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INCREASED SUSCEPTIBILITY TO MALARIA DURING THE EARLY POSTPARTUM PERIOD

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ABSTRACT

Background Pregnancy is associated with increased susceptibility to malaria. It is generally agreed that this increased risk ends with delivery, but the possible persistence of increased susceptibility during the puerperium has not been investigated.

Methods From June 1, 1990, to December 31, 1998, we monitored exposure to malaria, parasitemia, and morbidity among the residents of a village in Senegal in which the rate of transmission of malaria was high. In this population we analyzed 71 pregnancies in 38 women from the year before conception through one year after delivery.

Results Among the 38 women, there were 58 episodes of clinical *Plasmodium falciparum* malaria during 61,081 person-days of observation. The incidence of malaria was 20.2 episodes per 1000 person-months during the year preceding conception and 12.0 episodes per 1000 person-months during the period from 91 to 365 days after delivery. The incidence of episodes of malaria increased significantly during the second and third trimesters of pregnancy and reached a maximum of 75.1 episodes per 1000 person-months during the first 60 days after delivery. The adjusted relative risk of an episode of malaria was 4.1 (95 percent confidence interval, 1.8 to 9.5) during the first 60 days post partum, as compared with the year preceding pregnancy. The duration of fever during the episodes of malaria was longer and the prevalence and density of asymptomatic malarial parasitemia were significantly higher during pregnancy and the early postpartum period than during the other periods.

Conclusions Among women who live in areas with high rates of transmission of malaria, the susceptibility to malaria is highest during the second and third trimesters of pregnancy and the early postpartum period. (N Engl J Med 2000;343:598-603.)

MALARIA causes serious complications in pregnant women,[1-5] especially in those who have a low level of acquired immunity before pregnancy. In these women, the rates of maternal mortality, stillbirth, and premature delivery are high. In areas where malaria is highly endemic, in which protective immunity is acquired during childhood, these effects of malaria are less marked. Nonetheless, the frequency and severity of malaria are greater during pregnancy than before pregnancy and among pregnant women than among those who are not pregnant.[3-5] Although data are virtually nonexistent, the special features of maternal malaria are thought to end with delivery, a view that is consistent with the hypothesis that adhesion of parasites to the placenta is responsible for the increased susceptibility of pregnant women to malaria.[6,7]

We analyzed longitudinal data collected before, during, and after pregnancy among women living in an African village in which the whole population was involved in a prospective study of the epidemiology of malaria and the mechanisms of protective immunity.

METHODS

Participants

The study was carried out from June 1, 1990, to December 31, 1998, in Dielmo, Senegal, a village of approximately 300 inhabitants where malaria is endemic. The entire population of this village was involved in a prospective study that has been described in detail elsewhere.[5,8] Briefly, to identify all episodes of illness, a field research station with a dispensary was built. The detection

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of cases was both active and passive. Each villager who had volunteered for the study was visited daily at home by a physician, technician, nurse, or medical field worker. In villagers who had fever, blood was obtained for thick blood films and detailed medical examinations were undertaken. Standardized questionnaires were completed for each episode of illness; these recorded physical findings, the studies performed, the treatment given, and the response to treatment. In addition, blood was obtained from each villager at base line for hemoglobin electrophoresis (to identify carriers of hemoglobin S), blood-group determination, and tests for glucose-6-phosphate dehydrogenase deficiency, and monthly thereafter for thick blood films for the identification of asymptomatic malaria infections.

Between June 1, 1990, and January 1, 1998, 81 deliveries occurred among 43 women who were participating in the study. Seventy-one deliveries occurred among 38 women who had lived in the village continuously and who were monitored daily either for a 33-month period starting 12 months before the date of conception and ending 12 months after delivery (in the case of 55 deliveries among 28 women) or during a minimum of 18 months, including at least the second and third trimesters of pregnancy and the first 3 months post partum (in the case of 16 deliveries among 16 women, including 6 of the women in the first group). Among the latter group there were two women who were already pregnant at the beginning of the study, eight women who became pregnant soon after arriving in Dielmo, three women who returned to Dielmo because they were pregnant, one woman who left the village after the early postpartum period, and two women who traveled frequently. Ten of the 81 deliveries were excluded from the analysis: 4 because the four women had been pregnant for more than three months at the beginning of the study, 4 because the women did not spend the early postpartum period in Dielmo, and 2 because the women were frequently absent from the village during pregnancy and the puerperium.

