MAJOR ARTICLE

Pregnancy and Fetal Outcomes After Exposure to Mefloquine in the Pre- and Periconception Period and During Pregnancy

Patricia Schlagenhauf,[1] William A. Blumentals,[2] Pia Suter,[2] Loredana Regep,[2] Gabriel Vital-Durand,[2] Martin T. Schaerer,[2] Margarita Suarez Boutros,[2] Hans-Georg Rhein,[2] and Miriam Adamcova[2]

[1]Division of Epidemiology and Communicable Diseases, University of Zurich Centre for Travel Medicine, Institute for Social and Preventive Medicine, Zurich, Switzerland; [2]F. Hoffmann-La Roche Ltd, Basel, Switzerland

Background. Pregnant women who travel to malarious areas and their clinicians need data on the safety of malaria chemoprophylaxis.

Methods. The effect of exposure to mefloquine on pregnancy and offspring outcomes was evaluated using the F. Hoffmann–La Roche global drug safety database for the time frame 31 January 1986 through 26 October 2010. We investigated pregnancy and fetal outcomes in maternal, paternal, and both-parent exposure cases with a focus on congenital malformations and fetal loss. The main outcome measures were birth defect prevalence and types of malformations.

Results. A total of 2506 cases of mefloquine exposure during pregnancy or in the pre- and periconception period were evaluated. Most cases were maternal prospective (outcome of the pregnancy unknown at the time of reporting; n = 2246 [89.6%]) followed by maternal retrospective cases (outcome of the pregnancy known at the time of reporting; n = 227 [9.0%]), with small numbers of paternal and both-parent exposure cases. Of the total 2246 mefloquine maternal prospective exposures (95.2%), 2139 occurred before conception and/or during the first trimester. Of 1383 maternal prospective cases with known outcome, 978 (70.7%) resulted in delivery, 405 (29.3%) resulted in abortion (112 spontaneous, 293 therapeutic), and 43 resulted in birth defects, corresponding to a birth defect prevalence of 4.39% (43 of 978). Prospective cases overall showed no specific pattern of birth malformations.

Conclusions. The drug safety database analysis of mefloquine exposure in pregnancy showed that the birth defect prevalence and fetal loss in maternal, prospectively monitored cases were comparable to background rates.

An estimated 80–90 million travelers visit malaria-endemic areas annually [1], and a significant proportion of these are women of childbearing potential. Malaria during pregnancy poses a significant risk to the mother, the fetus, and the neonate [2–4]. Malaria infection should be prevented if possible. Women who have little or no immunity, such as nonimmune travelers, are particularly prone to episodes of severe malaria with outcomes such as stillbirth, spontaneous abortion, or maternal death [3–5], which are probably due to high maternal fever leading to uterine contractions.

Travelers to high-risk areas of chloroquine-resistant *Plasmodium falciparum* need protective measures. Personal protection against mosquito bites is a key strategy, and a combination of insecticide-treated bed nets [6, 7] and DEET repellents is considered safe during pregnancy [5–8]. The efficacy of such measures for travelers is difficult to quantify [9], and most women at high risk also need chemoprophylaxis. Based on experience, chloroquine is considered safe to use during pregnancy [10]. However, because of resistance, this regimen has limited applicability.

Received 24 October 2011; accepted 30 January 2012; electronically published 10 April 2012.

Correspondence: Patricia Schlagenhauf, PhD, Division of Epidemiology and Communicable Diseases, University of Zurich Centre for Travel Medicine, Hirschengraben 84, Zurich, CH-8001, Switzerland (pat@ifspm.uzh.ch).

Clinical Infectious Diseases 2012;54(10):e124–131

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DOI: 10.1093/cid/cis215

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Doxycycline is generally contraindicated in pregnancy [11]. Some experts suggest that doxycycline use may be acceptable in early pregnancy, but data are limited [12]. Owing to insufficient data, the atovaquone-proguanil combination is not recommended, although the 2 components are not considered teratogenic. Thus, for ethical, safety, and logistical reasons, there is a lack of data on the use of antimalarials by pregnant women [13].

