MALARIA JOURNAL

RESEARCH Open Access

Mefloquine safety and tolerability in pregnancy: a systematic literature review

Raquel González[1,2*], Urban Hellgren[3], Brian Greenwood[4] and Clara Menéndez[1,2]

Abstract

Background: Control of malaria in pregnant women is still a major challenge as it constitutes an important cause of maternal and neonatal mortality. Mefloquine (MQ) has been used for malaria chemoprophylaxis in non-immune travellers for several decades and it constitutes a potential candidate for intermittent preventive treatment in pregnant women (IPTp).

Methods: The safety of MQ, including its safety in pregnancy, is controversial and a continuing subject of debate. Published studies which evaluated the use of MQ for malaria prevention or treatment in pregnant women and which reported data on drug tolerability and/or pregnancy outcomes have been reviewed systematically.

Results: Eighteen articles fitted the inclusion criteria, only one study was double-blind and placebo controlled. No differences were found in the risk of adverse pregnancy outcomes in women exposed to MQ compared to those exposed to other anti-malarials or to the general population. MQ combined with artesunate seems to be better tolerated than standard quinine therapy for treatment of non-severe falciparum malaria, but a MQ loading dose (10 mg/kg) is associated with more dizziness compared with placebo. When used for IPTp, MQ (15 mg/kg) may have more side effects than sulphadoxine- pyrimethamine.

Conclusions: In the published literature there are no indications that MQ use during pregnancy carries an increased risk for the foetus. Ideally, the use of MQ to prevent malaria should be based on a risk-benefit analysis of adverse effects against the risk of acquiring the infection. For this purpose double-blinded randomized controlled trials in African pregnant women are much needed.

Keywords: Mefloquine, Malaria, Pregnancy, Safety, Intermittent preventive treatment

Background

Malaria in pregnancy continues to be a global health problem, accounting for 15% of maternal deaths in some malaria endemic regions [1,2]. It also contributes to low birth weight (LBW) (<2,500 g), either through intrauterine growth retardation or pre-term delivery and to the occurrence of severe anaemia in the mother [3-15]. The World Health Organization (WHO) recommends a package of interventions to prevent the consequences of malaria during pregnancy in areas with stable transmission in sub-Saharan Africa including the use of insecticide-treated nets (ITNs), intermittent preventive treatment (IPT) with sulphadoxine-pyrimethamine (SP) and effective case management of malaria and anaemia [16]. In October 2012, the WHO policy recommendation on IPT in pregnancy (ITPp) with SP was updated and IPTp with SP is now recommended at each scheduled antenatal care (ANC) visit for pregnant women living in areas of moderate-to-high malaria transmission, provided that each dose is separated by at least a month [17]. The emergence of *Plasmodium falciparum* parasites resistant to SP has raised concern over the long-term efficacy and effectiveness of SP as IPTp [18-21]. As a result, alternative drugs are being evaluated for IPTp to replace SP in the short or the long term.

Mefloquine (MQ) has many of the characteristics needed for an anti-malarial to replace SP for IPTp [22]. These include: 1) a long half-life (median between 14 and 28 days at curative doses and between 12 and

* Correspondence: Raquel.gonzalez@cresib.cat
[1]Barcelona Centre for International Heath Research (CRESIB, Hospital Clínic- Universitat de Barcelona), Rosselló 132, 4-2, Barcelona E-08036, Spain
[2]Manhiça Health Research Centre (CISM), Maputo, Mozambique
Full list of author information is available at the end of the article

17 days at prophylactic doses); 2) single dose administration; 3) a well-characterized pharmacokinetic profile in pregnant women [23-25]; 4) infrequent MQ resistance in Africa; and, 5) an acceptable reproductive toxicity profile in animal studies. As a consequence, MQ is considered appropriate for chemoprophylaxis for pregnant women travellers of all gestational ages to high risk areas by various expert agencies such as the United States (US) Centers for Disease Control and Prevention (CDC) and the French Reference Centre on Teratogenic Agents (CRAT) [26,27]. In addition, the drug was recently reclassified as pregnancy category B (though initially rated as C) by the US- Food and Drug Administration (FDA) [28].

MQ was developed by the US Army in the late 1970s. It belongs to the arylaminoalcohols group of anti-malarial drugs and has blood schizonticidal properties [29]. The most common adverse effects related to its use are gastrointestinal and neurological. Severe central nervous system side effects occur in about 1:10,000 travellers taking MQ as chemoprophylaxis [30]. Risk factors reported to be associated with MQ-induced neuropsychiatric adverse events include a previous history of psychiatric problems, female sex, low body mass index (BMI) and first-time use of the drug [31]. Mefloquine is contra-indicated in subjects with a history of a neuropsychiatric illness, including epilepsy. The incidence of adverse events is higher when MQ is administered at the recommended treatment dosage (25 milligram (mg)/ kilogram (kg)) as compared to lower doses (15 mg/kg), suggesting a dose-related effect [32]. The frequency of adverse events is considerably lower when the drug is used at prophylactic doses (250 mg/week) than when it is used for treatment. Recently, the FDA has released a safety communication raising concerns about possible long-term psychiatric and neurological side effects following MQ use [33]. The drug is currently one of the most controversial anti-malarial medicines and the target of various special interest groups following its massive administration to US troops deployed in endemic areas since 1992 [34].

In view of the potential use of MQ for IPTp in malaria-endemic areas and existing concerns regarding its safety, a systematic literature review on the safety of MQ when given in pregnancy was carried out. The study included published articles reporting data on the safety of MQ administered for malaria treatment or prevention in pregnant women. This review also provided a background paper for WHO's Technical Expert Group on IPTp, which met in Geneva in July 2013 to consider the potential use of MQ for IPTp.

Methods

A comprehensive search for data on the safety of MQ in pregnancy in medical databases (PubMed, the Cochrane library, US National Institutes of Health Clinical Trials data base [35], WHO library) was made, and non-medical search engines were interrogated using "mefloquine", "pregnancy" as keywords/search terms from April to June 2013. Thirty-five abstracts were selected from the 136 initially listed titles for further review. Special consideration was given to original articles and systematic reviews but reports of case series were also included. An additional search introducing "safety" as a search term resulted in a further 25 articles for screening. Additional references were obtained from references provided in the articles identified through the search. The current review focuses on the safety of MQ use in pregnant women in terms of pregnancy outcomes and drug tolerability. Criteria for inclusion in the review were published articles written in English reporting results of studies that evaluated the safety of MQ (used alone or combined with other anti-malarials) in pregnant women for treatment and/or prevention of malaria. The main findings and conclusions generated by all the studies reviewed are organized by topic and the key parameters of these studies are summarized in two tables.

