

17 Nosten F et al. The effects of mefloquine treatment in pregnancy. *CID* 28, 808-15, 1999

Type of study	Retrospective cohort
Where	Thailand
When	1991-1994
Characteristics of the cohort	Newborns whose mothers were exposed to the studied drug, to other antimalarial drugs or with no malaria during pregnancy (extensive network of antenatal clinics-ANC)
Characteristics of the treated diseases	Plasmodium falciparum infections
Exposure definition	Pregnancies exposed during or in the 3 months before conception to mefloquine or mefloquine and other antimalarials (quinine/chloroquine) at a different time during pregnancy (group A). Exposure up to 3 months before conception was included prospectively because of the long terminal elimination half-life of mefloquine in adult females. The investigation was later extended to the entire pregnancy. Twins and women who had received mefloquine as prophylaxis excluded
Ascertainment of drug exposure	- Used records of all women seen in the ANC to identify exposed to mefloquine in pregnancy. All women found were interviewed - Five interviewers trained for the study, responsible for tracing the women and conducting the interviews. Exposure confirmed by cross-checking the women's answers to specific questions with records in the ANC database/clinic records of malaria treatment
Size of the studied cohort	3,587 pregnancies investigated: Exposed to the studied drug: 208 mefloquine (group A) Unexposed to the studied drug: - women exposed to other antimalarial drugs: 656 quinine only (group B), 909 any antimalarial treatment except mefloquine (group C, this would include group B) - women with no antimalarials (no confirmed or declared malaria episodes: 2,470 (group D) In the study population: 61 stillbirths, 313 abortions, 3,213 livebirths
Exposed cohort	Newborns exposed to the studied drug
Control cohort	Newborns not exposed to the studied drug: - women exposed to other antimalarial drugs - women with no malaria in pregnancy
Malformations definition	Not indicated
Malformations ascertainment/pregnancy outcome	Malformations of children alive at the time of the interview were examined by a nurse from the team and confirmed by a physician. Children who were too young at the time of the interview to have reached the development milestones were seen again later
Prevalence of malformations among control offspring	- group B: 1.4% - group C: 1.5% - group D: 1.7%
Analysis	- Crude and adjusted OR and 95% CI were estimated (logistic regression to control for potential confounders: mother's age, gravidity, camp location, number of documented malaria attacks) - Subanalyses performed to calculate the RR of adverse outcome associated with mefloquine during the periods: from -3 months to conception, from conception to 4 months' gestation, from >4 months' gestation to birth
Strengths	- The drug information was retrieved prospectively, data not affected by delivery outcome - Exposure information based on recorded data and patient recall - Validation of the questionnaires (all confirmed errors corrected)

	- Evaluation of the study's power analyses
Weaknesses	<ul style="list-style-type: none"> - Incomplete information on congenital malformations (only 39 of 66 investigated), full clinical details on stillbirths unavailable in most cases - The study was conducted in difficult circumstances (not possible for physicians to supervise all interviews, to assist in the deliveries) - The time of the ascertainment after delivery not indicated - Risk of recall bias for information collected from the mothers' interviews - Not indicated if information on maternal exposure status was available at the time of infant's examination - No information on pregnancies not traced
Main results	<p>Women who received mefloquine treatment during but not before pregnancy had a significantly greater risk of stillbirth than did women treated with quinine alone (OR 4.72, 95% CI 1.7-12.7), women exposed to other treatments (OR 5.10, 95% CI 2.0-13.1), and women who had no malaria (OR 3.50, 95% CI 1.6-7.6) (P<0.01). This association remained after adjustment for all identified confounding factors. Mefloquine was not associated with abortion, low birthweight, neurological retardation, or congenital malformations</p>