Mefloquine has been available to travelers since 1985. It is recommended for pregnant women who travel to chloroquine-resistant *P. falciparum* areas when travel cannot be deferred. The recommendations made by expert groups worldwide have been reviewed recently [14]. Expert recommendations data are needed to support clinical decisions. The US and Canadian guidelines allow the use of mefloquine chemoprophylaxis in all trimesters when travel cannot be deferred, with no recommendation regarding contraception for the 3 months after the use of mefloquine. The international standard prescribing information, the World Health Organization, and the UK authorities sanction the use of mefloquine when there is travel to a high-risk malaria area but are more restrictive in the first trimester and also recommend contraception for 3 months after use. All authorities agree that inadvertent use of mefloquine during pregnancy is not viewed as an indication to terminate a pregnancy. Many authorities recommend a benefit-risk analysis before prescribing mefloquine for pregnant women, particularly in the first trimester. Practitioners need up-to-date evidence to guide this decision making. Consequently, we conducted the present analysis using a drug safety database to investigate the safety for the fetus following exposure to mefloquine (as Lariam) in the periconception period and during pregnancy.

METHODS

All serious adverse events from clinical trials of mefloquine and all spontaneous reports of adverse events are coded and entered into the F. Hoffmann–La Roche global drug safety database. Events were classified using the standardized *Medical Dictionary for Regulatory Activities* (MedDRA version 13.1). All reports entered from 31 January 1986 to the cutoff date of 26 October 2010 and marked as ''pregnancy'' were retrieved and evaluated. Summary cases (ie, reports mentioning several pregnancies without the possibility to identify individuals) were excluded from the analysis as standard procedure. Maternal exposure, paternal exposure, and both-parent exposure were separately analyzed.

Pregnancy reports were either prospective (outcome of the pregnancy unknown at the time of first reporting) or, less often, retrospective (outcome of the pregnancy known at the time of first reporting). These 2 groups were separately evaluated. Pregnancy and fetal outcomes were stratified by exposure trimester. The exposure periods evaluated were pre- and periconception and the first, second, and third trimesters. We focused on congenital malformations after exposure to mefloquine based on maternal prospective reports. Pregnancy outcomes were categorized as follows: delivery, abortion (spontaneous, therapeutic), and unknown. Fetal outcomes were: birth defect, normal infant or normal fetus, other disorder, and unknown. The term ''birth defect'' or ''birth malformation,'' as used by the March of Dimes, refers to congenital anomalies identified by codes 740–759 of the *International Classification of Diseases*, Ninth Revision (ICD-9) [15]. Using US federal documentation, we defined a pregnancy outcome of fetal death before 20 completed weeks of gestation as a ''spontaneous abortion.'' After 20 weeks, fetal death was termed ''stillbirth'' [16]. The term ''teratogen'' was defined as a drug that may have the potential to cause developmental toxicity given the appropriate conditions at clinical doses used in humans [16]. The prevalence of birth defects and the occurrence of fetal loss in the maternal prospective cases exposed to mefloquine were compared with the background rates in the general population, as published by various databases. Birth malformations in maternal prospective cases including deliveries and abortions were divided into subgroups based on ICD-10, chapter XVII, ''Congenital malformations, deformations and chromosomal abnormalities,'' and compared with categories of birth defects from the March of Dimes [16].

RESULTS

A total of 2506 cases of mefloquine exposure during pregnancy or in the periconception period were evaluated. The reports originated primarily from France (n = 783), the United Kingdom (n = 661), Germany (n = 645), and the United States (n = 138), with peak reporting from 1994 to 1998. Most cases (n = 2477; 98.8%) were reported spontaneously; a small number of reports came from the literature (n = 26; 1.0%) or from clinical studies (n = 3; 0.1%). Most cases were reported by health professionals (n = 2287; 91.3%), followed by consumers (n = 103; 4.1%) and regulatory authorities (n = 36; 1.4%). The mean age was 29 years for the maternal prospective cases (range, 15–52 years; median, 29 years) and 30 years for the maternal retrospective cases (range, 19–45 years; median, 30 years).