At delivery, thick blood films were prepared from the mother's blood and from umbilical-cord blood. A small piece of placenta was taken, and a drop of blood from the cut surface was applied to a slide. We analyzed the variations in the incidence of clinical malaria and the levels of parasitemia in these women before, during, and after pregnancy. A preliminary analysis of data collected among 31 of these women who gave birth between 1990 and 1994 (48 pregnancies), which excluded the early postpartum period, has been reported previously.[5]

None of the women received antimalarial chemoprophylaxis. During pregnancy, all episodes of fever associated with a ratio of asexual malarial parasites (i.e., trophozoites) to leukocytes of at least 0.5 on the thick blood film were considered to represent possible attacks of malaria and were treated with antimalarial drugs. If a woman was not pregnant but had a fever and a ratio of parasites to leukocytes of at least 0.5 or if she was pregnant but had a fever and a ratio of parasites to leukocytes of less than 0.5, another blood sample was obtained for analysis the day after these findings were noted. Whether or not to administer antimalarial drug treatment was decided by a physician who was permanently stationed in the village, who took into account all the clinical, biologic, and epidemiologic data concerning the woman. All women with clinical malaria were visited at home three times a day until the fever and other symptoms subsided.

Urine tests were regularly carried out in the villagers to detect the presence of antimalarial drugs, with the use of the modified Saker–Solomons test.[9] Less than 2 percent of the results of 3798 tests carried out during the study period were compatible with self-treatment, and this proportion was only 0.7 percent among the study women.

The level of exposure to malaria was monitored throughout the study.[8,10] Nighttime collections of mosquitoes that landed on volunteer subjects who lived in Dielmo were carried out weekly or monthly from April 1990 to December 1998, and for each woman, the levels of exposure before, during, and after pregnancy were derived from monthly estimates of the rate of entomologic inoculation among these volunteer subjects.

The project protocol and the objectives were carefully explained to the assembled village population, and informed consent was obtained individually from all subjects. The protocol was approved by the ethics committee of the Pasteur Institute of Dakar and the Ministère du Plan et de la Coopération and the Ministère de la Recherche Scientifique of Senegal. Each year, the project was reexamined by the Conseil de Perfectionnement de l'Institut Pasteur de Dakar and the assembled population of the village; informed consent was individually renewed for all subjects. Before the project began, all women in Dielmo gave birth at home, none took antimalarial chemoprophylaxis, and none had prenatal visits. The ethical justification for not providing chemoprophylaxis during the study was based on the semi-immune status of the study women, the high level of chloroquine resistance in the area, and the permanent presence of a medical team in the village, with daily home visits to all study women and their children.

At the beginning of the study, all villagers from Dielmo and the neighboring hamlet of Santhe-Mouride volunteered for the project (total population enrolled in June 1990; 255 villagers, including 44 female villagers ranging from 15 to 45 years of age). During the last three months of 1990, 32 villagers from Santhe-Mouride withdrew from the project (including 5 female subjects who were 15 to 45 years of age). In subsequent years, 16 additional villagers from Santhe-Mouride withdrew (including 3 female subjects who were 15 to 45 years of age). However, the number of villagers enrolled in the study increased as a result of births and of people moving into the area. On January 1, 1998, the study population under medical surveillance (excluding those who had been absent from the village for more than two months) comprised 302 villagers, of whom 51 were female subjects between 15 and 45 years of age.

Definition of Episodes of Clinical Malaria

We evaluated all thick blood films by examining 200 oil-immersion fields on each slide (equivalent to about 0.5 μl of blood). The ratio of trophozoites to leukocytes was established for each plasmodium species. We counted as an episode of clinical *Plasmodium falciparum* malaria any case of fever (defined as an axillary temperature of at least 37.5°C) or fever-related symptoms (headache, vomiting, and a subjective sensation of fever) associated with a ratio of parasites to leukocytes that exceeded an age-dependent pyrogenic threshold previously identified in these subjects.[11,12] This threshold ranged from 1.15 parasites per leukocyte at the age of 16 years to 0.57 parasite per leukocyte at the age of 44 years.[11]

