Outcomes of Imported Malaria During Pregnancy Within Venezuelan States: Implications for Travel Advice

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DOI: 10.1111/j.1708-8305.2006.00099.x

Prevention of malaria in pregnant women is an utmost priority because the disease can cause serious maternal and neonatal complications. Maternal complications include marked anemia, increased risk of severe disease, and mortality, while the fetus or neonate is at risk of prematurity, anemia, and low birthweight. Pregnant women living in malaria endemic areas may be semiimmune to a particular Plasmodium spp. but when traveling to other regions, sometimes within their same country, where malaria epidemiology is different, may develop severe malaria complications. Here, we describe our experience in northeastern Venezuela associated with unfavorable outcomes of imported malaria cases among pregnant women who traveled to other Venezuelan regions with different malaria epidemiology. Travel medicine practitioners should be aware and educate their pregnant patients regarding the risk of malaria even when living in malaria endemic areas and traveling to other endemic areas such as occurs in Venezuela.

Malaria continues to represent a public health threat in developing countries, where between 350 to 500 million clinical episodes of malaria occur each year, resulting in over 1 million deaths.¹–³ In Venezuela, malaria is endemic in many states with various degrees of endemicity and intensity of transmission and different distribution of Plasmodium species.⁴–⁶ There are three regions of malaria transmission in Venezuela: the meridian or southern region constituted mainly by the states of Bolivar and Amazonas (where Plasmodium falciparum, Plasmodium vivax, and Plasmodium malariae are present); the oriental or northeastern region represented by the states of Sucre (just P vivax is present), Delta Amacuro, and Monagas (with P vivax and few cases of P falciparum); and the western region that covers the states of Barinas, Portuguesa, Tachira, Mérida, and Apure (mainly P vivax). The burden of disease associated with malaria infection in these three regions was responsible for 45,328 cases (86.8% P vivax and 12.4% P falciparum) in 2005, but 84% occurs just in two states, Bolivar (69%) and Amazonas (15%) (border states with Brazil) (Figure 1).⁷

Adults living in areas of moderate-to-high P falciparum transmission such as the State of Bolivar in southern Venezuela develop a semiimmune state to this malaria species after frequent episodes of malaria during childhood. Pregnant women represent a particular group of patients due to the fact that the clinical manifestations of malaria depend on the levels of transmission in a particular population given different levels of immunity. Even when some women may be considered semiimmune to malaria, pregnancy may render them at risk of complications of malaria because they may lose much of that previous immunity during pregnancy.⁸–¹⁰ Pregnant women living in the same country but in nonendemic areas or in endemic zones where P falciparum is not present, such as occurs in the State of Sucre in northeastern Venezuela,⁴ are prone to develop significant complications when traveling to other
endemic zones with different malaria epidemiology. This is a retrospective evaluation of the clinical features and pregnancy outcomes in three imported cases of *P. falciparum* infection in pregnant women from Sucre where *P. vivax* is endemic and who returned from the State of Bolivar where *P. falciparum* is the endemic malaria species.

**Methods and Results**

From January 2000 to December 2002, three pregnant women with *P. falciparum* malaria infection (diagnosed with thick and thin blood smears, with internal; and external regional and external federal quality controls) were admitted to Hospital Santos Aníbal Dominicci, Sucre, in northeastern Venezuela (this represented 1.62% of the total pregnant women admitted during those years at this institution). All women were multigravidae. Mean age was 29 years. The mean gestational age at presentation to the institution was 21 weeks, and none of the patients had any previous history of miscarriages or preterm deliveries. Clinical characteristics of patients are presented in Table 1. The mean hemoglobin level on admission was 7.5 g/dL; all patients developed anemia (<12.0 g/dL) (one, severe anemia, <5.0 g/dL). The mean platelet count on admission was 158,000 cells/µL. Among these patients, two of them developed thrombocytopenia (<150,000 cells/µL), and among these women, one had severe thrombocytopenia (<60,000 cells/µL) and normal renal function. Due to severe thrombocytopenia and endometrial bleeding, platelet transfusion was administered in this patient. Miscarriage was observed in two patients (No. 1 and 2, Table 1). The third woman delivered a normal newborn (with a normal birthweight) after she was discharged. After antimalarial treatment with quinine [10 mg/kg q8h (30 mg/kg/d) × 7 days] and supportive care, all patients were successfully discharged. No maternal deaths or additional complications were seen in these patients.