The majority of cases were maternal prospective (n = 2246; 89.6%; Tables 1 and 2) followed by maternal retrospective cases (n = 227; 9%; Tables 3 and 4) and small numbers of paternal (5 prospective, 4 retrospective) and

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Table 1. Pregnancy Outcomes in Maternal Prospective Cases (n = 2246)

Pregnancy Outcome	Offspring Status							Total	
	Birth Defect	Unavailable for Follow-up[a]	Normal Infant	Normal Fetus	Other Disorder[b]	Pregnancy Ongoing[a]	Unknown[a]	No.	%
Delivery	43	0	889	0	43	0	3	978	43.5
Unavailable for follow-up[c]	0	434	0	0	0	0	6	440	19.6
Pregnancy ongoing[c]	0	1	0	0	0	6	0	7	0.3
Spontaneous abortion	1	1	0	3	6	0	101	112	5.0
Therapeutic abortion	8	0	0	1	6	0	278	293	13.0
Unknown[c]	1	0	0	0	1	365	49	416	18.5
Total	53	436	889	4	56	371	437	2246	100.0

Of the 2246 women, 221 were white, 22 were black, 6 were Asian, and 12 were reportedly of ''other'' ethnic origin; for the majority of women (1985 of 2246), ethnic origin was unknown.

[a] Fetal outcomes were unknown in these groups (pregnancy ongoing, unavailable for follow-up, and unknown).

[b] Fifty-six maternal prospective cases of other disorders with 78 events included various adverse events related to the pregnancy and delivery. The most frequently reported were neonatal jaundice (n = 12), premature delivery (n = 8), placental disorder (n = 8), fetal growth restriction (n = 6), small-for-dates infant (n = 4), fetal distress syndrome (n = 4), stillbirth or intrauterine death (n = 3), bradycardia (n = 2), blighted ovum (n = 2), unspecified neonatal disorder (n = 2), and neonatal asphyxia (n = 2). The rest of the ''other disorders'' data set (n = 25) included different pregnancy- and delivery-related reported terms, n = 1 for each reported item.

[c] Pregnancy outcomes unknown (pregnancy ongoing, unavailable for follow-up and outcome unknown).

both-parent (22 prospective, 2 retrospective) exposure cases. Most women exposed to mefloquine were using the drug for malaria chemoprophylaxis. Treatment doses were recorded for 21 maternal prospective and 12 maternal retrospective cases.

Of the 2246 maternal prospective cases, 1383 with known pregnancy outcome resulted in 978 deliveries with 43 birth defects, 43 other pregnancy-related or perinatal disorders, and 889 normal infants. This corresponds to a birth prevalence of 4.39% congenital malformations (43 of 978 births).

Twelve women who delivered infants with birth defects had a medical history of drug abuse (n = 1), alcohol use (n = 1), hypothyroidism (n = 1), hepatitis B (n = 1), smoking (n = 2), preeclampsia (n = 1), spontaneous abortions (n = 2), previous miscarriages (n = 2), and family history of epilepsy or other unspecified mental handicap (n = 1). Six of these 43 women had no relevant medical history, and the medical history of the majority of women (n = 25) who gave birth to infants with birth malformations was unknown. All but 2 of these 43 women received 250 mg mefloquine weekly. The duration of mefloquine use was between 6 and 91 days.

With regard to the time of exposure, 2139 of the 2246 mefloquine maternal prospective exposures (95.2%) occurred before conception and/or during the first trimester of pregnancy (Table 4). All congenital malformations occurred in infants of women who had taken mefloquine during this period of exposure (Table 2).

