

The Effects of Mefloquine Treatment in Pregnancy

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We investigated the relationship between mefloquine antimalarial treatment and the outcome of pregnancy in Karen women living in an area along the western border of Thailand where multidrug-resistant *Plasmodium falciparum* infections are common. Of 3,587 pregnancies investigated, 208 (5.8%) were exposed to mefloquine, 656 (18.3%) to quinine only, and 909 (25.3%) to other antimalarials, and 2,470 (68.9%) had no documented malaria. There were 61 stillbirths and 313 abortions. Women who received mefloquine treatment during but not before pregnancy had a significantly greater risk of stillbirth than did women treated with quinine alone (odds ratio [OR], 4.72; 95% confidence interval [CI], 1.7–12.7), women exposed to other treatments (OR, 5.10; 95% CI, 2–13.1), and women who had no malaria (OR, 3.50; 95% CI, 1.6–7.6) ($P < .01$). This association remained after adjustment for all identified confounding factors. Mefloquine was not associated with abortion, low birth weight, neurological retardation, or congenital malformations. Mefloquine treatment during pregnancy was associated with an increased risk of stillbirth.

The use of the antimalarial mefloquine has increased in recent years because of the spread of *Plasmodium falciparum* strains that are resistant to other available drugs. Mefloquine is prescribed widely as prophylaxis for malaria in travelers and for the treatment of uncomplicated *P. falciparum* infections in areas of endemicity where the level of resistance is high, such as in Southeast Asia and South America [1]. The toxicity of mefloquine has been studied extensively [2] and the drug is relatively well tolerated. Potentially serious neuropsychiatric reactions [3] occur in ~1/10,000 healthy subjects receiving mefloquine prophylaxis, 1/1,000 Asian patients, 1/200 Caucasian or black African patients with uncomplicated malaria, and 1/20 patients recovering from severe malaria following mefloquine treatment [4].

The manufacturer of mefloquine (Lariam; Hoffman La Roche, Basel, Switzerland) recommends avoidance of mefloquine during pregnancy because of lack of data on its safety for the fetus [5]. In animal studies, mefloquine causes fetal toxicity at doses 5–20 times higher than those recommended for human use [2].

As part of the detailed postmarketing monitoring by the manufacturer in collaboration with the World Health Organization (Geneva), a total of 1,500 pregnancies exposed to mefloquine immediately before or during the first 3 months of pregnancy have been documented prospectively [6]. More than 95% of the women took mefloquine for prophylaxis, and the outcomes for 971 (64%) could be evaluated. There were 8 stillbirths (0.8%) and 79 spontaneous abortions (1 chromosomal disorder and 4 placental disorders); 246 women had abortions induced because of concerns over the potential risks (5 malformations were observed). Of the remaining 646 women who delivered, 26 (4%) (95% CI, 2.5–5.6) had a baby with one or more congenital malformations, 33 had other pregnancy-related problems, and 587 had normal babies. Thus, the prevalence of congenital malformations or adverse outcomes in this cohort was not significantly different from the prevalence observed in the general population (1.5%–2.0%) [7]. However, an accurate risk ratio cannot be calculated from these retrospective data because the number of exposed pregnant women is unknown. Studies on the use of mefloquine in prophylaxis during the second half of pregnancy have concluded that the drug is safe [8, 9], but there are few data on the effects of fetal exposure to mefloquine given for the treatment of malaria during early gestation, and the drug is not recommended for treatment unless there is no effective alternative (i.e., for malaria resistant to other drugs).

In the populations living along the western Thai border, multidrug-resistant *P. falciparum* infections during pregnancy are associated with significant rates of maternal and fetal mortality and morbidity [10]. An extensive network of antenatal clinics (ANCs) was therefore set up in 1986 among the communities of displaced Karen people living in this area. Treatment of falciparum malaria relied on quinine and/or on mefloquine in the second and third trimesters. We have used the detailed

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records of all women seen in the ANCs to identify those who were exposed to mefloquine in pregnancy. All women who could be found were interviewed. We have compared the outcomes of these pregnancies to those of women exposed to other antimalarial drugs or who did not have malaria in pregnancy.

