Am. J. Trop. Med. Hyg., 89(3), 2013, pp. 520–526
doi:10.4269/ajtmh.12-0205

Maternal Clinical Findings in Malaria in Pregnancy in a Region of Northwestern Colombia

Juan Gabriel Piñeros,* Alberto Tobon-Castaño, Gonzalo Álvarez, Carmencita Portilla, and Silvia Blair
Malaria Group, Universidad de Antioquia, Medellín, Colombia

Abstract. In malaria-endemic regions of Latin America, little is known about malaria in pregnancy. To characterize the clinical and laboratory findings of maternal infection, we evaluated 166 cases of pregnant women infected with *Plasmodium* spp. in a prospective study conducted in northwestern Colombia during 2005–2006. A total of 89.8% (149 of 166) had fever or a history of fever in the past 48 hours, 9.0% (15 of 166) had severe malaria, of which 66.7% was caused by *Plasmodium vivax* and 33.3% by *P. falciparum*. Hepatic dysfunction was the main complication (9 of 15) observed. The proportion of severe cases was similar for both species ($P = 0.41$). In malaria-endemic areas of Colombia, malaria in pregnancy has a broad clinical spectrum. In pregnant women, *P. vivax* infection frequently leads to organ-specific complications.

INTRODUCTION

Malaria is the most devastating parasitic disease in the world. It impacts maternal health and causes severe anemia, abortion, premature labor, bleedings, and several clinical complications inherent to the infection, which threaten the lives of pregnant women. Of approximately 125.2 million women who become pregnant in malaria-endemic regions annually,[1] 24 million are affected by the disease.[2]

Pregnant women modulate their immune system towards an anti-inflammatory profile enabling them to tolerate the fetal and placental tissues, which creates a micro-environment conducive to growth and development of infectious agents, thus making them more susceptible to infections.[3,4] Concerning malaria, this modulation means a higher disease frequency, a higher parasite density, and more complications in pregnant women. In hyperendemic and stable transmission areas, maternal infections by *Plasmodium* spp. are usually asymptomatic because of immunity acquisition at an early age.[5] In contrast, in unstable transmission areas, the risk of clinical complications, such as cerebral malaria, hypoglycemia, respiratory distress syndrome, and hemolytic anemia, is estimated to be three times higher.[6]

There have been few clinical studies that investigated the effects of malaria in pregnant women in malaria-endemic regions of Latin America, where infections by *Plasmodium vivax* are more prevalent.[7] A search performed in the electronic databases PUBMED, MEDLINE, and BIREME in October of 2012, using the MeSH terms malaria, pregnancy, clinical findings, and Latin America, resulted in four publications on the subject.[8–11]

To characterize the clinical and laboratory findings of malaria in pregnancy (MIP) in a non-Amazonian endemic region of Colombia, we enrolled pregnant women who had been diagnosed with infection by *Plasmodium* spp. during the follow-up of a prospective study. Only maternal data were described and discussed. As secondary aims, we compared clinical and laboratory characteristics of infections with *P. vivax* and *P. falciparum* and the association of certain signs and symptoms to specific severe disease criteria.

*Address correspondence to Juan Gabriel Piñeros, Malaria Group, Universidad de Antioquia, Calle 62#52–59, Laboratorio 610, Medellín 050010, Colombia. E-mail: jgpinerosj@gmail.com

MATERIALS AND METHODS

Study site. The study conducted during April 2005–December 2006 in local hospitals of Carepa (7°45′12″N, 76°39′21″W), Turbo (8°5′42″N, 76°44′23″W), and Necoclí (8°25′39″N, 76°46′58″W) municipalities in the region of Uraba, which is located in the extreme northwestern Colombia, bordering Panama, near the Darien Tropical Rainforest (Figure 1). Malaria has been one of the main public health problems in the region because of its magnitude. During 2000–2010, 16,578 annual malaria cases were reported (range = 5,068–30,429 cases), and an average annual malaria incidence rate of 43.9 cases/1,000 inhabitants (range = 8.9–65.7 cases/1,000 inhabitants) was calculated. A total of 76.4% of infections were with *P. vivax* and 23.5% with *P. falciparum*[12] (Figure 2).

Study design. This was a descriptive study that enrolled women with MIP. Cases were recruited from a hospital-based cohort of pregnant women who had participated in an epidemiologic study conducted by the Malaria Group at the University of Antioquia. At the same time as an initial diagnosis of *Plasmodium* spp. infection by blood smear was made, the expectant mothers were evaluated by field physicians who had been trained on applying a standardized clinical evaluation protocol for malaria cases and identifying signs of danger or complications. Because of limited financial resources, requests for clinical laboratory tests (blood chemistry and complete blood count) were based on the results of a physical examination. The clinical laboratory tests were used to identify possible complications and classify cases of acute uncomplicated malaria or severe malaria. All pregnant women received antimalarial treatment according to national protocols.[13]

Case definition. Pregnant women infected with *Plasmodium* spp. during pregnancy or labor were classified according to the following criteria: Afebrile MIP was defined as non-febrile infection with no history of fever in the last 48 hours. Uncomplicated MIP was defined as fever or a history of fever in the last 48 hours without a diagnosis of severe malaria. Severe MIP was defined as a diagnosis of clinical complications of malaria according to World Health Organization (WHO) criteria.[6] MIP with signs of danger was defined as clinical or parasitologic danger signs according to criteria proposed by Tobon.[14] These criteria have been evaluated in several clinical studies conducted in Colombia and Latin America and were used in a surveillance system of antimalarial drug to classify the severity risk of patient included in the follow-up.[15–17]

