

## Short Report: Spontaneous Postpartum Clearance of *Plasmodium falciparum* Parasitemia in Pregnant Women, Benin

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**Abstract.** The question of malaria in the postpartum period is controversial. Malaria was investigated during a randomized trial of intermittent preventive treatment in pregnancy in Benin. Women infected at delivery were tested for parasitemia in the early postpartum period; they had not received treatment unless they were symptomatic. Among the 35 of 1,346 infected women, parasitologic follow-up results could not be interpreted in 15 because they were treated for symptoms, 18 cleared parasitemia spontaneously within five days postpartum, and 2 had a strong decrease in parasitemia before being treated. Because the placenta is the privileged site for sequestration of parasites, it facilitates their persistence during pregnancy, and its elimination may rapidly induce their clearance.

In malaria-endemic areas, pregnant women are more likely to be infected with malaria than non-pregnant women.<sup>1</sup> Recent studies have demonstrated that this propensity for malaria to develop during pregnancy is attributed, at least in part, to expression of *Plasmodium falciparum* peculiar variant antigen on the membrane of the infected erythrocyte, which enables its adherence to specific placental receptors. The accumulation of parasites in the placenta may contribute to low birth weight and maternal anemia,<sup>2</sup> particularly in primigravidae who have not acquired specific immunity to those variant parasites.<sup>3</sup>

Although the effects of malaria in pregnancy are well documented, little is known about malaria in the postpartum period. A study published in the 1980s showed that women who were parasitemic at delivery cleared their parasitemia spontaneously within 48 hours postpartum.<sup>4</sup> Recently, two longitudinal studies found that women remained at high risk for malaria in the early postpartum period, as during pregnancy.<sup>1,5</sup> To investigate this issue, which may have important consequences for the management of women who recently delivered a child, we studied the immediate postpartum spontaneous evolution of malaria infections at delivery in pregnant women in Benin.

Data were collected during a clinical trial on intermittent preventive treatment in pregnancy (IPTp), which was conducted during July 2005–April 2008 in Benin.<sup>6</sup> The study protocol was described elsewhere<sup>6</sup> and was reviewed and approved by ethics committees in France and Benin.

Briefly, pregnant women were randomized to receive two doses of IPTp with either sulfadoxine-pyrimethamine or mefloquine. At delivery, malaria thick blood smears were prepared from maternal peripheral blood and from the maternal side of the placenta. All women who had a positive peripheral thick blood smear at delivery were tested for parasitemia 24 hours later and then daily until no parasites were detected. Control blood smears were prepared at the hospital before discharge or during scheduled visits at home. For logistical reasons, in selected cases, blood smears were not prepared on day 1 after delivery, but on days 2–5. If these women had symptoms of

malaria at delivery or during follow-up or if there was a doubt on their likeliness to attend the maternity clinic in case of clinical signs (e.g., women living in remote areas), they were given a 7-day quinine treatment.

During a six-week period after delivery, all women were encouraged to attend the study maternity clinic if they had symptoms suggestive of malaria. On this occasion, a thick blood smear was prepared and women were treated if malaria was confirmed. Finally, all women had a scheduled appointment at week 6 after delivery to test for current symptoms suggestive of malaria and history of fever or malaria within the past six weeks.

Thick blood smears were considered positive if an asexual stage parasite was detected after examination of 200 microscope fields. Cross-readings were made for all blood smears. In case of discrepancy, a third reading was made.

Data analysis was performed by using STATA version 9.0 (Stata Corp., College Station, TX). When applicable, chi-square and *t*-tests were used. Otherwise, Fisher's exact test and the Kruskal-Wallis test were used.

Eighty-four percent (1,346 of 1,601) of the women had a peripheral thick blood smear prepared at delivery, and 35 (2.5%) were infected with *P. falciparum*. Infected women were more likely to be primigravid, not to have received the second IPTp dose, to be parasitemic at the second IPTp administration, and to have received sulfadoxine-pyrimethamine for IPTp than uninfected women.

Among 35 women who were infected at delivery, 15 were not tested for parasitemia within the next few days: 13 were treated because of clinical signs, mainly fever ( $n = 11$ ) or because we doubted they would return to the maternity clinic for control ( $n = 2$ ). Two were temporarily lost to follow-up (but were healthy when seen again several weeks later). Among the remaining 20 women who were followed-up without treatment, 18 cleared their parasitemia spontaneously and 2 had a 5–7-fold decreased parasite density before being treated for symptoms or for practical reasons (Table 1).