Patients and Methods

Study Design

The investigation was a retrospective comparison of the outcomes of pregnancies in women exposed to mefloquine to those of women not exposed to mefloquine, either because they were treated with other antimalarials or they had no documented episodes of malaria during pregnancy. The study was designed initially to investigate the potential effects on outcome of mefloquine treatment exposure just before and in early pregnancy (i.e., -3 to +4 months' gestation). Exposure up to 3 months before conception was included prospectively because of the long terminal elimination half-life of mefloquine in adult females (~3 weeks) [11]. The investigation was later extended to the entire pregnancy.

Population

The study population consisted of Karen women living in the refugee camps along the malarious northwestern border of Thailand. Health care was provided by Médecins sans Frontières (MSF) and food was distributed by a consortium of charities. In a census conducted in 1992, it was estimated that 8,960 women were older than 15 years, in a total population of 32,000. The annual birth rate was estimated to be 40 per 1,000. The number of children <1 year of age was ~1,400. The mortality rate among infants (aged <1 y) was estimated to be 160/1,000.

Epidemiology and Treatment of Malaria

The main medical problem confronting the population is multidrug-resistant falciparum malaria [12]. The epidemiology of malaria in this community has been described recently [13]. In brief, this is an area of low and seasonal transmission of *P. falciparum* and *Plasmodium vivax*, and the two groups at greatest risk of severe infections are children <5 years of age and pregnant women. The incidence of falciparum malaria in this population was estimated to be 400 per 1,000 per year in 1994. Between 1985 and 1990 uncomplicated falciparum malaria in nonpregnant patients was treated with the combination mefloquine/sulfadoxine/pyrimethamine (Fansimef, Hoffman La Roche) [14]. In 1991 this was changed to high-dose (25 mg/kg) mefloquine alone because of increased resistance of *P. falciparum* [15]. All treatments with mefloquine were supervised. The clinics were the only source of prescriptions of the drug in the camps. Mefloquine was prescribed only for

microscopically confirmed uncomplicated *P. falciparum* infections.

Since 1986, pregnant women living in the camps have been invited to attend a weekly consultation aimed at the early detection and treatment of malarial infections. The antenatal consultations were conducted by the staff of the Shoklo Malaria Research Unit (SMRU) in the northern camps of Bonoklo, Shoklo, and Mae Salit (total population, 15,000), 20–50 km north of the Thai border town of Mae Than, and by the staff of MSF in the southern camps of Kamolekaw, Maela, Wangka, and Mawker. In this community falciparum malaria is associated with significant maternal mortality and morbidity [10]. Although mortality was reduced considerably by early weekly screening, parasitemic episodes due to *P. falciparum* were still associated with maternal anemia and a reduction in the mean birth weight. These deleterious effects were most marked in the primigravida but were also evident in the second and third pregnancies.

During the first 12 weeks of pregnancy, uncomplicated *P. falciparum* infections were treated with quinine sulfate (from the Government Pharmaceutical Organization of Thailand) at a dosage of 10 mg salt/kg three times a day for 7 days. *P. falciparum* episodes during the second and third trimesters were treated with either quinine (as above) or single-dose mefloquine (25 mg base/kg; Lariam). The two organizations providing antenatal care had different treatment policies; SMRU used mefloquine more readily because of the decline in quinine efficacy and the poor compliance with 7-day quinine regimens, whereas MSF tended to use quinine as first-line treatment and to reserve mefloquine for treatment failures. All clinical and laboratory information from the ANCs was recorded on individual records and entered into a computerized database. This data set, containing 5,012 records (pregnancies), was used to trace women who might have been exposed to mefloquine during pregnancy after 1987.

Interviews, Data Collection

Five Karen interviewers were trained specifically for the study and were responsible for tracing the women and conducting the interviews. The 2,411 women (from the 5,012 records of the ANC database) who could be traced were interviewed in their own language. Exposure was confirmed by cross-checking the women's answers to specific questions with their records in the ANC database and the clinic records of malaria treatment. The interviewing teams used a demonstration set of unlabelled tablets to help the women identify which antimalarial drugs they might have been given before or during pregnancy.

The outcome variables investigated were stillbirth, abortion, and malformation rates; birth weight; and the baby's neurological development, assessed from the age that the baby sat, walked, and talked. Malformations of children alive at the time of the interview were examined by a nurse from the team and confirmed by a physician from the SMRU. Children who were

too young at the time of the interview to have reached the development milestones were seen again later.