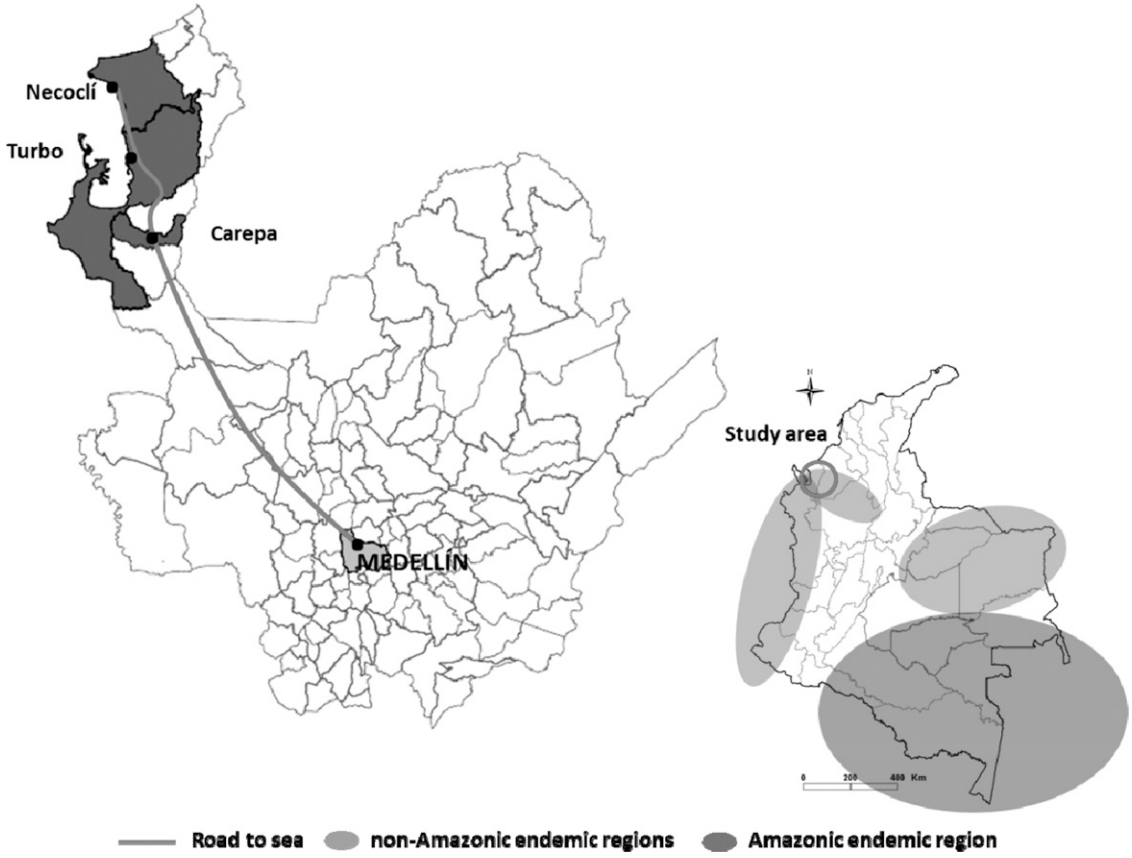

FIGURE 1. Location of study area in Colombia.

The MIP signs of danger were altered level of consciousness (score on the Glasgow coma scale of 13–10/15), at least one convulsion in the past 24 hours, coluria (dark urine and presence of blood or hemoglobin confirmed by dipstick test), jaundice (yellow pigmentation of sclera, conjunctiva, skin or mucous membrane), tachypnea for gestational age without fever (respiratory rate > 24 before week 20 of gestation and > 28 after week 20), spontaneous bleedings (ecchymosis and petechias in skin or mucosa, melena or hematemesis), intense pallor and heart murmur, persistent vomiting (> 4 episodes in

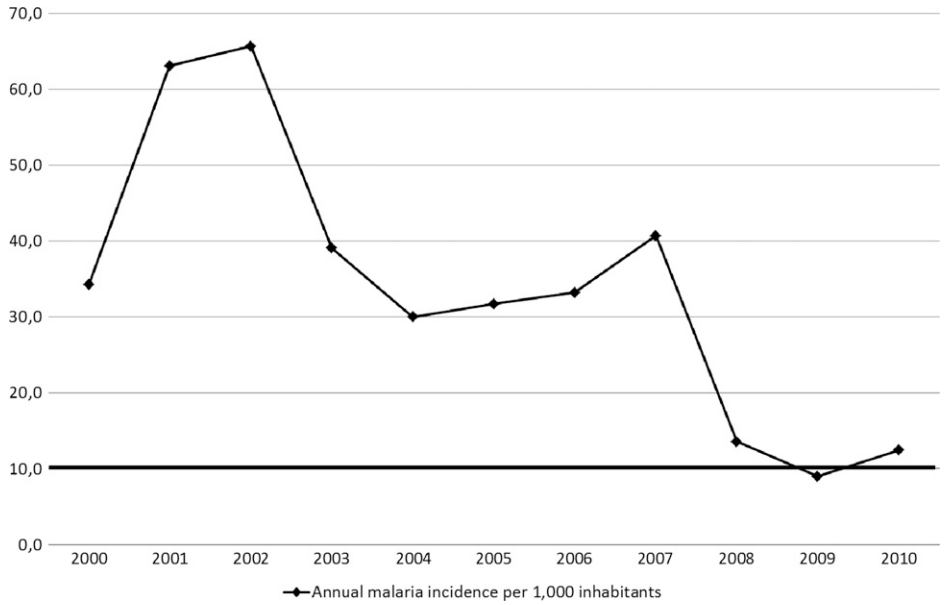

FIGURE 2. Malaria incidence in Uraba region, Colombia, 2000–2010 (based on information of Antioquia Health Services. Available at: http://www.dssa.gov.co/index.php/estadisticas/eventos-de-salud-publica).