Table 2. Offspring Status According to Period of Mefloquine Exposure in Maternal Prospective Cases (n = 2246)

Time of Exposure for Mother	Offspring Status							Total	
	Birth Defect	Unavailable for Follow-up	Normal Infant	Normal Fetus	Other Disorder	Pregnancy Ongoing	Unknown	No.	%
Trimester 1	16	174	297	1	21	122	177	808	36.0
Trimesters 1 + 2	1	0	7	0	2	3	1	14	0.6
Trimesters 1 + 3	0	1	0	0	0	0	0	1	0.0
Trimesters 1–3	0	0	3	0	0	0	1	4	0.2
Trimester 2	0	1	3	0	0	4	1	9	0.4
Trimester 3	0	0	1	0	0	1	1	3	0.1
Before	15	113	240	0	15	102	107	592	26.4
Before + trimesters 1 + 2	0	1	0	0	0	0	0	1	0.0
Before + trimester 1	21	131	328	3	17	102	137	739	32.9
Before + trimester 3	0	0	1	0	0	0	0	1	0.0
Unknown	0	15	9	0	1	37	12	74	3.3
Total	53	436	889	4	56	371	437	2246	100.0

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Table 3. Pregnancy Outcomes in Maternal Retrospective Cases (n = 227)

Pregnancy Outcome	Offspring Status							Total	
	Birth Defect	Unavailable for Follow-up	Normal Infant	Normal Fetus	Other Disorder	Pregnancy Ongoing	Unknown	No.	%
Delivery	30[a]	1	98	0	11	0	1	141	62.1
Pregnancy ongoing	0	0	0	0	0	1	0	1	0.4
Spontaneous abortion	1	0	0	3	3	0	31	38	16.7
Therapeutic abortion	19	0	0	1	4	0	17	41	18.1
Unknown	2	0	1	0	0	3	0	6	2.6
Total	52	1	99	4	18	4	49	227	100.0

[a] Includes 1 stillbirth with Patau syndrome (trisomy 13).

In the majority of spontaneous and therapeutic abortions, the offspring status was unknown. Three of the 8 women who underwent therapeutic abortion and had a fetus with birth defects had a medical history of toxoplasmosis (n = 1), ectopic pregnancy (n = 1), or induced abortion (n = 1); 1 of the 8 had no relevant medical history. All received 250 mg mefloquine weekly for 1–50 days. There was 1 birth defect in the spontaneous abortion group (1 of 112 pregnancies) and 1 in the unknown-outcome group (1 of 416 pregnancies). Six of these 10 cases did not include details on medical history. Three prospective stillbirth cases were identified; 1 case was coded as ''stillbirth,'' and 2 as ''intrauterine death.'' The first included narrative referring to stillbirth and death due to toxoplasmosis; the second included placental hypoplasia with maturation dissociation of villi and *Endangiopathia obliterans*.

Of 22 prospective both-parent exposure cases, 14 (63.6%) resulted in delivery and 1 (4.5%) in spontaneous abortion. The 14 deliveries resulted in 2 birth defects and 12 normal infants; no other pregnancy-related or perinatal disorder was reported. One of 2 women who gave birth to infants with birth defects was a tobacco user and had taken 250 mg mefloquine weekly for 19 days; the other received the same dose for 50 days and her medical history was unknown. As in the maternal prospective cases, 2 birth defects occurred in prospective cases of both-parent exposure (after mefloquine use) in the periconception period and during the first trimester. The spectrum of birth defects reported in all prospective cases was divided into 10 subcategories (Table 5). There was no specific pattern of malformations.