In the 18 women who cleared their parasitemia spontaneously, parasite clearance occurred within 5 days (median = 2 days). In all cases, loss of parasitemia was observed in the first control blood smear, except for one woman who had a 10-fold decreased parasitemia by day 1 before becoming negative by day 3. Women who were tested for parasitemia and those who were not tested had similar baseline characteristics except for symptoms and high parasitemia at delivery, which

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TABLE 1  
Parasitologic follow-up of 35 women infected with *Plasmodium falciparum* at delivery, Benin

Characteristic	No.	Day in the postpartum period				
		1	2	3	4	5
Spontaneous parasite clearance*	18	4/5	5/5	2/2	4/4	3/3
Decreased parasitemia†	2	1	1			
Antimalarial drug before control	13					
Lost to follow-up	2					

\* Data are numbers of women with a negative thick blood smear/number of women tested for parasitemia. One woman had a 10-fold decreased parasitemia by day 1 (85,143 parasites/mm<sup>3</sup> at delivery vs. 804 parasites/mm<sup>3</sup> at day 1) before becoming negative by day 3.

† One woman had a 5-fold decreased parasitemia at 14 hours (compared with delivery) before being treated for practical reasons (4,160 parasites/mm<sup>3</sup> at delivery vs. 846 parasites/mm<sup>3</sup> at 14 hours), and one woman had a 7-fold decreased parasitemia by day 2 before being treated because of symptoms (25,333 parasites/mm<sup>3</sup> at delivery vs. 3,655 parasites/mm<sup>3</sup> by day 2).

were significantly higher for women who were not tested (Table 2).

At the week 6 postpartum scheduled appointment, 3 of the 35 women reported that they had malaria since delivery; only one attended the maternity clinic and had a negative thick blood smear. Of women who were seen at week 6 (n = 1,434), 37 reported that they had malaria since delivery; 24 of them (92%) attended the maternity clinic and a thick blood smear was prepared. This blood smear was positive for only three of them (on days 14, 15, and 30 after delivery).

Twenty-two years after the first published results,<sup>4</sup> we confirm that pregnant women infected at delivery can clear parasitemia spontaneously in the early postpartum period. This phenomenon was described in all 18 untreated women tested for parasitemia in the early postpartum period. Thirteen other women were administered an antimalarial treatment soon after delivery, mainly because of clinical signs, and their ability to clear parasites is still not clear. These findings may be a source of bias because they represented nearly half the population studied. However, because they were symptomatic, they had to be treated for ethical reasons. It is therefore impossible to assume what the clinical course of *P. falciparum* infections would have been in these women.

Spontaneous parasite clearance was observed within five days and was dependent on when women were tested for parasitemia. Because some control blood smears could not

be made within the first few hours after delivery, the median parasite clearance time (PCT) may actually be even shorter. In the above-cited study, in which blood was obtained from women four times/day, parasite clearance occurred within 48 hours in almost all cases.<sup>4</sup> We could not assess the impact of gravidity on PCT because the first control blood smear was obtained from primigravidae and multigravidae at different times. However, PCT is likely to be shorter in multigravidae because of immunity acquired against pregnancy-associated parasites during successive pregnancies.

Such frequent and rapid clearance of parasites in the postpartum period suggests that the placenta may play an important role. Because the placenta is a privileged site for sequestration and multiplication of parasites, it facilitates the persistence of parasitemia during pregnancy, and the rapid clearance of parasites in the postpartum period is the likely consequence of its elimination. This hypothesis is supported by studies that demonstrated that parasite populations in placental and peripheral blood are derived mostly from a single population<sup>7</sup> and that they shared similar phenotypes of adherence to chondroitin sulfate A, the infected erythrocytes placental receptor.<sup>8</sup>

Nevertheless, recent studies showed that women could have an increased risk of malaria in a two-month period after delivery compared with non-pregnant women or women before pregnancy.<sup>1,5</sup> These apparently conflicting results could be explained either by a temporary clearing of parasites in the immediate postpartum period, followed by a phenomenon of parasite resurfacing in the blood, or by new infections by non-placental parasites. In their study, Ramharther and others suggested that both mechanisms played a role, although most malaria cases were new infections acquired after delivery.<sup>5</sup> In our study, malaria cases were detected passively during the first six weeks after delivery. We reported a low rate of symptomatic malaria infections. Using active case detection, we likely would have found more cases (either new malarial infections or recrudescence parasitemia).