24 hours), persistent diarrhea (> 4 episodes in 24 hours), hyperpyrexia (axillar temperature > 39.5°C), hypothermia (axillar temperature < 35.5°C), and severe dehydration signs (dryness, impaired urinary elimination, and/or tachycardia and hypotension).

Laboratory procedures. Malaria infection was diagnosed by using a thick blood film. Blood samples were obtained by capillary puncture of a finger after asepsis and antisepsis. The first blood drop was discarded and subsequent blood drops were used for diagnosis. Thick blood smears were stained with Field's stain and viewed under a light microscope at 100 × magnification by an expert in microscopic diagnostic technique. Parasitemia was estimated against 200 leukocytes (8,000 leukocytes/μL as a standard value) and was expressed as parasites/microliter. For *P. falciparum*, parasitemia was calculated by counting ring forms and for *P. vivax* by counting all asexual forms. The thick blood smear was considered negative when no parasite forms were observed in at least 200 microscopic fields or when only gametocytes of *P. falciparum* were observed. All samples were revised by a second bacteriologist who confirmed the results.[18]

Clinical laboratory measurements were performed at local hospitals by using automated equipment (MEK-8918 hematology analyzer and spectrophotometer RA-50).

Data analysis. Demographic and clinical data were entered into a database created by using the Statistical Package for Social Sciences version 17.0 for Windows (SPSS Inc., Chicago, IL). Descriptive statistics was used to establish the general characteristics of infected pregnant women, the clinical characteristics of the infection, and the clinical laboratory findings. Median and interquartile range (IQR) or mean and confidence interval were calculated for continuous variables (according to normal distribution of data), and absolute frequency and percentages were used for categorical variables. Mann-Whitney's test, chi-square test and Fisher's exact test were applied to compare clinical and laboratories findings of infections with *P. vivax and P. falciparum*, as well as the frequency of signs of danger between severe and uncomplicated MIP cases. A significance level of 5% was used.

RESULTS

A total of 220 pregnant women were diagnosed with infection by *Plasmodium* spp. in peripheral blood during the follow-up. Of these women, 166 had a physical examination (Figure 3) at the time of diagnosis. A total of 78.3% (n = 130) were infected with *P. vivax* and 21.7% (n = 36) with *P. falciparum*. The general characteristics of MIP cases included (n = 166) and the ones not included (n = 54) in the clinical analysis are shown in Table 1. Only the number of antenatal care visits was statistically different between the groups ($P = 0.02$).

TABLE 1

General characteristics of pregnant women with malaria included or not included in clinical analysis, Colombia*

Variable	MIP cases included in analysis (n = 166), median (Q1–Q3)	MIP cases not included in analysis (n = 54), median (Q1–Q3)	*P*
Age (years)	23 (18–29)	21 (18–24)	0.079
Years of residence in malaria area	16 (5–22)	17.5 (6.5–20.8)	0.867
Previous pregnancies	2 (1–3)	1 (1–2)	0.292
Episodes of malaria in previous year	0 (0–1)	0 (0–1)	0.749
Antenatal care visits	5 (3–7)	4 (3–6)	0.02
Episodes of malaria in current pregnancy	1 (1–2)	1 (1–1)	0.228

*MIP = malaria in pregnancy.

The 166 pregnant women infected with malaria were 13–43 years of age (median = 23 years, IQR = 18–29 years); 33.9% were < 20 years of age and 1.8% were < 15 years of age. A total of 79.5% had resided in a malaria-endemic area for > 5 years (median = 16 years, IQR = 5–22 years), 78.2% had been pregnant at least once before, and 21.8% reported > 3 pregnancies. The median number of antenatal care visits for the 166 pregnant women was 5 (IQR = 3–7 visits).

Clinical manifestations of MIP. Seventeen (10.2%) of the 166 women examined did not report fever associated with infection and were identified during the antenatal care screening. The remaining 149 women had consultations at malaria diagnosis sites, antenatal care programs, or emergency units of local hospitals for symptoms of illness. All women received antimalarial treatment according to severity of infection and parasite species. None of these women died.

Duration of illness before consultation showed a range of 1–35 days and a median of 4 days (IQR = 3–6 days) for pregnant women infected with *P. vivax* and a median of 3 days (IQR = 3–6 days) for those infected with *P. falciparum* ($P = 0.943$). The classic triad of fever, chills, and sweating was present in 87.9% of pregnant women; other symptoms present from the onset of the disease until the time of consultation