Validation of the Questionnaires

It was possible to review and verify 2,440 questionnaires (68%) from the study sample pregnancies and compare them to the ANC records. For 2,138 (87.6%) of the study questionnaires, there were no differences in malaria episodes documented in the ANC cards and reported by the mothers in the study. For 1,744 (71.5%) of the cases, there was no difference in exposure to malaria and treatments recorded. The mean time between delivery and interview was significantly higher for women who forgot to declare a malaria episode when interviewed. For the validity of declaration of stillbirth, there was no significant difference in the percentages of potential errors of classification between the two main categories of exposure, i.e., mefloquine vs. no mefloquine. Altogether, there was correct classification of outcome for 88% of the comparable observations. Thus, the misclassification observed can be defined as nondifferential. All confirmed errors were corrected with the assumption that the ANC card (completed during pregnancy) was the true reflection of reality.

Definitions

The exposure groups chosen prospectively for analysis were pregnancies exposed during or in the 3 months before conception to (1) mefloquine (Lariam or Fansimef) or mefloquine and other antimalarials (Fansidar [Hoffman La Roche], quinine, or chloroquine) at a different time during pregnancy (*group A*); (2) quinine only (*group B*); (3) any antimalarial treatment except mefloquine (*group C*; this would include *group B*); or (4) no antimalarials (no confirmed or declared malaria episodes) (*group D*).

The gestational age at the time of drug exposure was calculated from the date of the last menstruation or, preferably, the fundal height in the last days before delivery and the newborn's Dubowitz score (when available). Stillbirth was defined as the delivery after >28 weeks' gestation of a fetus that did not breathe. Abortion was defined as the expulsion of a fetus before the 28th week of gestation. The cut-off gestational age for abortion is higher than in developed countries because in this setting, in the absence of resuscitation facilities and intensive care, a fetus 28 weeks old or younger is not viable. Because most of the deliveries in this community occur at home and without supervision, the diagnosis of stillbirth was mainly self-reported. The birth weight was measured within 24 hours with a Salter scale (Salter, Birmingham, United Kingdom), and low birth weight was defined as a body weight of <2,500 g. For assessment of neurological development, the mean ages for sitting, walking, and talking were calculated, and retardation was defined as a value more than 2 standard deviations above the mean for the population.

Data Entry, Statistics

All data were entered on site with use of Dbase IV (Borland International, Scotts Valley, CA). Twins and women who had received mefloquine as prophylaxis were excluded from the analysis. The distributions of the studied population and the overall population registered in the ANC file were compared for age and gravidity (by Student's *t* test) and for medical site, exposure to malaria and antimalarial drugs, and abortion and stillbirth rates (by χ^2 tests). All the distributions of the demographic variables were presented and statistical tests were performed to identify any confounding variables for exposure. Univariate analyses were performed to see if use of mefloquine (compared with use of quinine, other antimalarial drugs, and no antimalarials) during pregnancy was a risk factor for stillbirth, abortion, perinatal death, neurological retardation, unexplained abnormalities, and low birth weight. Multiple logistic regression was used to adjust for any confounding variables identified.

Subanalyses were also performed to calculate the relative risk of adverse outcome associated with mefloquine during the periods of from -3 months to conception, from conception to 4 months' gestation, and from >4 months' gestation to birth. The level of significance for all analyses was 5%. The analyses were computed with use of the statistical packages Epi Info (version 6, CDC public domain software) and SPSS for Windows (SPSS Benelux, Gorinchem, the Netherlands). The original goal was to have a sample size of 2,790 pregnancies, of whom 186 had been exposed to mefloquine, in order to detect a relative risk of 3 (80% power, 5% level of significance) for any adverse outcome.

Results

From 5,012 records in the ANC database, a total of 3,587 pregnancies were investigated between July 1991 and June 1994. For the 1,425 remaining pregnancies, the women could not be traced. Table 1 summarizes the demographic characteristics of this cohort. The study cohort was generally comparable to the overall ANC population. The proportion of women who had at least one episode of falciparum malaria was similar in both populations: 28.3% (27.0%–29.6%) and 28.1% (26.6%–29.5%), respectively. However, the rate of past abortion was lower in the study cohort than in the overall ANC population. Furthermore, the proportion of pregnant women living in southern camps who were recruited for the study was higher than the proportion in the overall pregnant-women population ($P < .001$).

There were 208 pregnancies (5.8%) exposed to mefloquine (*group A*), 656 (18.3%) exposed to quinine only (*group B*), and 909 (25.3%) exposed to antimalarial drugs other than mefloquine (*group C*). In 2,470 pregnancies (68.9%), there was no documented malaria or antimalarial treatment (*group D*). Women who grew up in an area where malaria is endemic had a lower risk of having malaria during their pregnancy (RR,

Table 1. Descriptive statistics concerning the study sample of pregnancies and all pregnancies seen at the antenatal clinics (ANCs) for displaced Karen women living in Thai camps.