DISCUSSION

Pregnant women traveling to chloroquine-resistant *P. falciparum* malaria-endemic areas need malaria prophylaxis. In addition, women who use mefloquine prophylaxis may experience unplanned pregnancy and need advice on the safety of the prescribed antimalarial drug, particularly with regard to its teratogenic potential in the periconception and first-trimester periods, and information on fetal loss (spontaneous abortion

Table 4. Offspring Status According to Period of Mefloquine Exposure in Maternal Retrospective Cases (n = 227)

Time of Exposure for Mother	Offspring Status							Total	
	Birth Defect	Unavailable for Follow-up	Normal Infant	Normal Fetus	Other Disorder	Pregnancy Ongoing	Unknown	No.	%
Trimester 1	21	1	35	3	5	2	13	80	35.2
Trimesters 1 + 2	1	0	4	0	0	0	0	5	2.2
Trimesters 1–3	0	0	1	0	0	0	0	1	0.4
Trimester 2	2	0	2	0	0	1	0	5	2.2
Trimesters 2 + 3	1	0	0	0	1	0	0	2	0.9
Trimester 3	2	0	1	0	0	0	0	3	1.3
Before	13	0	22	0	2	0	10	47	20.7
Before + trimesters 1–3	0	0	1	0	0	0	0	1	0.4
Before + trimester 1	7	0	29	1	7	0	20	64	28.2
Unknown	5	0	4	0	3	1	6	19	8.4
Total	52	1	99	4	18	4	49	227	100.0

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Table 5. Characteristics of Birth Defects and Associated Pregnancy-Related and Perinatal Disorders Reported in All Prospective Cases

Location	Maternal Exposure (53 Prospective Cases, 70 Events)[a]	Paternal Exposure, (No Prospective Cases)	Both-Parent Exposure, (3 Prospective Cases, 4 Events)
Nervous system	5	0	0
Eye, ear, face, and neck	8	0	0
Digestive system	3	0	0
Circulatory system	8	0	1
Urinary, genital organs	11	0	2
Musculoskeletal system	11	0	0
Chromosomal abnormalities	6	0	0
Multiple	1	0	0
Other pregnancy related disorders and not otherwise specified[b]	17	0	1
Total	70	0	4

[a] Cases may have more than one event.

[b] Seventeen other pregnancy-related events such as fetal growth restriction, neonatal hyperbilirubinemia, hypoglycemia, neonatal jaundice, polycythemia, premature infant, congenital pneumonia, unspecified congenital cysts, dermoid cysts, congenital hernia, intrauterine death, induced abortion, imminent abortion, and sacral skin dimple were reported in association with these malformations.

and stillbirth). It is important that available data on drug exposure during pregnancy be routinely reviewed to enable evidence-based decision making. Furthermore, new policy decisions on use of mefloquine in pregnancy will be influenced by data on the safety of mefloquine in pregnancy. This is currently of particular importance as it relates to global health because mefloquine is a potential partner drug in artemisinin combination treatments that will be recommended in pregnancy or for women of childbearing potential in endemic areas.

The drug safety database analysis showed an overall birth prevalence of 4.39% of congenital malformations in maternal prospective cases, with no specific pattern of malformations. The exposure period of 95.3% of these maternal cases was periconception and the first trimester. To assess whether the use of a drug might be associated with an increased prevalence of birth malformations, the rate of birth defects found in the database analysis should be compared with the background rates in the general population, using various birth defect databases. The prevalence of congenital malformations in the general population varied by country, pregnancy registry, and year of reporting. According to the March of Dimes [15], approximately 4% of infants annually (1/28) are born with a major birth defect or congenital malformation, for which the etiology is largely unknown [16–18]. European Surveillance of Congenital Anomalies reported a 2.37% total prevalence of major congenital anomalies in the years 2000–2004 [19]. Older publications report a prevalence of congenital malformations of between 0.8% and 6.5% [20].

The grouping of birth defects in our study was similar to the leading categories of birth defects in the general population as published by the March of Dimes and the Food and Drug Administration [15, 16]. There was no specific pattern of malformations in our study. The leading categories of musculoskeletal (11 of 978, 1.1%; 95% confidence interval [CI], .6%–2.0%]), urogenital (11 of 978; 1.1%; 95% CI, .6%–2.0%), and circulatory (8 of 978; 0.8%; 95% CI, .4%–1.16%) were comparable to findings in general population databases. Six of the prospective birth defects in our study were chromosomal abnormalities, which are usually genetic in origin and therefore probably not caused by mefloquine.