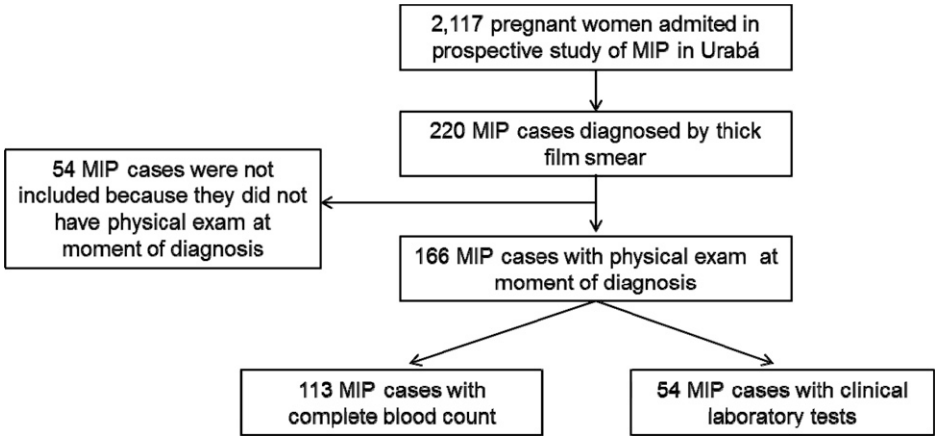

FIGURE 3. Flowchart showing recruitment of malaria in pregnancy (MIP) cases in Uraba, Colombia.

TABLE 2
Clinical laboratory results for pregnant women with malaria, Colombia

Laboratory parameter	MIP* by *Plasmodium vivax*		MIP by *P. falciparum*	
	No.	Median (Q1–Q3)	No.	Median (Q1–Q3)
Hemoglobin (g/dL)	90	10.4 (9.4–11.4)	23	10.3 (9.1–10.9)
Creatinine (mg/dL)	40	0.7 (0.6–0.9)	13	0.8 (0.7–0.9)
Blood urine nitrogen (mg/dL)	27	12.0 (9.0–19.0)	9	15.0 (11.8–20.8)
Total bilirubin (mg/dL)	39	1.2 (0.7–2.3)	12	1.6 (0.6–2.6)
Direct bilirubin (mg/dL)	39	0.5 (0.2–1.0)	12	0.5 (0.2–1.4)
Alanine aminotransferase (U/L)	26	15.0 (12.0–22.3)	4	31.0 (20.0–53.3)
Glucose (mg/dL)	42	88.0 (74.0–103.3)	12	93.5 (73.0–102.0)
Platelets/μL	90	141,500 (96,500–179,500)	23	109,000 (80,000–190,000)
Parasite density (parasites/μL)	130	2,640 (480–6,390)	36	4,400 (960–10,515)

*MIP = malaria in pregnancy.

were headache (97.6%), musculoskeletal pain (83.1%), and asthenia and adynamia (74.5%). A history of fever was most frequently reported in pregnant women infected with *P. vivax* compared with those infected with *P. falciparum* (92.3% vs. 80.6%; $\chi^2 = 4.236$, $P = 0.04$). At the time of diagnosis, only 42 (25.6%) of the 166 pregnant women had fever. The most frequent clinical signs at the time of physical examination were conjunctival pallor (54.2%), palm pallor (30.1%), tachycardia (27.4%), fever (25.6%), abdominal pain on palpation (20.5%), and tachypnea (17.1%). Jaundice was less frequent in pregnant women infected with *P. vivax* than in the group infected with *P. falciparum* (8.5% vs. 22.9%, $\chi^2 = 3.950$, $P = 0.048$).

Laboratory findings in pregnant women with malaria. The median parasitemia among MIP cases caused by *P. falciparum* was 4,400 rings/μL (IQR = 600–6,760 rings/μL); 77.8% (28 of 36) had a parasitemia < 10,000 rings/μL and 94.4% (34 of 36) had a parasitemia < 50,000 rings/μL. Only 2.8% (1 of 36) of the counts were > 100,000 rings/μL. For MIP cases caused by *P. vivax,* a median of 2,640 parasites/μL (IQR = 600–6,760 parasites/μL) was calculated; no women showed parasite densities > 20,000 parasites/μL. Four pregnant women infected with *P. falciparum* had schizonts circulating in peripheral blood; and only in one patient was this finding accompanied by dysfunction of a specific organ (hepatic dysfunction).

Complete blood count. A complete blood count was performed in 113 pregnant women during the malaria episode; the median hemoglobin level was 10.3 (IQR = 9.4–11.4) g/dL. Anemia (hemoglobin level < 11 g/dL) was diagnosed in 66.4% (75 of 113) of pregnant women and 4.0% (3 of 75) had severe anemia (hemoglobin level < 7.0 g/dL). The lowest hemoglobin concentration was 5.4 g/dL in a pregnant woman infected with *P. vivax*. The median platelet count was 140,000 (IQR = 95,000–181,000) platelets/μL; 57.5% (65 of 113) of pregnant women had thrombocytopenia (count < 150,000 platelets/μL) and 3.5% (4 of 113) had severe thrombocytopenia (count < 50,000 platelets/μL).