**Discussion**

The concept of imported malaria has been recognized for more than half a century and has progressively increased not only in countries that were classified as being free of this disease due to human migration and growing number of tourism to endemic areas but also for countries with endemic and nonendemic zones. Among these countries...
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Table 1. Demographic and clinical characteristics of three pregnant women with imported malaria due to Plasmodium falciparum who were hospitalized in the Hospital Santos Aníbal Dominicci, Sucre, Venezuela, 2000 to 2002

<table>
<thead>
<tr>
<th>Patient no.</th>
<th>Age (y)</th>
<th>Gestational age (wk)</th>
<th>Gravidity</th>
<th>Underlying condition</th>
<th>Presenting symptoms</th>
<th>Hemoglobin levels (g/dL)</th>
<th>Platelets count (cells × 10^3/mL)</th>
<th>Platelets transfusion required</th>
<th>Antimalarial treatment</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>30</td>
<td>21</td>
<td>MG</td>
<td>No</td>
<td>Genital bleeding</td>
<td>10</td>
<td>127.0</td>
<td>No</td>
<td>Q</td>
<td>Miscarriage</td>
</tr>
<tr>
<td>2</td>
<td>30</td>
<td>21</td>
<td>MG</td>
<td>No</td>
<td>Genital bleeding</td>
<td>10</td>
<td>52.0</td>
<td>Yes</td>
<td>Q</td>
<td>Miscarriage</td>
</tr>
<tr>
<td>3</td>
<td>27</td>
<td>22</td>
<td>MG</td>
<td>No</td>
<td>Fever, chills, prostration</td>
<td>12</td>
<td>295.0</td>
<td>No</td>
<td>Q</td>
<td>Recovered</td>
</tr>
</tbody>
</table>

MG = multigravidae; Q = quinine.

including Venezuela, strengthened surveillance would help to prevent or identify earlier the introduction of other Plasmodium species or resistant strains that may complicate the clinical course of infection in vulnerable groups such as pregnant women. Malaria acquired during pregnancy is one of the major causes of maternal morbidity that may lead to unfavorable maternal and fetal outcomes.

Pregnant women traveling from nonendemic countries or regions, or by nonimmune women who become pregnant (particularly the primigravidae) while they are in an endemic area, makes the risk of acquiring imported malaria a life-threatening situation. The threat of malaria caused by P. falciparum for both the mother and the newborn is related to the potential fatal clinical outcomes of this type of malaria, which could become eventually resistant to antimalarial drugs such as chloroquine and quinine.

Infection of pregnant women with P. falciparum has been associated with abortion, intrauterine growth retardation, low birthweight, neonatal mortality, and congenital infection. Therapy could be complicated by concerns about the safety of antimalarial agents for the fetus and newborn as well as drug resistance. While chloroquine and quinine are safe for use in pregnancy, drug resistance is now common, especially when the etiologic organism is P. falciparum. In the Amazon region of Brazil, P. falciparum quinine resistance has been reported in the past decade. In Venezuela, the use of quinine regimen has been associated with a failure rate of 11% to 24% and has been widely used, despite the fact that this country was a pioneer in the establishment of effective control strategies against malaria.

Given the increasing incidence of malaria in pregnant women, newer therapeutical regimens have been tried in these zones (eg, mefloquine–artesunate). The national malaria treatment guidelines, at the time these women were seen, recommended the use of quinine to treat P. falciparum infection in pregnant women. However, after malaria surveillance programs and those clinical trials such as the discussed herein were carried out, major changes to the antimalarial therapeutic armamentarium were implemented in different areas of Venezuela. The recognition of spread of chloroquine- and quinine-resistant P. falciparum in the meridian region and the possible spread of these cases into other regions led to the national implementation of the combination of mefloquine and artesunate for the treatment of P. falciparum in these locations.

There are concerns about the safety of administering some new antimalarial agents during...
pregnancy, such as artemisinin derivates, but many reports including one from the World Health Organization have stated their safety profiles (except in the first trimester for which additional data are still required). Concerns about the safety and availability of some antimalarial agents potentially limit options for treatment and prophylaxis. For these reasons counseling, education and specific advice (including the most appropriate drug indication) from travel medicine practitioners for pregnant women are of utmost importance to prevent malaria and complications as seen by us and by others in these particular populations.

Declaration of Interests
The authors state that they have no conflicts of interest to disclose.

References
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