Results

Figure 1 shows the flow diagram of the article selection process. Eighteen articles which met the inclusion criteria were included in the final selection: eight reported safety data of MQ when used for malaria treatment (Table 1) and ten evaluated MQ in pregnant women for malaria prevention (See Additional file 1).

The safety of mefloquine when used for the treatment of malaria in pregnancy

The first reports on the use of MQ in pregnant women are from the late 1980s [36,37]. Most experience on its use in treatment of malaria in pregnancy comes from Southeast Asia where MQ was administered primarily in combination with artesunate (AS) and where increasing resistance to MQ has been reported [38,39]. In Thailand, this combination (MQ-AS) was shown to be more effective than quinine (QN) in clearing parasites and fever in pregnant women with uncomplicated malaria [40,41]. Studies are currently on going in sub-Saharan Africa to evaluate MQ-AS efficacy for malaria treatment in pregnancy [42].

A non-randomized, comparative MQ treatment study conducted in 372 pregnant women with uncomplicated falciparum malaria in Thailand between 1991 and 1996 reported no differences in the rates of congenital anomalies and stillbirth among women who were treated with a single dose of MQ (25 mg/kg; n = 194) and those treated with QN for seven days (30 mg/kg/day; n = 93), or MQ + QN (n = 85) [43]. The most common adverse effects following MQ administration were dizziness (36%)

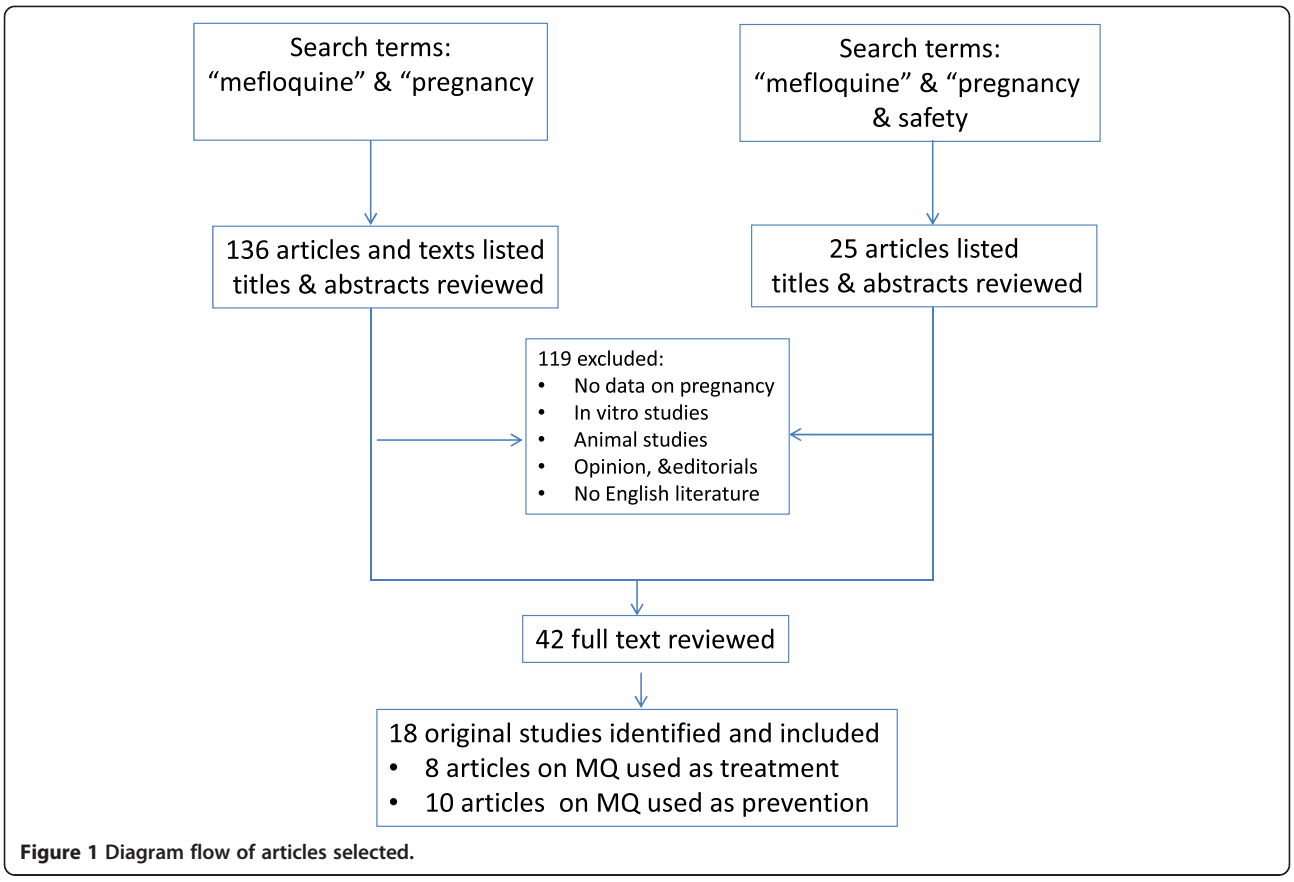

Figure 1 Diagram flow of articles selected.

and anorexia (23%) and the most common adverse effects after QN were dizziness (42%) and tinnitus (35%). The study was not blinded and the groups were not well matched and thus findings on tolerability are of limited value.