Clinical laboratory tests. The most frequently requested clinical laboratory test was for glycemia (54 of 166 pregnant women) and the least requested was for alanine aminotransferase (ALT), (30 of 166). The median serum creatinine level was 0.7 (IQR = 0.6–0.9) mg/dL (reference range = 0.4 to 0.8 mg/dL), and the median blood urea nitrogen (BUN) level was 13.8 (IQR = 9.3–18.8) mg/dL (reference range = 7.8–18.0 mg/dL). Thirteen patients had serum creatinine levels > 0.8 g/mL and 20 had BUN levels > 12 mg/dL. In six patients, both of these levels were abnormal and the serum creatinine:BUN ratio was > 8, which in pregnant women indicates acute renal failure of prerenal origin. The medians of serum total bilirubin (TB) and serum direct bilirubin (DB) levels were 1.2 (IQR = 0.6–2.3) mg/dL (reference range = 0.2–1.0 mg/dL) and 0.5 (IQR = 0.2–1.3) mg/dL (reference range = 0.0–0.3 mg/dL), respectively. A total of 57.7% of pregnant women had a TB level > 1.0 mg/dL, and 13.5% had a TB level > 3.0 mg/dL. A total of 64.7% had a DB level > 0.3 mg/dL and 25% had a DB level > 1.0 mg/dL; two pregnant women had levels > 2.0 g/dL: one was infected with *P. falciparum* (2.4 g/dL) and the other was infected with *vivax* (3.1 g/dL). The median ALT level was 16.0 (IQR = 12.9–25.3) U/L (reference range = 10.0–40.0 UI/L). A total of 13.3% (4 of 30) had levels > 40 U/L and one patient with MIP caused by *P. vivax* had a level three times above the reference range (228 U/L). The median venous plasma glucose level was 88.5 mg/dL (IQR = 74.0–102.3 mg/dL) at the time of malaria diagnosis. Mild-to-moderate hypoglycemia (range = 40–70 mg/dL) was found in 13.2% (7 of 54) of the patients; none had severe hypoglycemia (< 40 mg/dL). There were no differences in the clinical laboratory levels ($P > 0.05$) according to parasite species (Table 2).

Severe malaria in pregnancy. Based on WHO criteria for severe falciparum malaria, 9.0% (15 of 166) of MIP cases were classified as having severe infections. A total of 66.7% (10 of 15) were infected with *P. vivax* and 33.3% (5 of 15) were infected with *P. falciparum*. In 86.7% (13 of 15) of patients with severe malaria, only one complication was found; 13.3% (2 of 15) had > 1 complication. Hepatic dysfunction was the most frequent complication in all patients with severe cases (9 of 15 patients). The frequency of complications in MIP by species is summarized in Table 3.

TABLE 3
Frequency of complications in pregnant women with severe malaria by *Plasmodium* species, Colombia

Quantity of complication type	MIP* by *P. vivax* (n = 10)		MIP by *P. falciparum* (n = 5)	
	No.	%	No.	%
One complication				
Hepatic dysfunction	6	40.0	2	28.6
Hyperparasitemia†	–	–	1	14.3
Severe anemia	2	13.3	1	14.3
Hemoglobinuria	1	6.7	–	–
More than one complication				
Hepatic dysfunction plus spontaneous bleedings	1	6.7	–	–
Renal dysfunction plus spontaneous bleedings	–	–	1	14.3

*MIP = malaria in pregnancy.
†Only in *P. falciparum* malaria cases.

TABLE 4
Danger signs in pregnant women with malaria (based on criteria of Tobón[14]), Colombia

Sign	No.	%
Coluria	20	12.0
Jaundice	19	11.4
Tachypnea for gestational age without fever	17	10.2
Hyperpyrexia (axillar temperature > 39.5°C)	6	3.6
Severe dehydration signs	5	3.0
Hypothermia (axillar temperature < 35.5°C)	4	2.4
Persistent vomiting (> 4 times in 24 hours)	4	2.4
Intense pallor and heart murmur	3	1.8
Spontaneous bleedings	3	1.8
Altered level of consciousness (Glasgow coma score 13–10/15)	1	0.6
Convulsions	1	0.6

Danger signs of malaria. Among the 166 pregnant women, 60 showed at least one danger sign of severe malaria at the time of clinical evaluation. The most frequent were coluria (12.0%), jaundice (11.4%), tachypnea without fever (10.2%), hyperpyrexia (3.6%), and signs of severe dehydration (3.0%) (Table 4). Intense pallor plus heart murmur showed a correlation with severe anemia (χ^2 =15.992, P = 0.05, by Fisher' exact test). Jaundice was more frequent in patients with TB levels > 3.0 mg/dL (χ^2 =13.449, P = 0.019, by Fisher's exact test) and in those with spontaneous bleedings (χ^2 = 4.725, P = 0.051, by Fisher's exact test). Coluria showed a correlation with TB levels > 3.0 mg/dL (χ^2 = 0.638, P = 0.032, by Fisher's exact test). Clinical syndromes identified in 166 pregnant women with malaria according to *Plasmodium* spp. are shown in Table 5.

DISCUSSION

This study is the first report on maternal clinical and laboratory characteristics of MIP in Colombia. A total of 10.2% of pregnant women examined were afebrile. This percentage can be considered high in the epidemiologic context of Colombia because other studies reported the absence of afebrile infections in regions of active transmission.[19] However, afebrile infections in pregnant women have frequently been reported in some areas of unstable transmission in Latin America: 1.7% in Honduras and 21.1% in Brazil.[8,10] One of the difficulties in determining and classifying asymptomatic infections in pregnant women is that it is impossible to follow-up patients who did not have treatment because of the high risk of maternal and neonatal adverse effects associated with the infection. A high percentage (19.4%) of pregnant women infected with *P. falciparum* were afebrile; this might have been caused by immunity acquired to the parasite present in these regions. A certain degree of immunity can be developed before reaching the reproductive age, and although symptoms are alleviated, infection is not prevented. This finding highlights the need to promote active control of the infection during antenatal visits in unstable transmission areas,[20] with the objective of decreasing the risk of complications such as maternal anemia or congenital malaria.[21,22]

TABLE 5
Clinical syndromes identified in 166 pregnant women with malaria according to *Plasmodium* species, Colombia