Variable	ANC files (<i>n</i> = 5,012)	Study sample (<i>n</i> = 3,587)	<i>P</i> value
Age (y) of mother at time of pregnancy: mean \pm SD	26.2 \pm 6.14	26.6 \pm 6.14	.01*
Age group: no. (%) of women	<i>n</i> = 4,931	<i>n</i> = 2,694	
<20 y	673 (13.4)	323 (12.0)	
20–30 y	3,204 (63.9)	1,694 (62.9)	
>30 y	1,054 (21.0)	677 (25.1)	
Gravidity no.: mean \pm SD	3.5 \pm 2.47	3.5 \pm 2.45	0.35*
Gravida group:			
no. (%) of women	<i>n</i> = 4,693	<i>n</i> = 3,587	0.13†
I	1,087 (21.7)	843 (23.5)	
≥II	3,606 (71.9)	2,744 (76.5)	
History of	<i>n</i> = 4,717	<i>n</i> = 2,411	
Abortion: no./100 pregnancies	14.2	12.1	<.001†
Stillbirth: no./100 live births	NA	1.7	
Malaria: no. (%) of women	NA	2,252 (93.4)	
Camp site/ANC:			
no. (%) of women			
North/SMRU	2,695 (53.8)	1,530 (42.7)	<.001†
South/MSF	2,317 (46.2)	2,057 (57.3)	

NOTE. MSF = Médecins sans Frontières; NA = not applicable; SMRU = Shoklo Malaria Research Unit.

* Comparisons were made with the Student's *t* test.

† Comparisons were made with the χ^2 test.

0.80; 95% CI, 0.74–0.85). The pregnant women exposed to mefloquine were slightly but significantly younger than the women exposed to other treatments. Their ages (mean \pm SD) were 25 \pm 6 and 26 \pm 6 years, respectively (*P* = .035). Both groups were significantly younger than the women who did not experience malaria during their pregnancy (27 \pm 6 years; *P* < .001).

There was a higher proportion of primigravidae in the mefloquine-exposed group (32%) than in the group of women exposed to other antimalarials (29.7%) or in the nonexposed group (20.5%) (*P* < .001). The proportion who had malaria was higher among the women who lived in the northern camps (599/1,530, 39%) than among those at the southern sites (518/2,057, 25%) (*P* < .001). Furthermore, of the 599 treatments given in the northern camps, 119 (7.8%) included mefloquine, compared with only 89 (4.3%) of the 518 treatments given in the southern camps (*P* < .001). Thus, the four identified confounding factors relative to mefloquine exposure were maternal age, gravidity, camp location (north or south), and the malaria attack rates.

Outcome of Pregnancy

The outcome of pregnancy was documented in all cases in the study population, but the birth weight was recorded for

only 83.1% of the live births. The birth weight (mean \pm SD) in the 2,670 recorded live births in the study was similar to that in the 4,105 recorded live births in the overall ANC population: 2,929 \pm 528 g vs. 2,904 \pm 543 g (*P* = .06). The proportions of low birth weights were 14.7 and 15.1, respectively, per 100 live births (*P* = .6). The rate of stillbirth (61/3,213; 1.9 per 100 live births) in the study population was not significantly different from the rate in the ANC population (104/4,696; 2.2 per 100 live births) (*P* = .18). However, the abortion rate in the study cohort (313 of 3,587 pregnancies; 8.7%) was significantly higher than the rate reported in the overall population (196/4,996; 3.9%) (*P* < .001).

Risk Factors for Stillbirths

All pregnancies that ended in abortion were excluded from this analysis. The overall rate of stillbirths was 1.9 per 100 live births (61/3,213). Pregnancies ended in stillbirth for 4.5% (9) of the 200 women who received mefloquine during pregnancy (group A), 1.6% (10) of the 633 women treated with quinine only (group B), 1.4% (12) of the 873 women treated with any antimalarial drug(s) except mefloquine (group C), and 1.8% (40) of the 2,201 women who did not have malaria or antimalarials during pregnancy (group D) (*P* = .012). Women exposed to mefloquine either during pregnancy or in the 3 months before conception (group A) were at greater risk of having a stillbirth than were women in groups B (OR = 4.0; 95% CI, 1.4–11.6), C (OR = 4.5; 95% CI, 1.6–12.9), and D (OR = 3.1; 95% CI, 1.2–7.6) (table 2).