In 1999, a report was published on a retrospective analysis of the pregnancy outcomes of women exposed to MQ in Thailand, based on ANC registries and self-reported information from interviews [44]. This study showed an increased risk of stillbirths in women treated with 25 mg/kg of MQ (9/208, 4.5%) compared to those treated with other anti-malarials (10/656 [1.6%] in those exposed to QN, and 12/909 [1.4%] in those exposed to other anti-malarials). Despite the fact that the study had some limitations (such as possible recall bias and the small number of stillbirths observed in the MQ group), the article led CDC to recommend that MQ should not be used for malaria treatment in pregnancy if other effective anti-malarial medicines were available, as well as raising much general concern and open debate about the safety of this drug in pregnancy. Harinasuta *et al.* had previously reported no differences in the rates of stillbirths between study groups in a small clinical trial which had compared MQ (two doses of 500 mg, n = 85) with QN (1800 mg for seven days, n =72) for the treatment of multiresistant falciparum malaria in pregnant Thai women [45]. Another randomized study from the same region in Thailand, which compared MQ-AS (n = 54) with QN (n = 42) for the treatment of falciparum malaria in pregnant women in the second and third trimesters, found no differences in the rates of congenital anomalies, stillbirths or birth weight between the treatment groups [40]. Those treated with QN (10 mg/kg × 3 for seven days) compared with those treated with MQ (15 mg/kg on day 1 + 10 mg/kg on day 2) and AS (4 mg/kg/day for three days) had significantly more dizziness (87 *versus* 45%) and tinnitus (66 *versus* 17%). However, the study was not blinded and included only a small number of women.

A small, non-comparative study (n = 40) conducted between 1998 and 2001 among Sudanese pregnant women who presented with malaria after a full course of chloroquine (CQ) therapy and who were then treated with MQ (25 mg/kg), concluded that MQ could be used safely during the second and third trimesters of gestation as no abortions, stillbirths or congenital anomalies were observed [46]. The main complaints of recipients were nausea and itching. In a similar, non-comparative study undertaken in Nigeria, where a much lower MQ dose (12.5 mg/kg) was used, only minimal side effects were

Table 1 Studies which evaluated the safety of mefloquine for treatment of malaria in pregnant women

Reference	Study year and location	Study design	Study women	MQ safety on pregnancy outcomes	MQ tolerability	Comments
Harinasuta *et al.* 1990 [45]	Thailand	Clinical trial which compared MQ to QN for the treatment of multi-resistant falciparum malaria	N = 85 women (all trimesters) treated with MQ *vs* N = 72 treated with QN	No differences in stillbirth rates between groups	All mild and transient adverse events.	Small sample size Limited information on procedures and results available
Okeyeh *et al.* 1996 [47]	Nigeria	Non comparative MQ treatment study in pregnant women (12.5 mg/kg)	N = 33 women in 2nd and 3rd trimester	No stillbirths and congenital malformations reported	Minimal side effects	Small sample size Low dose of MQ used
Sowunmi *et al.* 1998 [49]	Nigeria	Open label trial which compared artemether to artemether + MQ in the treatment of uncomplicated malaria	N = 45 women in 2nd and 3rd trimesters n = 23 artemether n = 22 artemether + MQ	No abortion, stillbirth or congenital anomalies were observed	Minimal adverse events reported in the artemether – MQ group (dizziness and abdominal pain) in 2/45 patients	Small sample size Open label trial
McGready *et al.* 1998 [43]	1991-96 Thailand	Non- randomized comparative MQ treatment study, cohort series	N = 372 n = 194 treated with MQ (in 2nd and 3rd trimesters) n = 93 treated with QN n = 85 MQ + QN	Similar rates of congenital anomalies and stillbirths among groups	The most common adverse effects following MQ were dizziness (36%) and anorexia (23%)	Open label cohort series Groups not well matched
Nosten *et al.* 1999 [44]	1991-94 Thailand	Retrospective analysis of the pregnancy outcomes of women exposed to MQ compared to those not exposed (based on ANC registries and self-reported information from interviews)	N = 208 pregnancies exposed to MQ (mainly 2nd and 3rd trimesters) *vs* N = 656 exposed to QN *vs* N = 909 exposed to other anti-malarials *vs* N = 2,470 not exposed to anti-malarials	Increased risk of reported stillbirths in women exposed to MQ: (9/208) 4.5% (MQ group) *vs* (10/656) 1.6% (QN group) *vs* (12/909) 1.4% (other anti-malarials) *vs* (40/2470) 1.8% (not exposed)	No data available	Analysis with several limitations 1) Four women out of the nine with a stillbirth had been exposed to other anti-malarials; 2) Recall bias possible (results based on self-reported data)
McGready *et al.* 2000 [40]	1995-97 Thailand	Open randomized comparison of different malaria treatments in pregnant women in the 2nd and 3rd trimesters	N = 108 n = 42 QN 7 days *vs* n = 66 MQ (25 mg/kg) + AS 3 days	No differences in the rates of congenital anomalies, stillbirths or birth weight between the treatment groups	No serious adverse effects were reported Dizziness was more frequent in the QN group than in the MQ (87 *vs* 45%)	Small sample size MQ combined with AS Open label

Table 1 Studies which evaluated the safety of mefloquine for treatment of malaria in pregnant women *(Continued)*

Bounyasong 2001 [48]	Thailand	Open randomized comparison of different malaria treatments in pregnant women in the 2nd and 3rd trimesters	N = 60 n = 29 QN 7 days *vs* n = 28 AS + MQ 3 Lost to follow-up	No data available	QN group reported more adverse effects than the MQ group (nausea, vomiting, vertigo, tinnitus and hypoglycaemia)	Small sample size MQ combined with AS Open label
Adam *et al.* 2004 [46]	1998-2001 Sudan	Prospective study which evaluated the efficacy and safety of MQ in women who presented with malaria after a full course of CQ therapy	N = 40 Pregnant women in the 2nd or 3rd trimester of gestation	No abortion, stillbirth and congenital anomalies were observed	35% reported nausea and 17.5% itching	Small sample size Non comparative study

reported [47]. Two additional, small, randomized but not blinded *P. falciparum* treatment studies have been published [48,49]. In a study from Nigeria (n = 45), intramuscular artemether for five days was compared with artemether given in combination with MQ 15 mg/kg on the first two days of treatment. Reported adverse effects were minimal and all newborn babies were normal at birth [49]. The second study from Thailand (n = 60) found that women treated with standard QN regimen (10 mg/kg/day for seven days) in the second to third trimester had significantly more nausea, vomiting, vertigo tinnitus and hypoglycaemia compared with those who received the standard MQ (25 mg/kg) + AS regimen [48]. The physical and neurological developments of the babies in this study were normal (followed up to 12 months after delivery) and there were no congenital abnormalities.