For a large proportion of the prospective spontaneous and therapeutic abortions (<20 weeks postconception), the offspring status was unknown, which precluded additional detailed analysis. Among cases with known offspring status, most were in the therapeutic abortion group (8 of 293). The prevalence of therapeutic abortions with confirmed birth defects in all prospective cases in our analysis was comparable to the background rate of induced abortions in the general population reported in the literature [19]. We observed 3 stillbirths with other disorders, which was comparable to the background rate in the general population [21].

Our analysis has some limitations. We did not have a control group and instead compared our data with available literature and other database sources, which is considered weaker evidence than a controlled study. All observed differences in birth defects in the comparator databases could occur frequently as a result of sampling variation,

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coding, baseline factors, follow-up completeness, reporting years, regions, countries, environment, socioeconomic status, or lifestyle and may not represent true differences between the proportions of infants with birth defects in the comparison groups. A further limitation is underreporting. We focused on prospective cases, but data were available on fetal outcome in just 44.6% of the cases in our study, despite several attempts at follow-up. We also list data on retrospective cases (Tables 3 and 4), but these cases are not discussed in detail because retrospective reporting is known to be associated with bias and must be interpreted with caution. A mother of an infant born with a major birth defect may be more likely to recall gestational exposures than the mother of a normal infant. This is a recognized phenomenon in retrospective reporting. For example, Bar-Oz et al found that the rate of congenital malformations after first-trimester exposure to itraconazole was 4 times higher when ascertained retrospectively rather than prospectively [22]. Furthermore, our analysis does not have the power to detect abnormal outcomes that occur at relatively low background rates or rare abnormalities, and the issues of long-term social or functional development cannot be monitored.

The strength of our evaluation is its focus on the target group and detailed scrutiny of the evidence of mefloquine use in this group using a global drug safety database. To the best of our knowledge, ours is the largest source of information currently available to study the use of mefloquine. Most exposures documented here occurred in the periconception and first-trimester periods, a critical time for the fetus because first-trimester exposure is generally associated with an increased rate of occurrence of malformations [18]. Mefloquine is known to cross the placenta and it has a long half-life, which ranges from 2 to 4 weeks, with an average of 3 weeks.

Because no single approach can delineate the entire spectrum of outcomes associated with drug exposure during pregnancy and to put our research into context, we screened all available literature on the use of mefloquine chemoprophylaxis in pregnancy using the search terms ''mefloquine,'' ''prophylaxis,'' and ''pregnancy.'' Our current evaluation supports the results of an earlier postmarketing data evaluation that had a data cutoff date of 10 September 1996 and showed no increase in congenital malformations in 1526 mefloquine-exposed women (4%) over the expected background rate [23].

Other literature includes early animal studies with mefloquine, which provide only weak evidence and cannot be extrapolated to humans. Teratogenic and embryotoxic effects of mefloquine in these animal studies were observed after administration of doses usually in excess of 100 mg/kg. In comparison, the dose of mefloquine chemoprophylaxis for women is 5 mg/kg once weekly.

The issue of fetal loss as ''spontaneous abortion'' or ''stillbirth'' in mefloquine-exposed mothers is important. In the 2246 maternal prospective cases, 112 spontaneous abortions were reported (5%), and 3 stillbirths. This is comparable to background rates in the general population, where 1 in 7 (16%) pregnancies result in spontaneous abortion and 1 in 200 result in stillbirth [16]. A large study in Denmark showed that the risk of spontaneous abortion in women aged 20–24 years was 8.9%, increasing with age to 74.7% in women aged ≥45 years [24]. The mean age of women in our maternal prospective cases was 29 years (range, 15–52 years; median, 29 years).