These odds ratios were adjusted for the following confounding variables: mother's age, gravidity, camp location, and number of documented malaria attacks. The 61 stillbirths were later divided into two categories: those that could be explained on the basis of the information available (38 patient records), and those for which no information was available (23 records not

Table 2. Multiple logistic regression analysis of the risk of stillbirth.

Risk factor for stillbirth*	<i>N</i>	OR (95% CI)	<i>P</i> value
Mefloquine (alone or with other antimalarials)	184		
vs. Quinine only	592	3.96 (1.35–11.61)	.012
vs. All other treatments	819	4.52 (1.58–12.92)	.005
vs. No malaria/no antimalarials	1,657	3.06 (1.23–7.60)	.016
Quinine only	592		
vs. No malaria	1,657	1.01 (0.43–2.36)	.982
Any antimalarial treatment except mefloquine	819		
vs. No malaria/antimalarials	1,657	0.83 (0.37–1.87)	.650

* Patients who had abortions were not included in the analysis.

Table 3. Main causes of stillbirth (verified cases).

Cause	<i>n</i>	No. of recipients		
		Mefloquine	Other antimalarial(s)	No malaria or antimalarials
Prolonged labor	9	1	0	8
Dystocia	6	1	1	4
Eclampsia	3	1	1	1
Placenta previa/abruptio	7	3	0	4
Uterine rupture	1	0	0	1
Accidental	2	1	0	1
Cord proclintia	1	1	0	0
Fever	2	1	1	0
Unknown	5	0	3	2

verifiable). Table 3 summarizes the main causes of stillbirth. There were no significant differences between the groups of mefloquine-exposed and -unexposed pregnancies in terms of the proportion of explained stillbirths ($\chi^2 = 0.4$; $P = .8$). However, it should be noted that for all the stillbirths occurring in the mefloquine-treated group there was a possible explanation (table 3).

As the primary objective was to identify potential effects of mefloquine exposure in the early stage of gestation, the analysis was performed for each of the predefined time periods of exposure: (1) from 3 months before conception to conception, (2) from conception to 4 months' gestation, and (3) from >4 months' gestation to birth. The time delay between the treatment and the event (stillbirth) could not be included in the logistic regression analysis because a number of women received antimalarial treatments twice or more during their pregnancy. Before adjustment for confounders, mefloquine was a significant risk factor for stillbirth from the time of conception to 4 months' gestation and from >4 months' gestation to delivery (table 4). For the 3 months before conception, mefloquine was not found to be a significant risk factor for stillbirth.

After adjustment for all the confounding variables for each time period, mefloquine exposure in the first 4 months of pregnancy was still associated with an increased risk of stillbirth in comparison with the risk for women in groups B and C. Pregnancies exposed to mefloquine after the fourth month of gestation were 4.5 times (95% CI, 0.97–20.5), 5.0 times (95% CI, 1.2–21.4), and 4.0 times (95% CI, 1.1–14.5) more likely to have a stillbirth than were those in groups B, C, and D, respectively (table 5).

Of the 9 mefloquine-exposed pregnancies that resulted in stillbirths, 5 received mefloquine only, and 2 had only one malaria episode at the second and fifth months of gestation, respectively, and received mefloquine in combination with another drug (Fansimef). The other two mefloquine exposures had two episodes of malaria each. One of them received quinine during the fifth month of gestation and mefloquine alone at 6 months. The other received mefloquine in combination with

another drug (Fansimef) during the first month of gestation and quinine during the eighth month of gestation.

After the end of the study period (i.e., since 1994), a further 3,533 pregnancies were followed in the antenatal consultations. In this entirely separate cohort, 3,032 pregnancy outcomes could be documented. There were 55 stillbirths (1.6%) and 205 abortions (5.8%). In this cohort an increased risk of stillbirth was also found for women treated with mefloquine during gestation. However, after adjustment for possible confounders, the risk was significant when the mefloquine group was compared with recipients of quinine and other antimalarial drugs (OR, 3.4; 95% CI, 1.04–10.9; $P = .04$) but not when it was compared with the no-malaria/antimalarial group (OR, 1.5; 95% CI, 0.73–3.1; $P = .26$) or the group treated with quinine alone (OR, 2.7; 95% CI, 0.43–16.9; $P = .29$).