The safety of mefloquine when used for the prevention of malaria in pregnancy

One of the first reported studies on the use of MQ as prophylaxis in pregnancy described a placebo-controlled, double-blind trial conducted in 1987-90 in Thailand [50]. This trial, which evaluated MQ efficacy (250 mg/kg weekly) as malaria prophylaxis in pregnancy, enrolled 339 women in the second trimester of gestation in two study phases. The first phase was conducted between 1987 and 1988 and enrolled 60 women in the MQ group (they received an initial loading dose of 10 mg/kg before starting weekly prophylaxis) and 59 in the placebo group. The subsequent, second phase was conducted between 1989 and 1990 and enrolled 111 in the MQ group and 109 in the placebo arm. The MQ prophylactic dose used was the standard 250 mg once weekly for the first four weeks after which it was reduced to 125 mg once weekly until delivery. Overall, the rates of abortions, congenital anomalies, prematurity, and stillbirths were similar between groups. An increased risk of stillbirth was observed in the MQ group (12.5 *versus* 0%) in the first phase of the trial but this was not confirmed in the second phase. During the same period, pregnant women attending the same ANC but not participating in the study had a 6.7% rate of stillbirth. In the second phase, a weekly questionnaire, which asked about 20 symptoms, was used. There were no differences between the placebo and the MQ groups in reported adverse events. In addition, there were no differences in terms of liver, renal, neurological, or cardiac toxicity and no serious drug-related side effects were reported. The only significant finding was that MQ loading caused more transient dizziness than the placebo (28 *versus* 14%). The study concluded that MQ was safe and effective in the second half of pregnancy and that MQ prophylaxis was well tolerated.

During the same period, the Mangochi Malaria Research Project compared four malaria preventive regimens in pregnant Malawian women: 1) CQ treatment in an initial dose of 25 mg/kg followed by 300 mg weekly (n = 741); 2) CQ 25 mg/kg monthly (n = 1,459); 3) CQ 300 mg weekly (n = 661); and, 4) MQ in an initial treatment dose of 750 mg followed by 250 mg weekly (n = 932) [14,51,52]. This large, open-label trial enrolled 4,187 women and found similar overall rates of reported adverse effects following each treatment, as well as similar rates of abortion and stillbirth between groups. However, women who received MQ reported less itching and more dizziness compared to those who received CQ, although this was a non-blinded study and significance testing was not performed. The frequency of reported adverse events was lower after the fourth dose than after the first dose.

A subsequent analysis of a case series of 72 American soldiers who took weekly MQ prophylaxis without prior knowledge of their pregnancy showed a high frequency of spontaneous abortion (12/72) [53]. However, the authors considered that the high number of reported elective abortions (n = 17), losses to follow-up (n = 19) and potential exposure to other stress factors could have increased the rate of abortions in this particular population. In addition, no control group was available for comparison.

In 1998, a study of 1,627 reports of MQ exposure during pregnancy received by the Roche post-marketing surveillance system (mainly for chemoprophylaxis) between 1986 and 1996, reported a 4% prevalence of congenital malformations in infants of women in the cohort, a prevalence similar to that found in the general population [54]. The study included over 600 reports on MQ exposure during the 1st trimester of gestation and it concluded that MQ could be used in pregnant women for prophylaxis. Phillips-Howard *et al.* also found no difference in the rates of adverse pregnancy outcomes among women exposed to MQ (n = 99) compared to women exposed to other anti-malarials (n = 137) in an analysis of reported use of MQ during the first trimester of pregnancy in European travellers [55].

More recently, an open-label, randomized, controlled trial (RCT) which compared MQ (15 mg/kg) with SP for IPTp was conducted in HIV-negative, pregnant women (805 in the MQ group and 804 in the SP) in Benin from 2005 to 2008 [22]. In this study, the incidence of spontaneous abortions (0.4% in MQ and 0.1% in the SP group), stillbirths (2.8% in the MQ and 2% in the SP group) and congenital anomalies (1% in the MQ and 0.5% in the SP group) did not differ significantly between groups. On the other hand, based on a questionnaire collected one week after drug intake, women who received MQ had a much higher frequency of reported adverse events than those who received SP: 52% vomiting and 50% dizziness, compared to 12 and 13% in the SP

group, respectively. Most of the symptoms were mild and resolved quickly and spontaneously. The study was not blinded, which makes tolerability assessment difficult. The authors also suggest a possible enhanced anticipation of adverse events in the community where discussions had been organized before the first administration of IPTp.

A later analysis, which used data from the Beninese RCT described above and from another IPTp-MQ open trial, which compared MQ tolerability between HIV-infected (n = 94) and uninfected pregnant women (n = 385), found that adverse events such as vomiting and dizziness were less frequently reported in HIV-infected women than in uninfected women (33 *versus* 56% and 39 *versus* 51%, respectively) [56]. In both studies, adverse events were more frequent after the first IPTp-MQ than at the second. However, this is a comparison between two different, non-blinded studies using different protocols and done during different time periods so validity of this comparison must be interpreted with great caution.

A further analysis of 2,506 reports of MQ exposure during pregnancy, mainly when used for chemoprophylaxis, from the F Hoffman-La Roche global drug safety database has recently been published and concluded that the prevalence of birth defects (4.4%) (43/978) and foetal loss were comparable in women exposed to MQ in pregnancy to background rates of the general population [57]. This analysis included part of the reports analyzed previously by Phillips-Howard *et al.* [55].

Discussion

In spite of several decades of experience with the use of MQ in the treatment of malaria, reports of only two RCTs were found which specifically evaluated MQ safety in pregnant women and only one of these was blind and placebo controlled [22,50]. This may be due to the fact that pregnant women are systematically excluded from drug trials for ethical, legal and sociological concerns because of fear of toxicity to the foetus [29].

