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[Intervention Protocol]

Mefloquine for preventing malaria in pregnant women

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ABSTRACT

This is the protocol for a review and there is no abstract. The objectives are as follows:

To assess the effects of mefloquine for preventing malaria in pregnant women. Specifically, to evaluate the:

- efficacy, safety and tolerability of mefloquine for preventing malaria in pregnant women.
- effect of HIV status, gravidity and ITN use on mefloquine efficacy.

BACKGROUND

Description of the condition

Malaria is the most important parasitic disease worldwide and is endemic in parts of Africa, Asia and South America. Pregnant women are at a higher risk of malaria infection than non-pregnant women in the same age group, and are also at higher risk of severe illness (Brabin 1983; Desai 2007). Malaria infection during pregnancy, particularly the first or second pregnancy, is also associated with adverse outcomes for both the mother (severe anaemia) and the infant (low birth weight, neonatal mortality; Radeva-Petrova 2014, Ataide 2014; Menendez 2010; Steketee 2001; Schwarz 2008; Guyatt 2004).

To reduce the burden and consequences of malaria in pregnancy (MiP), the World Health Organization (WHO) currently recommends that pregnant women who live in moderate to high malaria transmission areas in Africa i) sleep under an insecticide treated net (ITN) (Gamble 2006) and ii) receive intermittent-preventive treatment (IPT) with sulfadoxine-pyrimethamine (SP) at each scheduled antenatal care visit (provided that the doses are at least one month apart) (WHO 2013). IPT is a form of malaria chemoprevention that was tested and adopted as policy in response to malaria parasites developing resistance to weekly prophylaxis with chloroquine (WHO 2004). The long elimination half-life of SP allowed intermittent dosing (at least a month apart) while still providing prophylactic cover for the intervening weeks (White 2005). IPT is therefore defined as the 'administration of a curative treatment dose of an effective antimalarial drug at predefined intervals

during pregnancy' regardless of the presence or absence of current infection (White 2005).

SP remains the drug used for IPT in pregnancy, even though resistance to it is spreading rapidly in many parts of southern and eastern Africa (Ter Kuile 2007; WHO 2012). This is spurring researchers and policy makers to seek safe and effective alternatives to SP.

Description of the intervention

Mefloquine (MQ) is a 4-methanolquinoline related to quinine. It was originally developed by the US military for preventing malaria in soldiers, but has also been widely used for preventing malaria in travellers (Schlagenhauf 2010). Like SP, mefloquine has a long elimination half-life of two to four weeks; in travellers, weekly dosing at 250 mg is used (FDA 2004), while in pregnant women monthly dosing at treatment doses is feasible.

Mefloquine was first investigated as a prophylactic treatment for pregnant women in the 1990s. An observational study by Nosten 1999 raised concerns that mefloquine may be associated with an increased risk of stillbirths, however this was not confirmed in other trials (Nosten 1994; Steketee 1996). The safety of mefloquine in pregnancy has recently been considered in a systematic review that concluded there is no evidence that mefloquine use in pregnancy carries an increased risk for the foetus (Gonzalez 2014). The drug is known to be associated with a range of mild

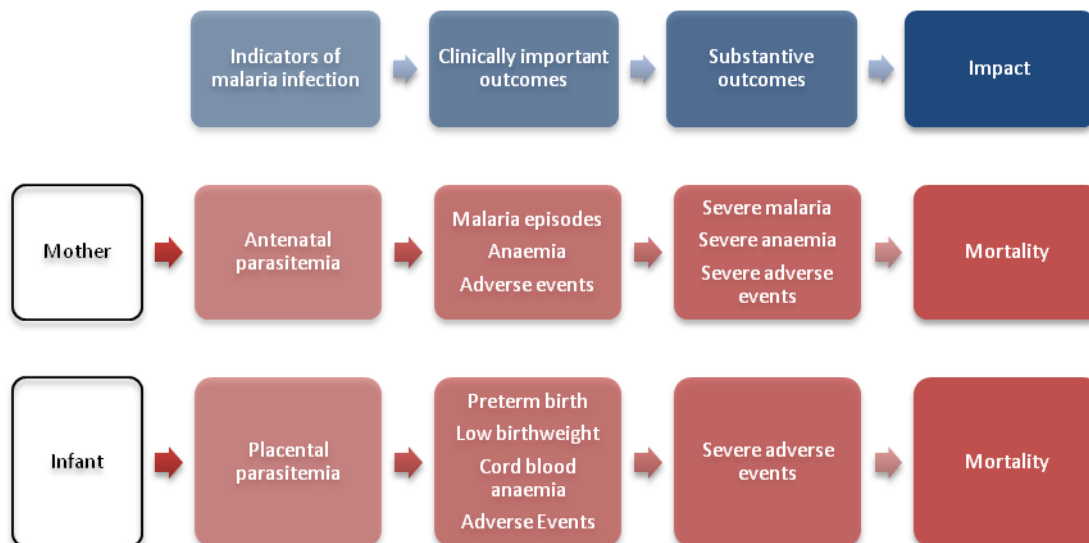
side effects, such as vomiting, nausea and dizziness (Bardaji 2012; Sevene 2010). Severe neuropsychiatric side effects have been described and occur in about one in 10,000 travellers taking mefloquine as chemoprophylaxis (Steffen 1993). Studies conducted in Beninese pregnant women found that dizziness and vomiting are the most frequent adverse effects related to mefloquine given as IPT in pregnancy (Briand 2009; Denoeud-Ndam 2012).

