The Effects of Inadvertent Exposure of Mefloquine Chemoprophylaxis on Pregnancy Outcomes and Infants of US Army Servicewomen

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During US military operations in Somalia, mefloquine, a drug for malaria chemoprophylaxis, was not approved for use in pregnant women. Some female soldiers inadvertently used mefloquine before becoming aware of their pregnancy. A registry was established to follow the outcomes of these pregnancies. Questionnaires were administered at the time the pregnancy was diagnosed, after termination or delivery, and at 1 year after birth. Seventy-two soldiers were eligible for the registry. There were 17 elective abortions, 12 spontaneous abortions, 1 molar pregnancy, and 23 live births. The outcome for 19 soldiers was unknown. An unexpected high rate of spontaneous abortions was observed. All infants were healthy at birth, with no major congenital malformations. One infant died at 4 months of viral pneumonitis. At 1 year of age, 13 infants were reported to be healthy, with normal cognitive and motor development. This study provides additional postmarketing data that mefloquine does not cause gross congenital malformations.

There are few antimalarial drugs that are effective and can be used safely for chemoprophylaxis in pregnant women [1]. Mefloquine (Lariam, Hoffman-La Roche, Nutley, NJ), the recommended drug for chemoprophylaxis in most malarious areas because of its effectiveness against chloroquine-resistant Plasmodium falciparum [2], was not initially approved for use in pregnant women. Animal studies indicated some teratogenicity in mice and rats at doses of 100 mg/kg/day [3]. This is much higher than the chemoprophylactic dosage for a 70-kg person of 0.5 mg/kg/day. One study in a refugee population indicated that mefloquine could be safely administered in the latter half of pregnancy (>20 weeks of gestation) [4], but there are few data about its effect on the fetus during the first trimester. Although the risk to the human fetus is thought to be low, there is insufficient information available to establish the absolute safety of mefloquine use during pregnancy [5].

While pregnant soldiers are not deployable, their fetuses may be inadvertently exposed to mefloquine if the soldier has not become aware of her condition before or during the deployment. This situation occurred when female soldiers were deployed to Somalia during Operations Restore Hope and Continue Hope, 1992–1994. All soldiers, except those for whom it was contraindicated, used mefloquine (250 mg each week) for malaria chemoprophylaxis. Loading doses of mefloquine were not used. Before the deployment, female soldiers were advised that mefloquine taken during pregnancy posed a potential risk to the fetus, that they should not become pregnant while on mefloquine, and that pregnancy should be delayed for at least 2 months following the last dose of mefloquine. In March 1993, the Division of Preventive Medicine at Walter Reed Army Institute of Research was asked by the US Army Office of the Surgeon General to establish a registry of all female soldiers who had been deployed to Somalia and had inadvertently taken mefloquine during pregnancy or shortly before conception. In this report, we will describe the outcome of these pregnancies and the health of exposed infants.

Methods

Upon laboratory confirmation of the pregnancy in Somalia, mefloquine chemoprophylaxis was discontinued, and the soldiers were transported to nonmalarious areas. The names and social security numbers of these soldiers were forwarded to the registry. Because of the premature termination of the mefloquine regimen, each soldier was counseled about her risk for malaria. They were told that the risk of congenital abnormalities to the fetus from exposure to mefloquine was thought to be low and that there were no known medical reasons for terminating their pregnancy [6]. Each soldier was also informed of the registry. Army physicians outside Somalia were notified of the registry and were directed to similarly counsel all pregnant soldiers who had been inadvertently...
exposed to mefloquine and to forward the soldiers’ names and social security numbers to the registry.

Information about the pregnancy, delivery, and infant was obtained from three questionnaires. The first, given when the soldier was first identified as pregnant, gathered demographic data and mefloquine exposure history. A second questionnaire was administered to collect information on the outcome of the pregnancy. If the soldier carried her baby to term, data were also collected on prior pregnancy histories and outcomes, the current pregnancy and delivery history, and the infant. The third questionnaire was completed 1 year after the birth of the infant and documented the health and development of the child. The questionnaires were completed by health care providers after a chart review or a telephone interview with the soldier. Soldiers were considered lost to follow-up if we were unable after six attempts to contact them by telephone or if the soldier had been discharged from the army.

**Results**

Seventy-two soldiers were identified as having used mefloquine during their pregnancy. Of these, 17 had elective abortions, 12 had spontaneous abortions, 1 had a molar pregnancy, and 23 had live births. The outcome of the pregnancy was not known for 19 of the 72 soldiers. Of these 19 soldiers, 14 had left the service before information about the pregnancy outcome could be obtained and 2 refused to participate. Three were still on active duty, but information could not be obtained.