	P. vivax (n = 130)		*P. falciparum* (n = 36)		
Clinical classification	No.	%	No.	%	*P*
Afebrile infection	10	7.7	7	19.4	0.08
Acute uncomplicated malaria	110	84.6	24	66.7	0.02
Severe malaria	10	7.7	5	13.9	0.41
Malaria with danger signs	43	33.1	17	47.2	0.12

Pregnant women are three times more susceptible to malaria-related complications than non-pregnant women. In addition, infection increases mortality in this group, which may reach up to 50%.[23] *Plasmodium falciparum* is the species most frequently associated with severe disease and the risk of death. In our study, criteria for severe malaria were observed in 7.7% (10 of 130) pregnant women infected with *P. vivax* and in 13.9% (5 of 36) of those infected with *P. falciparum*, but no statistically significant differences were observed. Excluding hyperparasitemia, 11.1% (4 of 36) of *P. falciparum* MIP cases would be classified as severe because of organ-specific dysfunction. Frequency of severe organ dysfunction in pregnant women does not depend on parasite species (P = 0.75). Infections with *P. vivax* have been considered benign in comparison with infections with *P. falciparum*. This widely accepted concept has been questioned recently. Potentially mortal infections with *P. vivax* have been reported by Baird since 1998 in more than 20 countries that have active transmission of *P. vivax*.[24] Complications caused by this species are cerebral malaria (including generalized convulsions and epileptic state), severe hepatic dysfunction, respiratory distress syndrome and pulmonary edema, shock, acute renal insufficiency, spleen rupture, severe thrombocytopenia and hemorrhage, and severe anemia.[24]

In Latin America, severe morbidity caused by *P. vivax* was reported in pregnant women in Brazil and Venezuela. Hepatic dysfunction was found in 4.7% and 8.3% of pregnant women infected with this species, respectively.[9,10] The second study also diagnosed spontaneous bleedings in 25% of pregnant women. The reasons for this organ-specific damage caused by *P. vivax* infection in the population, and in pregnant women in particular, are not understood. Recent observations provided evidence for parasite sequestration in the pulmonary microvasculature.[25] In addition, recent studies report cytoadherence of *P. vivax*-infected erythrocytes to endothelial receptors.[26] Furthermore, microrheologic research showed increased aggregation, agglutination, and reduction in deformability of *P. vivax*-infected erythrocytes.[27]

Patients infected with *P. vivax* showed increased levels of interferon-γ and tumor necrosis factor showed a linear correlation with the possibility of developing severe malaria. At the same time, increased levels of interleukin-10 have been associated with a decreased possibility of severity.[28] Cytokine imbalance has been associated with severe anemia and alterations in hepatic and renal function tests, as well as with severe maternal anemia and low birth weight.[29]

Some findings suggest that it may be necessary to adapt the WHO criteria for severe malaria to particular population groups. According to WHO, renal failure associated with malaria is diagnosed by a serum creatinine level > 3.0 mg/dL or by a BUN level > 40 mg/dL.[6] During pregnancy, renal blood flow and glomerular filtration rate increase from 50% to 60%.[30] These changes lead to an increase in creatinine renal depuration that implicates a decrease of serum creatinine and BUN. If we applied WHO criteria, one case of renal dysfunction (serum creatinine level > 3 mg/dL) was identified. If standard clinical criteria for pregnant women had been used

(creatinine levels > 0.8 g/mL and BUN levels > 12 mg/dL), 33 cases with renal dysfunction of pre-renal origin caused by hypoperfusion secondary to malaria infection would have been identified. The fact that some of the mild or moderate renal dysfunctions were accompanied by other organ dysfunctions highlights the systematic process of inflammation that might cause severe disease and mortality.

The WHO defines hepatic dysfunction as TB levels > 3.0 mg/dL and ALT levels > 120 UI/L.[6] Although the liver does not show signs of important alterations during pregnancy, these criteria are exaggerated for an adult. The standard clinical criteria for hepatic function abnormality (TB level > 1.0 mg/dL, DB level > 0.3 mg/dL, and ALT levels > 40 UI/L),[30] is 3.5 times more sensitive in identifying patients with hepatic dysfunction than the WHO criteria. Because hepatic dysfunction is the main complication of MIP, one goal of clinical attention is to identify the cases as soon as possible to offer timely treatment.[15]

In hyperendemic and stable-transmission countries, a *P. falciparum* parasitemia > 4% of parasitized erythrocytes (approximately 200,000 rings/μL) is believed to increase the risk of complications.[31] In Latin America, patients with < 100,000 rings/μL are common. In Turbo and Tumaco, Colombia, only 10% of the severe cases showed parasitemia > 100,000 rings/μL. These patients generally had at least one organ dysfunction criterion. Another study reported parasitemia < 50,000 parasites/μL in 52% of the severe cases.[15] Some researchers do not consider hyperparasitemia of *P. falciparum* as a sign of severity unless it is accompanied by an organ dysfunction. It is important to point out that no range values have been established for *P. falciparum* counts in relation to risks for complications and deaths in pregnant women. Further studies are needed to establish a possible prognostic factor that would be useful for pregnant women.

The need for early identification of malaria-related complications has been frequently promoted because it is needed for timely treatment and decreasing the possibility of death. Danger signs may be an adequate tool for the early detection of complications.[14] Although such signs have not been established for pregnant women, the signs recommended for the general population were adopted in this study. A total of 36.1% of the pregnant women affected by malaria showed signs of danger, regardless of the parasite species with which they were infected.