The evidence provided by one large but not randomized, nor blinded study suggests that the tolerability to MQ when used as prophylaxis in pregnant women is similar to that of CQ, although the risk of dizziness might be higher with MQ [51]. The only randomized, controlled, double-blind trial which compared MQ tolerability to placebo, did not find differences in the rates of reported adverse effects between study arms in those not given a MQ loading dose [50]. An interim WHO report on MQ tolerability in pregnancy (Urban Hellgren, unpublished) points out the need for blinded studies to accurately estimate common and subjective side effects, especially for evaluation of tolerability and side effects of disputed medicines such as MQ [34,58]. This is particularly the case when cases of serious adverse events are disseminated widely in the general media. This may have contributed to the considerable controversy among international experts regarding the tolerability of MQ prophylaxis *versus* alternative regimens in travellers [26]. In the IPTp randomized but not blinded trial conducted in Benin, a dose of 15 mg of MQ was poorly tolerated compared with SP, with higher frequencies of adverse events such as vomiting and dizziness [22]. However, when study participants are aware of the possibility of specific adverse events either through the consent form or through general knowledge of the drug, reporting rates of those adverse events typically increase [59]. Such knowledge is also likely to affect the evaluation of relatedness to the drug treatment by the investigator. In this trial, it was observed that the frequency of related adverse events decreased with increasing number of doses, as in other studies of chemoprophylaxis with MQ in pregnancy, but also in reports from travellers indicating that a true tolerance effect might play a role [26,51]. However, the incidence of adverse events reporting also decreases with time in the placebo group in absence of drug treatment [60,61].

Neuro-psychiatric adverse events (such as anxiety, depression, behavioral changes, etc.) are difficult to assess and monitor, especially in resource- constrained settings where malaria is endemic. Thus it is possible that such adverse events are underreported, which makes assessment of these adverse events challenging. In addition, malaria symptoms in pregnant women may be difficult to distinguish from adverse events and consequently relatedness to the drug may be particularly difficult to assess [62].

Only a few small studies were found to have assessed foetal safety of MQ when administered for malaria treatment in pregnant women. Most of the safety data on MQ use in pregnancy come from the post-marketing surveillance system of the manufacturer (dominated by exposure as chemoprophylaxis) and from retrospective studies or studies from Southeast Asia [54,57,63,64]. There is a relative lack of safety studies on MQ treatment in pregnant women in sub-Saharan Africa.

Concerns regarding a potential increased risk in the rates of adverse pregnancy outcomes in women who have received MQ during pregnancy constitute one of the main controversial issues regarding MQ safety. However, the results from the single study, which reported an association between MQ treatment and stillbirth in Thailand [44] which initiated these concerns, have not been confirmed in larger studies conducted in sub-Saharan Africa [14,22]. Most of the identified studies included few participants and were underpowered to appropriately assess the risk of adverse pregnancy outcomes associated in pregnant women who had received MQ. A large, multicentre RCT, which has evaluated the efficacy and safety of IPTp

with MQ involving over 4,500 pregnant women has recently finished and is expected to provide further important information on MQ safety in pregnant women [65].

Only one article evaluating MQ safety in HIV-infected pregnant women [56] was found. However, the results of two small RCTs evaluating IPTp with MQ in HIV-infected women from Benin which reported similar results have been published recently [66].

Considering the overlapping geographical distribution of the HIV epidemic and malaria-endemic regions in sub-Saharan Africa, it is essential that studies on treatment and prevention of malaria in pregnancy include HIV-infected women and that research on potential drug interactions between anti-malarial drugs, including MQ, and antiretroviral drugs is undertaken [67].

Conclusions

The use of MQ to prevent malaria in pregnancy should be based on a risk-benefit analysis that balances the likelihood of adverse effects against the risk of acquiring the infection, as is the case for other anti-malarials used in pregnancy. Women's acceptability of a particular drug and their likely compliance also need to be considered when the choice of an anti-malarial drug for use in pregnancy is being considered. Based on the evidence reviewed, it can be concluded that MQ recipients did not have an increased risk of adverse pregnancy outcomes, including those in the first trimester of gestation.

There are only a few publications that have reported on maternal MQ tolerability in pregnant women when the drug has been used for malaria treatment, IPTp or prophylaxis. MQ combined with AS seems to be better tolerated than standard QN therapy for non-severe falciparum malaria but a MQ loading (10 mg/kg) dose is associated with more dizziness compared with placebo. When used for IPTp, MQ (15 mg/kg) may have more side effects than SP but this needs to be confirmed in double-blind randomized clinical trials.

There is a lack of RCTs evaluating MQ safety for malaria treatment and prevention in African pregnant women. Future trials should be designed to be double-blind to enable an objective assessment of MQ tolerability and need also to include HIV-infected women.

Additional file

Additional file 1: Table summarizing the studies that evaluated the safety of mefloquine for the prevention of malaria in pregnant women.

Abbreviations

ANC: Antenatal clinic; AS: Artesunate; BMI: Body mass index; CDC: Centers for Disease Control and Prevention; CQ: Chloroquine; FDA: Food and Drug Administration; IPTp: Intermittent preventive treatment in pregnancy; ITNs: Insecticide treated nets; kg: kilogram; LBW: Low birth weight; mg: Milligram; MQ: Mefloquine; QN: Quinine; RCT: Randomized controlled trial; SP: Sulphadoxine-pyrimethamine; US: United States; WHO: World Health Organization.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

All authors met International Committee of Medical Journal Editors' criteria for authorship. RG and UH conducted the literature search and reviewed the articles included. BG and CM participated in the review design and methodology. RG wrote the draft manuscript. All authors revised the manuscript critically, and read and approved the final manuscript.

Acknowledgements

The authors are grateful to Andrea Bosman and Golbahar Pahalavan for their helpful comments and suggestions on the manuscript. The present work was prepared as background paper for the WHO Expert Review Group (ERG) meeting on IPTp held in WHO headquarters in Geneva, 9-11 July, 2013.

Author details

[1]Barcelona Centre for International Heath Research (CRESIB, Hospital Clínic- Universitat de Barcelona), Rosselló 132, 4-2, Barcelona E-08036, Spain. [2]Manhiça Health Research Centre (CISM), Maputo, Mozambique. [3]Unit of Infectious Diseases, Department of Medicine, Karolinska University Hospital Huddinge, Karolinska Institutet, Stockholm, Sweden. [4]Faculty of Infectious and Tropical Diseases, London School of Hygiene & Tropical Medicine, London, UK.