Risk Factors for Abortions

The percentages of abortions were 3.9% in group A, 3.5% in B, 4.0% in C, and 10.9% in D ($P < .001$). Women who did not have malaria during pregnancy had a significantly higher risk for abortion than women exposed to mefloquine (RR = 2.8; 95% CI, 1.4–5.6; $P = .001$) or quinine (RR = 3.1; 95% CI, 2.1–4.7; $P < .001$).

Risk Factors for Low Birth Weight

Birth weight was not documented in 543 live births. Having at least one episode of malaria during pregnancy was a sig-

Table 4. Relative risk of stillbirth for different stages of pregnancy (not adjusted).

Stage, malaria treatment	Stillbirths (IR)*	RR (95% CI)
From –3 mo to conception		
Mefloquine (alone or with other antimalarials)	2/76 (2.6)	
vs. Quinine only	2/67 (3.0)	0.9 (0.12–6.4)
vs. All other treatments	2/103 (2)	1.4 (0.20–9.6)
vs. No malaria/no antimalarials	40/2,201 (1.8)	1.5 (0.34–6.1)
From conception to 4 mo		
Mefloquine (alone or with other antimalarials)	3/50 (6.0)	
vs. Quinine only	2/259 (0.8)	7.7 (1.3–45.0)
vs. All other treatments	3/350 (0.9)	7.0 (1.5–33.7)
vs. No malaria/no antimalarials	40/2,201 (1.8)	3.3 (1.1–10.3)
From 4 mo to end of pregnancy		
Mefloquine (alone or with other antimalarials)	4/60 (6.7)	
vs. Quinine only	6/395 (1.5)	4.4 (1.3–15.1)
vs. All other treatments	8/579 (1.4)	4.8 (1.5–15.6)
vs. No malaria/no antimalarials	40/2,201 (1.8)	3.7 (1.4–9.9)

NOTE. IR = incidence rate per 100.

* No. (%) of stillbirths per total no. of pregnant women in category.

Table 5. Risk of stillbirth after adjustment for all confounding variables in each time period.

Stage, malaria treatment	Stillbirths (IR)*	OR (95% CI)
From -3 mo to conception		
Mefloquine (alone or with other antimalarials)	2/70 (2.9)	
vs. Quinine only	2/62 (3.2)	1.3 (0.15–11.5)
vs. All other treatments	2/96 (2.1)	2.1 (0.24–18.4)
vs. No malaria/no antimalarials	19/1,657 (1.2)	2.3 (0.50–10.2)
From conception to 4 mo		
Mefloquine (alone or with other antimalarials)	2/44 (4.6)	
vs. Quinine only	1/237 (0.4)	24.5 (1.0–579)
vs. All other treatments	2/324 (0.6)	13.7 (1.5–126)
vs. No malaria/no antimalarials	19/1,657 (1.2)	3.9 (0.84–17.7)
From 4 mo to end of pregnancy		
Mefloquine (alone or with other antimalarials)	3/56 (5.4)	
vs. Quinine only	5/376 (1.3)	4.5 (0.97–20.5)
vs. All other treatments	6/551 (1.1)	5.0 (1.2–21.4)
vs. No malaria/no antimalarials	19/1,657 (1.2)	4.0 (1.1–14.5)

NOTE. IR = incidence rate per 100.

* No. (%) of stillbirths per no. of pregnant women in category.

nificant risk factor for low birth weight (OR = 1.5; 95% CI, 1.2–1.8; $P = .001$), independent of mother's age, gravidity, and camp location. The proportions of low birth weight were 21.3% in group A, 17.8% in group B, 17.6% in group C, and 12.7% in group D ($P < .001$). After adjustment for confounders, mefloquine exposure was found to be a significant risk factor for low birth weight only when compared with exposure to no antimalarials (OR = 1.7; 95% CI, 1.1–1.8; $P = .009$). Treatment with quinine only or quinine combined with other drugs was also associated with a significant risk of low birth weight (ORs = 1.4 and 1.4, respectively; 95% CIs, 1.1–1.9 and 1.1–1.8) when compared with no antimalarial treatment (no malaria).

The risk for low birth weight decreased with the mother's age (OR, 0.98; 95% CI, 0.95–0.99; $P = .032$), while primigravida pregnancies were found to be associated with an increased risk for low birth weight (OR = 1.52; 95% CI, 1.15–2.02; $P = .003$).