Statistical Analysis

We used a generalized-estimating-equation approach for statistical analysis of repeated measures,[13] since this approach can be used with normal, binomial, and Poisson distributions and is available in the Spida statistical package (Statistical Computing Laboratory, Eastwood, New South Wales, Australia). We used an exchangeable correlation structure in which the correlation between observations made on the same person at different times is assumed to be the same. We used the Wald test to compare differences between groups, and we calculated 95 percent confidence intervals. We compared transmission rates during the women's pregnancies and during control survey periods using a link function for a Poisson distribution. We analyzed the incidence of episodes of clinical malaria using a link function for a Poisson distribution and the number of days in a period as the exposure variable. The prevalence of asymptomatic malaria was measured on the basis of the findings in the monthly thick blood films and analyzed as a binomial response. To determine the mean parasite density during asymptomatic episodes, we calculated the geometric mean number of *P. falciparum* trophozoites from the ratio of the parasites to leukocytes determined in the monthly thick blood films, and we analyzed log-transformed values with a link function for a normally distributed response.

The effect of the period of study (the year before pregnancy, the trimesters of pregnancy, and the four trimesters of the post-

partum period) was tested as a dummy variable. To test the duration of the effects observed during the first three months post partum, this period was split in two — from 0 to 60 and from 61 to 90 days after delivery — and the second, third, and fourth three-month periods after delivery were combined. The effect of age (<20 years or ≥20 years) was tested as a binary variable. The effects of the previous pregnancy, prolonged residence in hypoendemic areas (as opposed to the hyperendemic study area), absences from Dielmo during the three years preceding the observation period, glucose-6-phosphate dehydrogenase deficiency, the sickle cell trait, a specific ABO or rhesus blood group, the level of exposure to infected mosquitoes, the use of mosquito netting around the bed, and placental infection at delivery were also evaluated and taken into account in multivariate analyses. The variables that represented the effects of the period of study and the level of exposure to infected mosquitoes were forced into all models. All other covariates were included in the initial models, but they remained in the final models only if their effects were significant ($P<0.05$). All possible interactions between the variables remaining in the models were tested.

RESULTS

During 61,081 person-days of clinical surveillance, there were 443 episodes of illness: 152 in which fever was documented, and 291 in which there were other symptoms. On the basis of the level of parasitemia, 58 of these episodes were attributed to *P. falciparum* malaria, during which fever was documented in 50 episodes and fever-related symptoms in 8 episodes. The incidence of episodes of clinical malaria was highest during the first 60 days after delivery (75.1 episodes per 1000 person-months) (Table 1). The incidence of episodes of malaria was also high between 61 and 90 days after delivery (45.4 episodes per 1000 person-months) and during the second and third trimesters of pregnancy (50.6 and 58.6 episodes per 1000 person-months, respectively).

The values during the second and third trimesters of pregnancy and during the first 60 days post partum were significantly higher than those during the year preceding pregnancy and during the later postpartum period, despite the fact that the cumulative exposure to the bites of infected anopheline mosquitoes was similar during these periods (Table 1). After adjustment for the level of exposure to infected mosquitoes, the effects within study subjects, parity, and the duration of residence in the village, the relative risk of an episode of malaria was 4.1 (95 percent confidence interval, 1.8 to 9.5) during the first 60 days after delivery, as compared with the year preceding pregnancy.

To investigate patterns of asymptomatic parasitemia before, during, and after pregnancy among these women, we included in the analysis the results of 1720 monthly thick blood films obtained at least one week before and two weeks after an episode of illness. Asexual forms of *P. falciparum* were seen in 712 thick blood films (41.4 percent). The prevalence and density of asymptomatic *P. falciparum* parasitemia were maximal during the second trimester of pregnancy, and multivariate analysis indicated that both were significantly higher from the first trimester of pregnancy through the second month post partum than during the other periods (Table 2).

We then investigated whether the occurrence of episodes of malaria during the first trimester of the postpartum period was related to asymptomatic maternal infection at delivery, placental infection (the frequency of placental infection on the basis of parasites was 32 percent, and the frequency of placental infection identified on the basis of parasites or pigment [indicative of recent infection] was 40 percent), or genetic and epidemiologic factors (ABO or rhesus blood group, hemoglobin AA vs. AS, presence or absence of glucose-6-phosphate dehydrogenase deficiency, and use or nonuse of mosquito netting around the bed). No relation was found. Older age, a higher number of previous pregnancies, and longer duration of residence in Dielmo were associated with a lower susceptibility to asymptomatic infection and to clinical malaria. There was no significant interaction between these covariates and the study periods.