We also scrutinized the literature on the use of mefloquine in pregnant women [25]. Although the scope of this article is limited to mefloquine prophylaxis use in nonimmune travelers, 3 important relevant studies of mefloquine prophylaxis in semi-immune pregnant women warrant mention here. The first study was in 339 semi-immune pregnant Thai women (>20 weeks of gestation), and mefloquine prophylaxis was well tolerated [26]. No significant adverse impact was observed on the mother, course of pregnancy, infant survival, or infant development (up to age 2 years). A higher overall rate of stillbirths was noted for mefloquine users (11 in 159 vs 4 in 152 for placebo). The authors concluded that mefloquine was safe and effective for antimalarial prophylaxis in the second half of pregnancy [26].

The second study [27, 28] in malaria chemoprophylaxis and treatment involved semi-immune women in the Mangochi District of Malawi. The study showed no significant differences in the frequency of abortions or stillbirths in women receiving chloroquine (n = 3077) or mefloquine (n = 1032) prophylaxis during the second and third trimesters.

A third study investigating the pharmacokinetics of mefloquine prophylaxis in 20 semi-immune women in the third trimester of pregnancy found no abnormalities in offspring who were followed up until 2 years of age [29]. This study showed increased clearance of mefloquine in late pregnancy, with implications for an increased chemoprophylaxis dosage in the third trimester.

All other studies focused on nonimmune women who used mefloquine during travel. In 1 evaluation of malaria chemoprophylaxis [30], 331 women exposed to mefloquine were compared with 153 women exposed to sulfadoxine-pyrimethamine. Fetal anomalies were lower in the mefloquine group (4.8%) than in the sulfadoxine-pyrimethamine group (7.8%). However, the mefloquine group had a significantly higher proportion of spontaneous abortions (9.1% vs 2.6%), although this was still within the background rate for the population studied.

Additional data on the use of mefloquine chemoprophylaxis in nonimmune pregnant women came from a case series of

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10 women exposed in the first trimester of pregnancy [31] (without malformations). Further data are published on US servicewomen [32] who inadvertently used mefloquine prior to becoming aware of their pregnancy during military operations. They had a high rate of spontaneous abortions, which was attributed to stressors in the combat environment. In 23 live births, there were no congenital malformations.

CONCLUSIONS

In summary, the prospective data shown here suggest that fetal loss and the birth prevalence of malformations (4.39%) in mefloquine-exposed mothers were comparable to background levels in the general population. No specific pattern of malformations was identified. This evidence corroborates the recommendation that inadvertent use of mefloquine in pregnancy does not constitute grounds for therapeutic abortions and provides guidance for women and their clinicians regarding the use of mefloquine prophylaxis in the pre- and periconception periods and during pregnancy.

Notes

Acknowledgments. P. S., W. A. B., P. S., L. R., G. V. D., M. T. S., M. S. B., H. G. R., and M. A. participated in the conception, design, and planning of the analysis and evaluation of data; P. S., M. T. S., M. S. B., H. G. R., and M. A. participated in data extraction and cleaning; P. S., H. G. R., and M. A. participated in literature review; P. S. drafted the first version of the manuscript; and W. A. B., H. G. R., and M. A. provided significant input to later versions. All authors gave input and revised, reviewed, and approved the final version of the manuscript.

Financial support. This database analysis was performed by drug safety and regulatory staff and consultants paid by F. Hoffmann–La Roche in response to the need of health authorities and practitioners to provide up-to-date pharmacovigilance data on the safety of mefloquine use in pregnancy.

Potential conflicts of interest. P. S. has received research funding, honoraria for speaking at conferences, and consultancy fees from F. Hoffmann–La Roche. She has also received honoraria from GlaxoSmithKline and Sigma-tau. W. A. B., P. S., L. R., G. V. D., M. T. S., M. S. B., H. G. R., and M. A. are employees of F. Hoffmann–La Roche.

All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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