Risk Factors for Neurological Retardation

The different antimalarial treatment regimens were not associated with different risks of neurological retardation in comparison with the risk for babies of mothers who did not have malaria during pregnancy. The overall proportion of babies with neurological retardation was 5.2%: 4.2% in group A, 7.2% in group B, 6.5% in group C, and 4.8% in group D. The

camp location was an independent risk factor for neurological retardation: babies delivered in southern camps were at higher risk of retardation (OR = 2.7; 95% CI, 1.9–4.0; $P < .001$). However, the median (range) time delay from delivery to the first interview in the group from the northern camp was 5 months (0–88 months), compared with 30 (3–53) months in the southern camp group ($P < .001$). Furthermore, the women seen in the southern clinics had a longer median (range) time delay to the first interview than the women in the northern camps: 7 (0–88) months vs. 5 (0–42) months ($P < .001$). Thus, memory bias may have influenced the maternal recollection of milestones.

Risk Factors for Congenital Malformations

Of the 66 malformations (1.7%) reported (table 6), only 39 could be investigated. There were no differences in the risk of congenital malformations or in the type of abnormalities in the various groups.

Discussion

In this study, mefloquine exposure during pregnancy was associated with an increased risk of stillbirth. This remained

Table 6. Congenital abnormalities in pregnant women, per antimalarial treatment group.

Treatment group (n)	Type of malformation	No of occurrences
Mefloquine (200)	Meningocele	1
	Cleft palate	1
	Cardiac	1
	Unknown	3
	Total	6 (3%)
Quinine (633)	Meningocele	1
	Phocomelia	1
	Spina bifida	1
	CNS	1
	Unknown	5
All other treatments (873)	Total	9 (1.4%)
	Meningocele	1
	Phocomelia	1
	Cardiac	2
	Spina bifida	1
No malaria/no antimalarials (2,201)	CNS	1
	Unknown	7
	Total	13 (1.5%)
	Meningocele	1
	Cleft palate	1
	Spina bifida	1
	Cardiac	12
	Phocomelia	2
	Amniotic bands	4
	Unknown	17
	Total	38 (1.7%)

true after adjustment for four identified possible confounding variables: mother's age, camp location, gravidity, and malaria attack rates. The risk was significant for the two predefined periods, which together comprised the entire pregnancy: from conception to 4 months and from >4 months to delivery. In the first period, mefloquine exposure (group A) carried a significantly higher risk than the two other treatment exposure groups (B and C) but not the group with no malaria exposure, although the number of stillbirths was small (2 in group A, 1 in group B, 2 in group C, and 19 in group D) and the confidence intervals were very wide (1.04–579 and 1.48–126 for groups B and C, respectively) (table 5).

For the second period, the risk of stillbirth following mefloquine exposure was again higher than in the other groups, but this difference did not reach significance when compared with the quinine-alone group (B). In identifying associations with stillbirth, it is obviously difficult to exclude all possible confounding factors, and it is difficult to envisage a mechanism that could explain this relatively rare effect, resulting from exposure to mefloquine anywhere between the first and the last month of gestation.

The stability and isolation of the camps made it possible to document almost all malaria episodes in a community that had no other source of mefloquine. The study population constitutes a representative sample of the entire cohort of pregnant women followed in the ANC during the same period, which makes a possible selection bias improbable. The differences in rates of abortions (both past and present) probably reflect more active data collection in the study than in the general population. Each woman recruited in the study was asked specifically about past miscarriages and about the outcome of the pregnancy investigated. By contrast, abortions in women outside the study were seldom reported, especially those occurring in the first trimester. However, the closer to term, the more likely it was that a fetal death would be noted by the midwives in charge of the ANC, and, in support of this, the rates of stillbirth in the study and the ANC were similar.

The apparent increased risk of abortion in the women who did not have malaria was expected because women who have an abortion (more often in the first trimester) are less likely to be infected during such short gestation. The majority of the study questionnaires could be verified against the medical records of the ANC. For the classification of mefloquine exposure and of the main endpoint (stillbirth), 90% of the records were found to be correct.

There are several reasons to be cautious in interpreting these results. The study was conducted over a 3-year period in difficult circumstances. The camps are scattered over a 120-km distance and relatively inaccessible. It was not possible for physicians to supervise all interviews, and it was even more difficult for them to assist in the deliveries. As a result, full clinical details on stillbirths were unavailable in most cases. The information was collected from the mothers' interviews; therefore, a memory bias could exist.