Received: 10 December 2013 Accepted: 24 February 2014
Published: 28 February 2014

References

1. Granja ACMF, Bergstrom S: **Avoidability of maternal death in Mozambique: audit and retrospective risk assessment in 106 consecutive cases.** *Afr J Health Sci* 2000, **7:**83–87.
2. Menendez C, Bardaji A, Sigauque B, Romagosa C, Sanz S, Serra-Casas E, Macete E, Berenguera A, David C, Dobano C, Naniche D, Mayor A, Ordi J, Mandomando I, Aponte JJ, Mabunda S, Alonso PL: **A randomized placebo-controlled trial of intermittent preventive treatment in pregnant women in the context of insecticide treated nets delivered through the antenatal clinic.** *PLoS One* 2008, **3:**e1934.
3. Brabin BJ: **An analysis of malaria in pregnancy in Africa.** *Bull World Health Organ* 1983, **61:**1005–1016.
4. Desai M, ter Kuile FO, Nosten F, McGready R, Asamoa K, Brabin B, Newman RD: **Epidemiology and burden of malaria in pregnancy.** *Lancet Infect Dis* 2007, **7:**93–104.
5. Greenwood BM GA, Snow RW, Byass P, Bennett S, Hatib N`Jie AB: **The effects of malaria chemoprophylaxis given by traditional birth attendantes on the course and outcome of pregnancy.** *Trans R Soc Trop Med Hyg* 1989, **83:**589–594.
6. Guyatt HL, Snow RW: **Impact of malaria during pregnancy on low birth weight in sub-Saharan Africa.** *Clin Microbiol Rev* 2004, **17:**760–769. table of contents.
7. Le Hesran JY, Fievet N, Thioulouse J, Personne P, Maubert B, M'Bidias S, Etye'ale D, Cot M, Deloron P: **Development of cellular immune responses to *Plasmodium falciparum* blood stage antigens from birth to 36 months of age in Cameroon.** *Acta Trop* 2006, **98:**261–269.
8. Menendez C, D'Alessandro U, ter Kuile FO: **Reducing the burden of malaria in pregnancy by preventive strategies.** *Lancet Infect Dis* 2007, **7:**126–135.
9. Menendez C, Mayor A: **Congenital malaria: the least known consequence of malaria in pregnancy.** *Semin Fetal Neonatal Med* 2007, **12:**207–213.
10. Menendez C, Ordi J, Ismail MR, Ventura PJ, Aponte JJ, Kahigwa E, Font F, Alonso PL: **The impact of placental malaria on gestational age and birth weight.** *J Infect Dis* 2000, **181:**1740–1745.
11. Schwarz NG, Adegnika AA, Breitling LP, Gabor J, Agnandji ST, Newman RD, Lell B, Issifou S, Yazdanbakhsh M, Luty AJ, Kremsner PG, Grobusch MP: **Placental malaria increases malaria risk in the first 30 months of life.** *Clin Infect Dis* 2008, **47:**1017–1025.
12. DE Shulman CE, Bulmer JN: **Malaria as a cause of severe anaemia in pregnancy.** *Lancet* 2002, **360:**494.