All episodes of malaria that occurred during pregnancy, the early postpartum period, or the control period were mild and rapidly cured. The maximal duration of fever documented during the daily visits to patients was 48 hours. Including the eight patients with clinical malaria who did not have a documented fever, the average duration of fever was 22 hours during pregnancy, 21 hours during the first trimester after delivery, and 11 hours during the year before pregnancy and the second, third, and fourth trimesters after delivery.

DISCUSSION

Our findings suggest that the pregnancy-associated increase in susceptibility to malaria persists for 60 days after delivery among women who live in areas where malaria is highly endemic. On the basis of findings in a limited number of studies in which parasitemia was measured post partum, the rate of parasitemia decreases after delivery.[4,14-16] However, many women take antimalarial drugs after delivery, and drug use was not investigated in most of these studies. Furthermore, our data suggest that the increased susceptibility of the mothers to clinical episodes of malaria during the early postpartum period was greater than their increased susceptibility to parasitemia.

The effect of pregnancy on a woman's resistance to disease has been the subject of considerable research and debate.[17-21] In the case of infectious diseases, there are logistical and methodologic problems in determining whether there is an increased risk of susceptibility to infection during pregnancy, and an increase in risk has been established only for a limited number of pathogens. The underlying mechanisms are unclear and may differ considerably among diseases. The increased susceptibility of pregnant women to malaria has been thought to be due either to sequestration of the parasites in the placenta or to

TABLE 1. CLINICAL AND ENTOMOLOGIC VARIABLES OBTAINED BY DAILY CLINICAL SURVEILLANCE BEFORE, DURING, AND AFTER 71 PREGNANCIES IN 38 WOMEN.*

VARIABLE	YEAR BEFORE PREGNANCY	TRIMESTER OF PREGNANCY			DAYS AFTER DELIVERY		
		1ST	2ND	3RD	1–60	61–90	91–365
No. of person-days of observation	19,598	5,441	6,014	6,224	4,052	2,011	17,741
No. of episodes of fever	37	11	17	28	20	5	34
No. of other illnesses	72	34	30	30	28	11	86
No. of episodes of clinical *Plasmodium falciparum* malaria	13	3	10	12	10	3	7
No. with documented fever	10	3	8	11	10	2	6
Level of exposure to infected vectors — no. of infected mosquitoes collected/1000 person-mo†	19,486	18,174	20,423	19,206	19,134	19,118	19,355
Incidence of episodes of clinical *P. falciparum* malaria/1000 person-mo (95% CI)	20.2 (10.7–34.5)	16.8 (3.5–49.0)	50.6 (24.3–93.2)	58.6 (30.3–102.5)	75.1 (36.5–138.2)	45.4 (9.4–132.6)	12.0 (4.8–24.7)
Crude relative risk (95% CI)	1.0	0.8 (0.2–2.9)	2.5 (1.1–5.7)	2.9 (1.3–6.4)	3.7 (1.6–8.5)	2.2 (0.7–7.9)	0.6 (0.2–1.5)
P value		0.77	0.03	0.008	0.005	0.21	0.27
Adjusted relative risk (95% CI)‡	1.0	1.0 (0.3–3.0)	2.8 (1.1–7.4)	3.1 (1.2–7.9)	4.1 (1.8–9.5)	2.6 (0.8–7.9)	0.7 (0.2–1.9)
P value		0.97	0.04	0.02	0.001	0.11	0.46

*CI denotes confidence interval.

†Nighttime collections of mosquitoes that landed on volunteer subjects who lived in Dielmo were carried out weekly or monthly from April 1990 to December 1998 to determine the levels of exposure to infected vectors. The values are therefore estimates of the rate of inoculation of *Plasmodium falciparum* into humans by mosquitoes.

‡The analysis was adjusted for the effects within study subjects, parity, the level of exposure to infected mosquitoes, and the duration of residence in Dielmo during the three years preceding the study. The relative risk of clinical malaria during the first 60 days after delivery as compared with 91 to 365 days after delivery was 6.2 (95 percent confidence interval, 3.1 to 12.2; $P<0.001$). The relative risk of clinical malaria during the first 90 days after delivery as compared with the year before pregnancy was 3.6 (95 percent confidence interval, 1.7 to 7.7; $P<0.001$). The relative risk of clinical malaria during the first 90 days after delivery as compared with 91 to 365 days after delivery was 5.4 (95 percent confidence interval, 2.6 to 11.2; $P<0.001$). The relative risk of clinical malaria during the first 60 days after delivery as compared with the year before pregnancy and 91 to 365 days after delivery was 4.9 (95 percent confidence interval, 2.7 to 8.6; $P<0.001$). The relative risk of clinical malaria during the first 90 days after delivery as compared with the year before pregnancy and 91 to 365 days after delivery was 4.3 (95 percent confidence interval, 2.5 to 7.1; $P<0.001$).

