil-atovaquone.

Case Report

A 29-year-old white female G1P0 at 37 weeks of gestation, with unremarkable past medical history and no toxic habits (e.g., alcohol, tobacco, or substance abuse), presented for prenatal care with complaints of fever, chills, and generalized body aches. She had been living and working in Malawi, Africa the year prior to presentation (in 2015). While in Malawi, she was on malaria prophylaxis with atovaquone and proguanil. She was then found to be pregnant and her prophylaxis was changed to mefloquine. She returned to the United States 3 months prior to presentation. Upon arrival, she discontinued prophylaxis. On her initial prenatal visit in the United States, she was diagnosed and treated for ascariasis with mebendazole. She then had to travel emergently to Malawi, where she stayed for 1 month, but this time she did not get any antimalarial prophylaxis.

She presented for her prenatal visit 2 weeks after her return to the United States (Figure 1) complaining of fever, chills, and generalized myalgia and was admitted to the hospital. She was afebrile, and blood pressure, pulse, and respiratory rate were normal and no jaundice or pale skin was noted, nor was lymphadenopathy. Results of a cardiopulmonary exam were unremarkable. The pregnant abdomen was appropriate for gestational age. Fetal ultrasound and amniotic fluid measurements were reassuring. Laboratory studies showed anemia with a hemoglobin of 9.4 gm/dl, no leukocytosis, and platelet count of 122 000/mcl. A hemolytic panel was within normal limits. Given the high suspicion of malaria due to her recent travel, a malaria blood smear was performed, and this showed 4% parasitemia with all ring forms. A sample was sent to the state laboratory for species identification. Given the high prevalence of chloroquine-resistant *P. falciparum* in Malawi, the patient was treated with mefloquine orally 250 mg,

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2 doses 8 h apart. The decision to treat with oral antimalarial was based on the stability of the patient, who did not have azotemia or acidosis, and had no hepatic or neurological involvement. Treatment was based on recommendations provided by the CDC Malaria Hotline. The patient improved clinically, a repeat malaria smear showed 0.0% parasitemia, and she was discharged home.

Two days after treatment, she presented again with fever, chills, and myalgia, associated with loose stools, headaches, and ear pain. Results of a physical exam were within normal limits, laboratory studies revealed hemoglobin of 8.3 gm/dl, thrombocytopenia of 88 000/mcl, no leukocytosis, normal creatinine, and mild elevation of alkaline phosphatase to 149 IU/L and transaminases (AST 57 IU/l, ALT 53 IU/L). Fetal ultrasound was reassuring. Serology for other potential etiologies like dengue fever, chikungunya, leptospira, human immunodeficiency virus (HIV), and hepatitis were obtained and were all negative. A malaria smear showed <0.01% parasitemia, with 2 ring forms. In light of this findings, her symptoms were deemed secondary to early recrudescence. She was treated with quinine sulfate 650 mg orally every 8 h for 3 days and clindamycin 20 mg/kg/day in 3 divided doses for 7 days. She improved clinically and was discharged home. The *Plasmodium* was later identified as *P. falciparum*.

The patient underwent a spontaneous delivery at full term without complications; the neonatal birth weight was 3.31 kg, Apgar score at 1 min was 8, and at 5 min was 9. Given the history of malaria, the placenta was sent for pathology evaluation, and it showed scattered healed infarcts. The state laboratory confirmed the presence of *Plasmodium falciparum*, sensitive to chloroquine, mefloquine, atovaquone, and artemisinin and resistant to sulfadoxine-pyrimethamine.

Discussion

This case highlights the importance of having a high index of suspicion and adequate history evaluation for early diagnosis and treatment of malaria. Patients returning from countries with a high prevalence of malaria and who have not received appropriate prophylaxis are at a high risk of infection, as are patients from endemic countries that have been living in the United States and return to their home countries to visit.

Prophylaxis and treatment of malaria during pregnancy depends on whether the patient is in an area of stable transmission or unstable transmission, or if the patient is a traveler to an endemic area, as was our patient.

The main challenge arises due to the development of resistance by the parasite to the drugs available, resistance of the mosquito to the insecticides, and the still-unclear safety profile of some of the antimalarial drugs during pregnancy.