13. Steketee RW, Nahlen BL, Parise ME, Menendez C: **The burden of malaria in pregnancy in malaria-endemic areas.** *Am J Trop Med Hyg* 2001, **64:**28–35.
14. Steketee RW, Wirima JJ, Hightower AW, Slutsker L, Heymann DL, Breman JG: **The effect of malaria and malaria prevention in pregnancy on offspring birthweight, prematurity, and intrauterine growth retardation in rural Malawi.** *Am J Trop Med Hyg* 1996, **55:**33–41.
15. van Geertruyden JP, Thomas F, Erhart A, D'Alessandro U: **The contribution of malaria in pregnancy to perinatal mortality.** *Am J Trop Med Hyg* 2004, **71:**35–40.
16. WHO: *A strategic framework for malaria prevention and control during pregnancy in the African region.* Geneva: World Health Organization; 2004. AFR/MAL/04/01.
17. WHO: *Intermittent Preventive Treatment of malaria in pregnancy using Sulfadoxine-Pyrimethamine (IPTp-SP). Updated WHO Policy Recommendation.* Geneva: World Health Organization; 2012. http://www.who.int/malaria/iptp_sp_updated_policy_recommendation_en_102012.pdf.
18. Iriemenam NC, Shah M, Gatei W, van Eijk AM, Ayisi J, Kariuki S, Vanden Eng J, Owino SO, Lal AA, Omosun YO, Otieno K, Desai M, Ter Kuile FO, Nahlen B, Moore J, Hamel MJ, Ouma P, Slutsker L, Shi YP: **Temporal trends of sulphadoxine-pyrimethamine (SP) drug-resistance molecular markers in *Plasmodium falciparum* parasites from pregnant women in western Kenya.** *Malar J* 2012, **11:**134.
19. Menendez C, Serra-Casas E, Scahill MD, Sanz S, Nhabomba A, Bardaji A, Sigauque B, Cistero P, Mandomando I, Dobano C, Alonso PL, Mayor A: **HIV and placental infection modulate the appearance of drug-resistant *Plasmodium falciparum* in pregnant women who receive intermittent preventive treatment.** *Clin Infect Dis* 2011, **52:**41–48.
20. Mockenhaupt FP, Bedu-Addo G, Eggelte TA, Hommerich L, Holmberg V, von Oertzen C, Bienzle U: **Rapid increase in the prevalence of sulfadoxine-pyrimethamine resistance among *Plasmodium falciparum* isolated from pregnant women in Ghana.** *J Infect Dis* 2008, **198:**1545–1549.
21. Taylor SM, Antonia A, Feng G, Mwapasa V, Chaluluka E, Molyneux M, ter Kuile FO, Rogerson SJ, Meshnick SR: **Adaptive evolution and fixation of drug-resistant *Plasmodium falciparum* genotypes in pregnancy-associated malaria: 9-year results from the QuEERPAM study.** *Infect Genet Evol* 2012, **12:**282–290.
22. Briand V, Bottero J, Noel H, Masse V, Cordel H, Guerra J, Kossou H, Fayomi B, Ayemonna P, Fievet N, Massougbodji A, Cot M: **Intermittent treatment for the prevention of malaria during pregnancy in Benin: a randomized, open-label equivalence trial comparing sulfadoxine-pyrimethamine with mefloquine.** *J Infect Dis* 2009, **200:**991–1001.
23. Na Bangchang K, Davis TM, Looareesuwan S, White NJ, Bunnag D, Karbwang J: **Mefloquine pharmacokinetics in pregnant women with acute falciparum malaria.** *Trans R Soc Trop Med Hyg* 1994, **88:**321–323.
24. Nosten F, Karbwang J, White NJ, Honeymoon N, Bangchang K, Bunnag D, Harinasuta T: **Mefloquine antimalarial prophylaxis in pregnancy: dose finding and pharmacokinetic study.** *Br J Clin Pharmacol* 1990, **30:**79–85.
25. Ward SA, Sevene EJ, Hastings IM, Nosten F, McGready R: **Antimalarial drugs and pregnancy: safety, pharmacokinetics, and pharmacovigilance.** *Lancet Infect Dis* 2007, **7:**136–144.
26. Schlagenhauf P, Adamcova M, Regep L, Schaerer MT, Rhein HG: **The position of mefloquine as a 21st century malaria chemoprophylaxis.** *Malar J* 2010, **9:**357.
27. Centre de Référence sur les Agents Tératogènes: *Mefloquine.* http://www.lecrat.org/, [accessed February 2014].
28. FDA: *New recommendations for mefloquine use in pregnancy.* http://www.cdc.gov/malaria/new_info/2011/mefloquine_pregnancy.html, [accessed August 2013].
29. Sevene E, Gonzalez R, Menendez C: **Current knowledge and challenges of antimalarial drugs for treatment and prevention in pregnancy.** *Expert Opin Pharmacother* 2010, **11:**1277–1293.
30. Steffen R, Fuchs E, Schildknecht J, Naef U, Funk M, Schlagenhauf P, Phillips-Howard P, Nevill C, Sturchler D: **Mefloquine compared with other malaria chemoprophylactic regimens in tourists visiting east Africa.** *Lancet* 1993, **341:**1299–1303.
31. van Riemsdijk MM, Sturkenboom MC, Ditters JM, Tulen JH, Ligthelm RJ, Overbosch D, Stricker BH: **Low body mass index is associated with an increased risk of neuropsychiatric adverse events and concentration impairment in women on mefloquine.** *Br J Clin Pharmacol* 2004, **57:**506–512.
32. ter Kuile FO, Nosten F, Thieren M, Luxemburger C, Edstein MD, Chongsuphajaisiddhi T, Phaipun L, Webster HK, White NJ: **High-dose mefloquine in the treatment of multidrug-resistant falciparum malaria.** *J Infect Dis* 1992, **166:**1393–1400.
33. FDA Drug Safety Communication: *FDA approves label changes for antimalarial drug mefloquine hydrochloride due to risk of serious psychiatric and nerve effects.* http://www.fda.gov/Drugs/DrugSafety/ucm362227.htm. 2013, [accessed July 2013].
34. Nevin RL: **Limitations of postmarketing surveillance in the analysis of risk of pregnancy loss associated with maternal mefloquine exposure.** *Clin Infect Dis* 2012, **55:**1167–1168. author reply 1168-1169.
35. U.S. National Institutes of Health: *Clinical Trials data base.* http://clinicaltrials.gov/, [accessed February 2014].
36. Collignon P, Hehir J, Mitchell D: **Successful treatment of falciparum malaria in pregnancy with mefloquine.** *Lancet* 1989, **1:**967.
37. Sweeney TR: **The present status of malaria chemotherapy: mefloquine, a novel antimalarial.** *Med Res Rev* 1981, **1:**281–301.
38. Carrara VI, Zwang J, Ashley EA, Price RN, Stepniewska K, Barends M, Brockman A, Anderson T, McGready R, Phaiphun L, Proux S, van Vugt M, Hutagalung R, Lwin KM, Phyo AP, Preechapornkul P, Imwong M, Pukrittayakamee S, Singhasivanon P, White NJ, Nosten F: **Changes in the treatment responses to artesunate-mefloquine on the northwestern border of Thailand during 13 years of continuous deployment.** *PLoS One* 2009, **4:**e4551.
39. Nosten F, van Vugt M, Price R, Luxemburger C, Thway KL, Brockman A, McGready R, ter Kuile F, Looareesuwan S, White NJ: **Effects of artesunate-mefloquine combination on incidence of *Plasmodium falciparum* malaria and mefloquine resistance in western Thailand: a prospective study.** *Lancet* 2000, **356:**297–302.
40. McGready R, Brockman A, Cho T, Cho D, van Vugt M, Luxemburger C, Chongsuphajaisiddhi T, White NJ, Nosten F: **Randomized comparison of mefloquine-artesunate versus quinine in the treatment of multidrug-resistant falciparum malaria in pregnancy.** *Trans R Soc Trop Med Hyg* 2000, **94:**689–693.
41. Orton LC, Omari AA: **Drugs for treating uncomplicated malaria in pregnant women.** *Cochr Database Syst Rev (Online)* 2008, **4:**CD004912.
42. Clinicaltrials.gov: *Safe and efficacious artemisinin-based combination treatments for african pregnant women with malaria (PREGACT).* http://clinicaltrials.gov/ct2/show/NCT00852423 2010-14.
43. McGready R, Cho T, Hkirijaroen L, Simpson J, Chongsuphajaisiddhi T, White NJ, Nosten F: **Quinine and mefloquine in the treatment of multidrug-resistan *Plasmodium falciparum* malaria in pregnancy.** *Ann Trop Med Parasit* 1998, **92:**643–653.
44. Nosten F, Vincenti M, Simpson J, Yei P, Thwai KL, de Vries A, Chongsuphajaisiddhi T, White NJ: **The effects of mefloquine treatment in pregnancy.** *Clin Infect Dis* 1999, **28:**808–815.
45. Harinasuta T, Kietinun S, Somlaw S, Bunnag D, Sheth U, Wernsdorfer W: **A clinical trial of mefloquine on multi-resistant falciparum malaria in pregnant women in Thailand.** *Bull Soc Fr Parasitol* 1990**:**429.
46. Adam I, Ali DA, Alwaseila A, Kheir MM, Elbashir MI: **Mefloquine in the treatment of falciparum malaria during pregnancy in Eastern Sudan.** *Saudi Med J* 2004, **25:**1400–1402.
47. Okeyeh JN, Lege-Oguntoye L, Emembolu JO, Agbo M: **Malaria in pregnancy: efficacy of a low dose of mefloquine in an area holoendemic for multi-drug resistant *Plasmodium falciparum*.** *Ann Trop Med Parasit* 1996, **90:**265–268.
48. Bounyasong S: **Randomized trial of artesunate and mefloquine in comparison with quinine sulfate to treat P. falciparum malaria pregnant women.** *J Med Assoc Thai* 2001, **84:**1289–1299.
49. Sowunmi A, Oduola AM, Ogundahunsi OA, Fehintola FA, Ilesanmi OA, Akinyinka OO, Arowojolu AO: **Randomised trial of artemether versus artemether and mefloquine for the treatment of chloroquine/sufadoxine-pyrimethamine-resistant falciparum malaria during pregnancy.** *J Obstet Gynaecol* 1998, **18:**322–327.
50. Nosten F, ter Kuile F, Maelankiri L, Chongsuphajaisiddhi T, Nopdonrattakoon L, Tangkitchot S, Boudreau E, Bunnag D, White NJ: **Mefloquine prophylaxis prevents malaria during pregnancy: a double-blind, placebo-controlled study.** *J Infect Dis* 1994, **169:**595–603.
51. Steketee RW, Wirima JJ, Slutsker L, Khoromana CO, Heymann DL, Breman JG: **Malaria treatment and prevention in pregnancy: indications for use and adverse events associated with use of chloroquine or mefloquine.** *Am J Trop Med Hyg* 1996, **55:**50–56.
52. Steketee RW, Wirima JJ, Slutsker L, Roberts JM, Khoromana CO, Heymann DL, Breman JG: **Malaria parasite infection during pregnancy and at delivery in**