The association of some danger signs with specific complications was established in a previous study.[15,16] In pregnant women, pallor plus heart murmur showed a correlation with severe anemia. A hemoglobin level < 11.0 g/dL is considered evidence of pallor and is accompanied by a heart murmur when the level is < 7.0 g/dL and leads to hemodynamic alterations to ensure adequate oxygenation of vital organs and the fetus. The diagnostic value of pallor as criteria for identifying anemia as an independent symptom or in combination with other symptoms has been evaluated in pregnant women. Severe anemia in expectant mothers is most frequently accompanied by other clinical manifestations (e.g., asthenia and adynamia, tachycardia, tachypnea). In Kenya, Shulman and others reported that conjunctival pallor accompanied by tachycardia or tachypnea was a more sensitive diagnosis criteria for anemia than pallor alone (81% vs. 69%).[32]

Another sign related to malaria related complications was jaundice. In this study, it was most frequently found in pregnant women with hepatic dysfunction and in those who had spontaneous bleedings. Although it was more frequent in the pregnant women with a TB level ≥ 3.0 mg/dL, we also found a significantly higher frequency in pregnant women with lower levels. This finding was also observed for pregnant women who had DB levels > 1.0 mg/dL. These findings suggest that jaundice could by caused by hepatic tissue damage rather than by the hemolytic process, and therefore indicates that this sign enables diagnosis of hepatic dysfunction cases in pregnant women with malaria at an early stage of severity. Spontaneous bleedings were probably caused by alterations in hepatic production of some coagulation factors associated with liver hypoxia. Coluria was more frequent in pregnant women who had TB levels > 3.0 mg/dL. This finding had been reported in malaria patients,[16] and its suitability in pregnant women is confirmed by results of the present study. In accordance with previous reports, this danger sign was associated with moderate-to-severe hepatic dysfunction.[16] These results confirm the role that some danger signs play in identifying severe malaria cases in pregnant women and highlights their suitability for malaria diagnosis.

This study had four main findings. In unstable-transmission malaria areas, MIP may include the whole clinical spectrum, from the afebrile infection to severe malaria. *Plasmodium vivax* maternal infections are frequently accompanied by organ-specific complications. Hepatic dysfunction and spontaneous bleedings are the most frequent complications in MIP cases and are present in > 70% of severe cases. Signs of danger in pregnant woman with malaria show a correlation with organ-specific dysfunction.

Received March 30, 2012. Accepted for publication May 3, 2013.

Published online July 29, 2013.

Acknowledgments: We thank the personnel from the local hospitals, the Vector Borne Disease Control Programs, and the Secretariats of Health of the Municipalities, the field personnel from the Malaria Group at the Universidad de Antioquia, the personnel from the Antonio Roldán Betancur Institute of Tropical Medicine at the Instituto de Ciencias de la Salud, and the mothers and newborn babies for participating in the study.

Financial support: This study was supported by the Colombian Science, Technology and Innovation Department within the framework of the Gestational and Congenital Malaria in Urabá project (1115-04-17041), the Antioquia District Health Department, and Estrategia de Sotenbilidad 2013-2014, Malaria Group, universidad de Antioquia.

Authors' addresses: Juan Gabriel Piñeros, Malaria Group, Universidad de Antioquia, Calle 62#52–59, Laboratorio 610, Medellín 050010, Colombia, E-mail: jgpinerosj@gmail.com. Alberto Tobon-Castaño, Gonzalo Álvarez, Carmencita Portilla, and Silvia Blair, Sede de Investigaciones Universitarias, Universidad de Antioquia, Medellín, Antioquia, Colombia, E-mails: albertobon@yahoo.com, lgonzalvarez@gmail.com, malaria@quimbaya.udea.edu.co, and silviablairt@gmail.com.

REFERENCES

1. Dellicour S, Tatem AJ, Guerra CA, Snow RW, ter Kuile FO, 2010. Quantifying the number of pregnancies at risk of malaria in 2007: a demographic study. *PLoS Med 7:* e1000221.
2. Steketee RW, Nahlen BL, Parise ME, Menendez C, 2001. The burden of malaria in pregnancy in malaria-endemic areas. *Am J Trop Med 64 (Suppl 1–2):* 28–35.
3. Okoko BJ, Enwere G, Ota MO, 2003. The epidemiology and consequences of maternal malaria: A review of immunological basis. *Acta Trop 87:* 193–205.
4. Rogerson SJ, Hviid L, Duffy PE, Leke RF, Taylor DW, 2007. Malaria in pregnancy: pathogenesis and immunity. *Lancet Infect Dis 7:* 105–117.