The number of stillbirths in the mefloquine group was only nine, and odds ratios presented here are small and the confidence intervals wide. This is a relatively large series documenting mefloquine treatment in pregnant women. Overall, 131 women were exposed to the drug after the start of the gestation. The outcomes of these mefloquine-exposed pregnancies were compared to those of women from the same community and the same ethnic group who were exposed either to other antimalarials or to neither malaria nor antimalarial drugs. Potential confounders were controlled for. The increased risk of stillbirth associated with mefloquine remained even when the women who received the fixed combination of mefloquine/sulphadoxine/pyrimethamine (Fansimef) were removed from the analysis (data not shown).

There are only five previous reports on the use of mefloquine in pregnancies of which the outcomes are documented. Harinasuta et al. [16] treated 85 women with mefloquine and compared the outcomes to those for 72 women treated with quinine. No differences in stillbirth rates were found. Steketee et al. [9] reported the outcome of 932 pregnancies of women exposed to mefloquine as weekly prophylaxis. Second-trimester death and perinatal mortality were stated as unrelated to the drug [9]. Phillips-Howard et al. reported the findings on a cohort of 331 women exposed to mefloquine during pregnancy [17]. In their study the rate of spontaneous abortions was significantly higher with use of mefloquine (9.1%) than with use of Fansidar (2.6%) ($P = .01$), but these were similar to the background rates in the unexposed population (between 7% and 11%). These authors also reported a higher rate of induced abortions among the mefloquine-exposed women. These findings are similar to those of Smoak et al. in a cohort of U.S. female soldiers [18].

Previously we conducted a double-blind, placebo-controlled trial of mefloquine antimalarial prophylaxis in the second half of pregnancy [8], in the same community as in this investigation. We observed an excess in the rate of stillbirths in the mefloquine group (RR = 2.63; 95% CI, 0.86–8.08) but concluded that, as the stillbirths resulted from a variety of identified causes and as the confidence interval was wide, this was probably a chance finding and not a result of maternal exposure to mefloquine. However, taken together with the current findings, this provides further support for a causal link in this community.

The finding that there was also an increased risk of stillbirth in pregnant women treated with mefloquine in the 3 years following the study presented here also provides support for a causal relationship between mefloquine and stillbirth, but it should be stressed that this result comes from an analysis of the ANC clinical records and not from interviews. The risk was statistically significant only in one of the comparisons (i.e., mefloquine vs. quinine and others) and again with a wide confidence interval (OR = 3.36; 95% CI, 1.04–10.85; $P = .04$).

The rates of fetal wastage and congenital abnormalities in this study do not differ from the rates in other areas with

comparable level of development. The rate of fetal loss (stillbirth) is estimated at 8/1,000 live births in China [19], 15/1,000 in Malawi [9], and 18/1,000 in rural Thailand (L. Nopdonrattakoon, Mae Sot Hospital, personal communication). The rate of congenital abnormalities is also within the published range of 1.5%–2.0% in the general population [7]. The rate of stillbirth among women attending the ANC from the same population, before the introduction of mefloquine, was 3.2% of live births [10]. We observed a decrease in the rate of reported stillbirth in the general population, from 3.9% in 1987 to 0.9% in 1996 ($P < .001$, per χ^2 test for linear trend), despite increased use of mefloquine by pregnant women.

The apparent effect of mefloquine exposure on birth weight can be explained by the confounding effect of malaria. Each of the three treatment groups had a similar risk of low birth weight when compared with the risk for the group not exposed to malaria or antimalarials. The mean reductions in birth weight for the primigravidae of group A (140 g; 95% CI, –4.2–284), group B (134 g; 95% CI, 31–209) and group C (120 g; 95% CI, 38–229) are similar to those observed in our earlier study when only quinine was used (151 g; 95% CI, 21–282) [10].

Data from this study and previous investigations provide evidence that mefloquine may be associated with stillbirth, but definite conclusions cannot be drawn. Furthermore, there are no insights into possible mechanisms to explain this association. Mefloquine is a very valuable antimalarial drug, and it has been the mainstay of treatment for falciparum malaria in this area, where resistance is such a problem. However, physicians should be aware of this potential risk and of data from the other sources reviewed to provide further evidence concerning this important issue. The current recommendation to avoid mefloquine in pregnancy (unless there is a compelling reason to do otherwise) should not be changed.

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