The molar pregnancy was diagnosed at 11 weeks of gestation in a black 22-year-old soldier. The ages of the 17 soldiers who had elective abortions ranged from 19 to 32 years (median, 23). Most were not married (n = 12, 71%). Two were married and 1 was divorced. The marital status of 2 soldiers was unknown.

The ages of the 12 soldiers who had spontaneous abortions ranged from 18 to 32 years (median, 22.5). The mean estimated gestational age at the time of the spontaneous abortion was 9.3 weeks (range, 6–12). The average number of mefloquine doses that the fetuses were exposed to was 5.7 (range, 2–12). The total doses of mefloquine taken by soldiers who had spontaneous abortions was similar to that among soldiers who had live births or elective abortions (analysis of variance, P = .12; figure 1). The rate of spontaneous abortions (12/36) in this cohort was 33% (95% confidence interval, 19.5%–49.8%).

There were 23 live births. Fourteen soldiers (61%) were single and 9 were married. Their ages ranged from 18 to 27 years (median, 21). Fourteen soldiers (61%) were primigravida. The average number of mefloquine doses that the fetuses were exposed to was 6.8 (range, 1–16). There were 9 female infants (39%). All of the infants were healthy at birth. Their average 1- and 5-min APGAR scores were 8.1 and 9.0, respectively. The infants’ sizes were appropriate for their gestational age. Their weight ranged from 2693 to 4167 g. There were no congenital malformations. Two abnormalities were noted on the neonatal physical examinations. One infant was jaundiced and the other had a pilonidal sinus.

One infant died at 4 months of age of viral pneumonitis. The cause of death was verified by autopsy, as noted on the death certificate. Health information on 13 other infants was obtained at 1 year of age. All were reported to be healthy and had normal cognitive and motor development. Two of the 13 infants were reported to be small for their ages, but both had small parents. Information was unavailable for 9 (39%) of the infants 1 year after their birth. Most of their mothers had left the army.

**Discussion**

Our data add further information about the use of mefloquine in pregnant women. We observed no congenital malformations in babies who were exposed to mefloquine in the first trimester, but this conclusion is limited by the small sample size. Our data are consistent with the few reports in the literature. Balocco and Bonati [1] did not find any malformations or perinatal pathologic symptoms in 11 babies born from 10 deliveries to mothers who had used mefloquine during the first trimester. In addition, there were no congenital birth defects reported in a group of 99 travelers whose fetuses had been inadvertently exposed to mefloquine in the first trimester [1].

The rate of spontaneous abortions observed in our registry is higher than that reported in other studies. Among the travelers mentioned above, the rate was 7.6% [1]. In a review of a pharmaceutical database that monitored 331 European women who had inadvertently taken mefloquine during the first trimester, the rate was 9% [1]. This was not statistically different from the rate in women who had used other antimalarial drugs or from a quoted 7%–12% background rate among women with clinically ascertained fetal loss.

There are several possible explanations for the higher rate of spontaneous abortions in our study. It may be a result of our close monitoring of all pregnancies that occurred within our cohort. This prospective surveillance system could note...
early pregnancy losses that might not have been reported in a passive data collecting system. The rate may also be inflated by the high number of elective abortions that occurred. Had these pregnancies progressed to normal deliveries, the denominator for the spontaneous abortion rate would have been greater. Misclassification of the outcomes could have occurred also. Information for some soldiers was self-reported through phone interviews. The soldier may have reported a spontaneous abortion rather than an elective abortion because they believed it to be more socially acceptable. We cannot exclude the possibility that the soldiers in Somalia were exposed to other stresses that could have increased the spontaneous abortion rate. Careful postmarketing surveillance of spontaneous abortion rates should be continued to determine if mefloquine exposure is a causal factor.

Currently, the FDA has categorized mefloquine as a pregnancy category C drug. This means that animal studies have shown an adverse effect on the fetus, but there are no adequate studies in humans; the benefits from the use of the drug in pregnant women may be acceptable despite its risk. Because malaria in pregnant women has a higher mortality rate and greater morbidity than in other adults [8], the risks of malaria in pregnancy may far outweigh any harmful effects of chemoprophylaxis. Recently, the Centers for Disease Control and Prevention (CDC) revised its recommendations for the use of mefloquine in pregnant women, stating that mefloquine may be considered for use if travel to high-risk areas with chloroquine-resistant *P. falciparum* is unavoidable [2]. Continued surveillance of pregnancies is needed to assess adverse reproductive outcomes that might occur at a low rate. Women and health care providers are asked to report the use of mefloquine in the first trimester to the Malaria Section, CDC, telephone (770) 488-7760 for continued assessment of pregnancy outcomes.

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References