5. Nosten F, Rogerson SJ, Beeson JG, McGready R, Mutabingwa TK, Brabin B, 2004. Malaria in pregnancy and the endemicity spectrum: What can we learn? *Trends Parasitol 20:* 425–432.
6. World Health Organization, 2010. *Guidelines for the treatment of malaria, Second edition. NLM classification: WC 770*. Available at: http://whqlibdoc.who.int/publications/2010/9789241547925_eng.pdf. Accessed August 2012.
7. Arevalo-Herrera M, Quiñones ML, Guerra C, Céspedes N, Giron S, Ahumada M, Piñeros JG, Padilla N, Terrientes Z, Rosas A, Padilla JC, Escalante AA, Beier JC, Herreia S, 2012. Malaria in selected non-Amazonian countries of Latin America. *Acta Trop 121:* 303–314.
8. Fernández RD, García Y, Alger J, 2001. Malaria y embarazo: observaciones clínico-epidemiológicas en dos zonas geográficas de Honduras. *Rev Med Hondur 69:* 8–18.
9. Gómez E, López E, Ache A, 2009. Malaria y embarazo. Parroquia San Isidro, municipio Sifontes, estado Bolívar, Venezuela, años 2005–2006. *Invest Clin 50:* 455–464.
10. Jarude R, Trindade R, Tavares-Neto J, 2003. Malária em grávidas de uma maternidade pública de Rio Branco (Acre, Brasil). *Rev Bras Ginecol Obstet 25:* 149–154.
11. Rodriguez-Morales AJ, Sanchez E, Vargas M, Piccolo C, Colina R, Arria M, Franco-Paredes C, 2006. Pregnancy outcomes associated with *Plasmodium vivax* malaria in northeastern Venezuela. *Am J Trop Med Hyg 74:* 755–757.
12. Dirección Seccional de Salud de Antioquia, 2010. *Eventos de Salud Pública: Enfermedades Transmitidas por Vectores a 2010*. Available at: http://www.dssa.gov.co/index.php/estadisticas/eventos-de-salud-publica. Accessed July 2012.
13. República de Colombia, Ministerio de Salud, Dirección General de Promoción y Prevención. *Guía de Atención de Malaria, 2000. Norma Técnica 31/03/2000*. Bogotá, Colombia: Diario Oficial 43.956.
14. Tobón A, 2009. Signos de peligro en el paciente con malaria. *Biomedica 29:* 320–329.
15. Tobón-Castaño A, Piñeros-Jiménez JG, Blair-Trujillo S, Carmona-Fonseca J, 2009. Clínica de la malaria complicada debida a *P. falciparum*. Estudio de casos y controles en Tumaco y Turbo (Colombia). *Iatreia 19:* 339–355.
16. Tobón-Castaño A, Cortina A, Miranda AF, Blair-Trujillo S, 2010. Orina oscura e ictericia como signos de peligro en malaria por *Plasmodium falciparum* en Colombia. *Rev Cubana Med Trop 62:* 28–35.
17. World Health Organization, 2009. *Methods for Surveillance of Antimalarial Drug Efficacy. NLM classification: QV 256*. Available at: http://whqlibdoc.who.int/publications/2009/9789241597531_eng.pdf. Accessed August 2012.
18. López-Antuñano FJ, Schmunis G, 1988. *Diagnóstico de Malaria. Series Técnicas 143*. Washington, DC: Organización Panamericana de la Salud.
19. Osorio L, Todd J, Bradley D, 2004. Ausencia de malaria asintomática en escolares de Quibdo, Choco. *Biomedica 24:* 13–19.
20. Greenwood B, Alonso P, ter Kuile FO, Hill J, Steketee RW, 2007. Malaria in pregnancy: Priorities for research. *Lancet Infect Dis 7:* 169–174.
21. Shulman CE, Dorman EK, 2003. Importance and prevention of malaria in pregnancy. *Trans R Soc Trop Med Hyg 97:* 30–35.
22. Davies HD, Keystone J, Lester ML, Gold R, 1992. Congenital malaria in infants of asymptomatic women. *CMAJ 146:* 1755–1756.
23. Schantz-Dunn J, Nour NM, 2009. Malaria and pregnancy: a global health perspective. *Rev Obstet Gynecol. 2:* 186–192.
24. Baird JK, 2007. Neglect of *Plasmodium vivax* malaria. *Trends Parasitol 23:* 533–539.
25. Anstey NM, Handojo T, Pain MC, Kenangalem E, Tjitra E, Price RN, Macguire GP, 2007. Lung injury in vivax malaria: pathophysiological evidence for pulmonary vascular sequestration and posttreatment alveolar-capillary inflammation. *J Infect Dis 195:* 589–596.
26. Carvalho BO, Lopes SC, Nogueira PA, Orlandi PP, Bargieri DY, Blanco YC, Mamoni R, Leite JA, Rodrigues MM, Soares IS, Oliveira TR, Wunderlich G, Lacerda MV, del Portillo HA, Araújo MO, Russell B, Suwanarusk R, Snounou G, Rénia L, Costa FT, 2010. On the cytoadhesion of *Plasmodium vivax*-infected erythrocytes. *J Infect Dis 202:* 638–647.
27. Jayavanth S, Park BC, 2007. Microrheologic dysfunctions in blood during malaria. *Indian J Exp Biol 45:* 111–120.
28. Andrade BB, Reis-Filho A, Souza-Neto SM, Clarêncio J, Camargo LM, Barral A, Barral-Netto M, 2010. Severe *Plasmodium vivax* malaria exhibits marked inflammatory imbalance. *Malar J 9:* 13.
29. Nosten F, McGready R, Simpson JA, Thwai KL, Balkan S, Cho T, Hkirijaroen L, Looaresuwan S, White NJ, 1999. Effects of *Plasmodium vivax* malaria in pregnancy. *Lancet 354:* 546–549.
30. Agudelo-Jaramillo B, Cadavid-Jaramillo AP, Bueno-Mendoza JC, Fisiología de la gestación. En: Botero J, Júbiz A, Henao G, eds. *Obstetricia y Ginecología. Texto Integrado*. Octava Edición. Medellín: Editorial CIB, 2008, 85–91.
31. World Health Organization, 2000. Severe falciparum malaria. *Trans R Soc Trop Med Hyg 94 (Suppl)*: 1–90.
32. Shulman CE, Levene M, Morison L, Dorman E, Peshu N, Marsh K, 2001. Screening for severe anaemia in pregnancy in Kenya, using pallor examination and self-reported morbidity. *Trans R Soc Trop Med Hyg 95:* 250–255.