Table 2. Incidence of Asymptomatic *Plasmodium falciparum* Parasitemia among 38 Women before, during, and after 71 Pregnancies.*

Variable	Year before Pregnancy	Trimester of Pregnancy: 1st	2nd	3rd	Delivery	Days after Delivery: 1–60	61–90	91–365
No. of routine blood films examined†	573	141	160	165	61	121	63	436
No. of blood films positive for *P. falciparum* trophozoites (%)	208 (36.3)	74 (52.5)	90 (56.3)	87 (52.7)	28 (45.9)	60 (49.6)	18 (28.6)	147 (33.7)
Crude odds ratio (95% CI)	1.0	1.9 (1.3–2.8)	2.3 (1.6–3.2)	2.0 (1.4–2.8)	1.4 (0.8–2.4)	1.7 (1.1–2.6)	0.7 (0.4–1.3)	0.9 (0.7–1.2)
Adjusted odds ratio (95% CI)‡	1.0	2.2 (1.5–3.2)	2.5 (1.7–3.6)	2.1 (1.4–3.1)	1.3 (0.7–2.4)	1.8 (1.1–2.7)	0.7 (0.4–1.3)	0.8 (0.6–1.1)
P value		<0.001	<0.001	<0.001	0.329	0.014	0.274	0.263
Geometric mean no. of *P. falciparum* trophozoites/μl of blood (95% CI)§	26 (20–35)	59 (36–97)	127 (78–206)	105 (65–170)	88 (36–216)	53 (30–93)	26 (8–86)	37 (26–54)
Crude coefficient of log-transformed values (95% CI)¶	1.0	2.2 (1.2–4.0)	5.1 (3.0–8.9)	3.9 (2.2–6.8)	3.3 (1.3–8.1)	2.0 (1.0–3.8)	1.0 (0.3–2.9)	1.3 (0.8–2.1)
Adjusted coefficient of log-transformed values (95% CI)‡¶	1.0	2.7 (1.6–4.6)	5.5 (3.6–11.5)	4.3 (2.6–7.0)	3.3 (1.4–7.5)	2.0 (1.1–3.6)	1.3 (0.5–3.3)	1.5 (0.9–2.4)
P value		<0.001	<0.001	<0.001	0.006	0.02	0.59	0.11

*Blood samples were obtained monthly. CI denotes confidence interval.

†The results of analyses of blood that was obtained less than one week before and two weeks after any episode of clinical malaria or illness were excluded.

‡The analysis was adjusted for the effects within study subjects, parity, the level of exposure to infected mosquitoes, and the duration of residence in Dielmo during the three years preceding the study.

§Negative blood films were excluded.

¶Values are expressed as 10 to the power *n*, where *n* is the parameter estimated in models for the log-transformed density of parasites of asymptomatic infections.

depression of selected components of the immune system in association with the increased production of several hormones or other proteins.[4,7,22-28]

The demonstration that a distinct subpopulation of parasites that bind chondroitin sulfate A is responsible for the adhesion of *P. falciparum* to the placenta supports the view that sequestration of parasites in the placenta is the chief mechanism involved in malarial parasitemia in pregnant women.[6,7,29,30] Some studies have, however, documented that cell-mediated immune responses to malaria antigens are decreased in pregnant women, and there is some evidence from studies of other pathogens that such a phenomenon may persist during the early postpartum period.[17,23-27] The high incidence of episodes of malaria during the first few months after delivery provides evidence to support the view that depression of components of immunity is the key factor involved in malaria in pregnant women.

The spread of resistance to antimalarial drugs has led to a reconsideration of the role of chemoprophylaxis in controlling malaria.[31] In areas of endemic disease where there are high levels of chloroquine resistance, intermittent treatment with sulfadoxine–pyrimethamine has been proposed for women in their first pregnancy. In areas where chloroquine is still effective, chemoprophylaxis has been abandoned for most groups at risk, including infants and children, but it continues to be recommended for pregnant women, especially those with little or no immunity. For these women, the increased susceptibility to malaria during the early postpartum period may have severe consequences; therefore, we suggest that malaria chemoprophylaxis should be continued for at least two months after delivery.

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