mother, placenta, and newborn: efficacy of chloroquine and mefloquine in rural Malawi. *Am J Trop Med Hyg* 1996, **55:**24–32.
53. Smoak BL, Writer JV, Keep LW, Cowan J, Chantelois JL: **The effects of inadvertent exposure of mefloquine chemoprophylaxis on pregnancy outcomes and infants of US Army servicewomen.** *J Infect Dis* 1997, **176:**831–833.
54. Vanhauwere B, Maradit H, Kerr L: **Post-marketing surveillance of prophylactic mefloquine (Lariam) use in pregnancy.** *Am J Trop Med Hyg* 1998, **58:**17–21.
55. Phillips-Howard PA, Steffen R, Kerr L, Vanhauwere B, Schildknecht J, Fuchs E, Edwards R: **Safety of mefloquine and other antimalarial agents in the first trimester of pregnancy.** *J Travel Med* 1998, **5:**121–126.
56. Denoeud-Ndam L, Clement MC, Briand V, Akakpo J, Agossou VK, Atadokpede F, Dossou-Gbete L, Komongui DG, Afangnihoun A, Girard PM, Zannou DM, Cot M: **Tolerability of mefloquine intermittent preventive treatment for malaria in HIV-infected pregnant women in Benin.** *J Acquir Immune Defic Syndrom* 2012, **61:**64–72.
57. Schlagenhauf P, Blumentals WA, Suter P, Regep L, Vital-Durand G, Schaerer MT, Boutros MS, Rhein HG, Adamcova M: **Pregnancy and fetal outcomes after exposure to mefloquine in the pre- and periconception period and during pregnancy.** *Clin Infect Dis* 2012, **54:**e124–e131.
58. Nevin RL: **Mefloquine gap junction blockade and risk of pregnancy loss.** *Biol Reprod* 2012, **87:**65.
59. Ioannidis JP, Evans SJ, Gotzsche PC, O'Neill RT, Altman DG, Schulz K, Moher D: **Better reporting of harms in randomized trials: an extension of the CONSORT statement.** *Ann Int Med* 2004, **141:**781–788.
60. Lutfullin A, Kuhlmann J, Wensing G: **Adverse events in volunteers participating in phase I clinical trials: a single-center five-year survey in 1,559 subjects.** *Int J Clin Pharmacol Ther* 2005, **43:**217–226.
61. Sibille M, Deigat N, Janin A, Kirkesseli S, Durand DV: **Adverse events in phase-I studies: a report in 1015 healthy volunteers.** *Eur J Clin Pharmacol* 1998, **54:**13–20.
62. Bardaji A, Sigauque B, Bruni L, Romagosa C, Sanz S, Mabunda S, Mandomando I, Aponte J, Sevene E, Alonso PL, Menendez C: **Clinical malaria in African pregnant women.** *Malar J* 2008, **7:**27.
63. Newman RD, Parise ME, Slutsker L, Nahlen B, Steketee RW: **Safety, efficacy and determinants of effectiveness of antimalarial drugs during pregnancy: implications for prevention programmes in *Plasmodium falciparum*-endemic sub-Saharan Africa.** *Trop Med Int Health* 2003, **8:**488–506.
64. Nosten FMR, d'Alessandro U, Bonell A, Verhoeff F, Menendez C, Mutabingwa T, Brabin B: **Antimalarial Drugs in Pregnancy: A Review.** *Curr Drug Saf* 2006, **1:**1–15.
65. Clinicaltrials.gov: *Evaluation of alternative antimalarial drugs for malaria in pregnancy (MiPPAD).* http://clinicaltrials.gov/show/NCT00811421 2009-13.
66. Denoeud-Ndam L, Zannou DM, Fourcade C, Taron-Brocard C, Porcher R, Atadokpede F, Komongui DG, Dossou-Gbete L, Afangnihoun A, Ndam NT, Girard PM, Cot M: **Cotrimoxazole prophylaxis versus mefloquine intermittent preventive treatment to prevent malaria in HIV-infected pregnant women: two randomized controlled trials.** *J Acquir Immune Defic Syndrom* 2014, **65:**198–206.
67. Gonzalez R, Ataide R, Naniche D, Menendez C, Mayor A: **HIV and malaria interactions: where do we stand?** *Expert Rev Anti Infect Ther* 2012, **10:**153–165.

doi:10.1186/1475-2875-13-75
Cite this article as: González *et al.*: Mefloquine safety and tolerability in pregnancy: a systematic literature review. *Malaria Journal* 2014 **13**:75.