In the United States, in cases presenting in pregnant travelers, like ours, prophylaxis and treatment vary depending upon the availability of drugs. The CDC recommends prophylaxis with chloroquine in areas of chloroquine-sensitive malaria, and mefloquine in areas of chloroquine-sensitive or -resistant malaria [15,16].

For treatment of uncomplicated chloroquine-sensitive *P. falciparum* malaria, chloroquine or hydroxychloroquine at any trimester during pregnancy is recommended. Mefloquine can also be used [15,16].

If the patient is diagnosed with uncomplicated chloroquine-resistant *P. falciparum* malaria, treatment depends on the trimester in which diagnosis is made. During the first trimester, treatment with quinine with clindamycin is recommended. The CDC does not recommend the use of atovaquone-proguanil and artemisinin combinations (artemether-lumefantrine, amodiaquine-artesunate, mefloquine-artesunate, or dihydroartemisin-piperaquine) during pregnancy, particularly during the first trimester. Moreover, the only artemisinin combination approved in the United States for non-pregnant patients is artemether-lumefantrine. It is important to mention that the WHO suggests its use if first-line treatment is unavailable, or if there is failure of treatment and benefits outweigh the risks, given that there is insufficient data on the safety of these medications in the first trimester [15,16].

During second and third trimesters, mefloquine, and quinine sulfate with clindamycin are recommended by the CDC. The World Health Organization recommends artemisinin combination therapy for 3 days [17]. The advantage of this combination therapy lies in the short-acting but potent effect of the artemisinin component in decreasing the number of circulating parasites in the first 3 days of treatment, with the long-term action of the partner drug to eliminate the remaining parasites [15,17,18].

In cases of uncomplicated infections with chloroquine-resistant *P. vivax*, the recommendation is to treat with mefloquine. In cases of *P. vivax* and *P. ovale* infections, radical treatment of hypnozoites with primaquine is warranted; however, it should not be given during pregnancy because the glucose 6 phosphate dehydrogenase (G6PD) level is unknown in the fetus. Instead, patient should receive weekly chloroquine prophylaxis until delivery. After this, the patient should be tested for G6PD deficiency and treated with primaquine [15–17].

In our case, the patient was on appropriate prophylaxis for her long stay in Malawi, an area of stable transmission *P. falciparum*

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malaria, and was appropriately switched to weekly mefloquine as per current recommendations at the time of pregnancy. Traveling back to Malawi emergently without prophylaxis exposed her to infection, with development of the disease.

Historically, *P. falciparum* in Malawi has expressed chloroquine resistance, but since the use of this drug was abandoned in 1993, the emergence of chloroquine-sensitive malaria has been demonstrated [19,20]. However, there are still chloroquine-resistant parasites in certain regions of Malawi (e.g., Blantyre, a major urban center) and on the borders with other countries that have different malaria control policies (particularly the border with Tanzania) [22,23], and further studies are needed on this topic.

Despite these findings, the decision to treat with mefloquine initially, instead of chloroquine, was made due to the risk of delaying appropriate treatment with subsequent deleterious consequences, and in compliance with CDC guidelines, since Malawi is still officially categorized as an area of chloroquine resistance. The patient tolerated the treatment without adverse effects.

Early recrudescence is thought to occur despite documented mefloquine sensitivity because this drug lacks long-term activity action. Therefore, the initial treatment doses were effective enough to cause clinical improvement but targeting certain blood stages (e.g., asexual), and the damaged parasite in the circulation was removed by the reticuloendothelial system, primarily the spleen. However, once therapeutic drug concentrations declined, the dormant parasite regrew, causing symptoms to reappear.

Conclusions

Malaria is a preventable and curable disease through education and appropriate follow-up, as well as early diagnosis to rule out severe infection and complications, and to avoid deaths. This is of critical importance in cases of malaria during pregnancy, in which deleterious outcomes for both mother and newborn can occur, with significant public health consequences.

For any pregnant patient from an endemic area or with history of recent travel to an endemic area, is important to discuss the use of prophylactic treatment, as well as the use of barrier methods, including insecticide-treated nets and wearing appropriate clothes (e.g., long-sleeved shirts and long pants), with the goal of decreasing exposure to mosquitoes, along with the use of a recommended insect repellent.

Once again, the best way to prevent death from malaria during pregnancy is adequate chemoprophylaxis and early detection and treatment according to the susceptibility pattern in the region where the infection occurs.

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