Since the study of Nguyen Dinh and others,<sup>4</sup> there is increasing evidence that the placenta is the main site for sequestration of pregnancy-associated malaria parasites, that those parasites have genotypic specificities, and that placental damage may alter placental functions, materno-fetal exchanges and fetal

TABLE 2  
Characteristics during pregnancy and at delivery for 35 women infected at delivery, by their parasitologic follow-up, in the postpartum period, Benin\*

Characteristic	No parasitologic follow-up† (n = 15)	Parasitologic follow-up‡ (n = 20)	P
Mean age, years, (SD)	22.7 (4.7)	24.2 (5.5)	0.41
No. (%) primigravidae	6 (40)§	9 (45)	0.77
No. (%) slept under a bed net the night before enrollment	6 (40)	10 (50)	0.56
No. (%) received mefloquine for IPTp	2 (15)	7 (39)	0.24
No. (%) did not receive second IPTp dose	2 (13)	2 (10)	0.99
No. (%) positive parasitemia at enrollment	1 (7)	1 (5)	0.99
No. (%) positive parasitemia at second IPTp administration	2 (15)	5 (28)	0.67
At delivery			
Median peripheral parasitemia/mm <sup>3</sup> (IQR)	28,000 (2,162–112,444)	2,734 (722–22,114)	0.02
No. (%) with parasitemia > 2,500 parasites/mm <sup>3</sup>	11 (73)	10 (50)	0.16
No. (%) with parasitemia > 10,000 parasites/mm <sup>3</sup>	9 (60)	6 (30)	0.08
No. (%) with clinical signs	11 (67)	0 (0)	0.001
No. (%) with placental malaria¶	13 (87)	15 (75)	0.67

\* Percentages were compared by using the chi-square test or Fisher's exact test, means and medians were compared by using the Student's *t*-test and the Kruskal Wallis test, respectively.

IPTp = intermittent preventive treatment in pregnancy; IQR = interquartile range.

† Women who received an antimalarial drug before being tested (n = 13) or women lost to follow-up after discharge from the maternity clinic (n = 2).

‡ Women who cleared their parasitemia spontaneously (n = 18) or had a decreased parasitemia in the early postpartum period before being treated (n = 2).

§ Among 11 symptomatic women, 6 (55%) were primigravid.

¶ Placental malaria was defined as the presence of asexual-stage parasites in the placental thick blood smear.

growth.<sup>9</sup> As suggested by our findings, the placenta also acts as a reservoir of parasites, which are cleared spontaneously after its removal, without the help of anti-malarial drugs. However, either by recrudescence of remaining parasites or by new infections, the early postpartum period appears to be a critical period in terms of susceptibility to malaria. Consequently, particular attention should be given to women who have recently delivered children, and in addition to the continuous protection by insecticide-treated bed nets which is strongly recommended, IPTp late in pregnancy could also be considered. In addition to its potentially high effect on birth weight when administered when fetal growth is the most important,<sup>10</sup> IPTp at the end of the third trimester may protect women from consequences of malaria in the early postpartum period. The follow-up of women just before and after delivery, with genotyping of placental and peripheral parasites, might help understanding the underlying mechanisms of such early infections. Also, increased risk for malarial infections in the postpartum period, their clinical relevance and public health consequences, and strategies to prevent them would require further investigation.

Received March 3, 2010. Accepted for publication September 20, 2010.

Acknowledgments: We thank the women who participated in this study; the midwives, nurses, and assistants who made the study possible; and Philippe Deloron for reviewing the manuscript.

Financial support: The study was supported by the Fonds de Solidarité Prioritaire (French Ministry of Foreign Affairs, project no. 2006-22) and the Institut de Recherche pour le Développement. Valérie Briand was sponsored by the Fondation pour la Recherche Médicale (grant FDM20060907976), the Fondation de France, and the Fondation Mérieux

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