Resistance to mefloquine has been reported in multi-drug resistance areas of Thailand (Carrara 2009; Nosten 2000), but it remains rare in Africa (Aubouy 2007; MacArthur 2001; Oduola 1987).

How the intervention might work

Malaria chemoprevention is thought to work through the clearance or suppression of asymptomatic malaria infections in the mother and the placenta (White 2005). This reduction in malaria parasitaemia may, however, be insufficient to justify recommendations for widespread prophylactic prescriptions, without subsequent benefits to clinically important outcomes in the mother and her baby. These outcomes may include a reduction in malaria episodes, a reduced risk of anaemia and improved birth weight, as well as more substantive outcomes such as a reduction in severe maternal illness or a lower mortality rate among mothers and infants (see Figure 1).

Figure 1.



The effects of malaria chemoprevention may depend on the local malaria epidemiology. In highly endemic areas with stable transmission, mothers may have partial immunity to malaria, causing parasitaemia without clinical disease, but this can still produce detrimental effects such as anaemia and low birth weights. In contrast, where malaria transmission is seasonal or unstable, natural immunity may be lower and the main effects of chemoprevention may be a reduction in clinical episodes or severe illness.

Primiparous women appear to be more at risk of adverse outcomes of malaria in pregnancy than multiparous women. This is thought to be due to women developing antibodies specific to placental-type parasites when exposed to *Plasmodium falciparum* during their first pregnancy. These antibodies are thus already present for subsequent pregnancies (Ataide 2014). This means multiparous women can exert a more specific and efficient immune response and so clear the infection at an earlier stage (Walker 2013).

Another potential effect modifier is HIV status (Menendez 2011). Many malaria endemic areas also have a high prevalence of HIV infection among pregnant women, which has been shown to increase the risk of malaria infection (van Eijk 2003, Gonzalez 2012). Compared with HIV-negative women, HIV-positive women are more likely to carry malaria parasites in their blood, have higher parasite densities, and have placental parasitaemia, anaemia and malaria symptoms (Ayisi 2003; van Eijk 2002; van Eijk 2003). This increased risk appears to be just the same for multigravidae (women in their third pregnancy or higher) as for women in their first or second pregnancy (van Eijk 2003). Heavy placental malaria infection may also increase the risk of perinatal mother-to-child transmission of HIV (Ayisi 2003).

The use of ITN during pregnancy has also been shown to have a beneficial impact on pregnancy outcomes (reduced prevalence of low birth rate, miscarriage and placental parasitaemia) in malaria-endemic Africa (Gamble 2007) and could modify the effect of IPT.

Why it is important to do this review

The WHO recommends IPT with SP for all pregnant women who live in moderate to high malaria transmission areas in Africa (WHO 2004; WHO 2013). However, studies have shown that resistance to SP in some regions of Eastern Africa has been growing rapidly over the past few years (Iriemenam 2012; Mockenhaupt 2008). Thus, there is an urgent need for other drugs with lower resistance patterns to be assessed for their ability to prevent malaria during pregnancy.

This review aims to evaluate the efficacy and safety of mefloquine for preventing malaria in pregnant women. Based on these findings, future guidelines on preventive agents for malaria could be developed.

OBJECTIVES

To assess the effects of mefloquine for preventing malaria in pregnant women. Specifically, to evaluate the:

- efficacy, safety and tolerability of mefloquine for preventing malaria in pregnant women.
- effect of HIV status, gravidity and ITN use on mefloquine efficacy.

METHODS

Criteria for considering studies for this review

Types of studies

Randomized and quasi-randomized controlled trials.

To evaluate the safety of mefloquine in pregnancy we will also include observational studies (such as non-randomized controlled studies and uncontrolled case series) in order to obtain larger participant samples.

Types of participants

Pregnant women of any gravidity and regardless of HIV status, living in endemic malaria areas.

To evaluate the safety of mefloquine in pregnancy, we will also include studies where mefloquine was used to prevent malaria in pregnant women travelling to malaria endemic areas.

Types of interventions

Interventions

Mefloquine given to pregnant women as intermittent preventive treatment or as chemoprophylaxis.

Controls

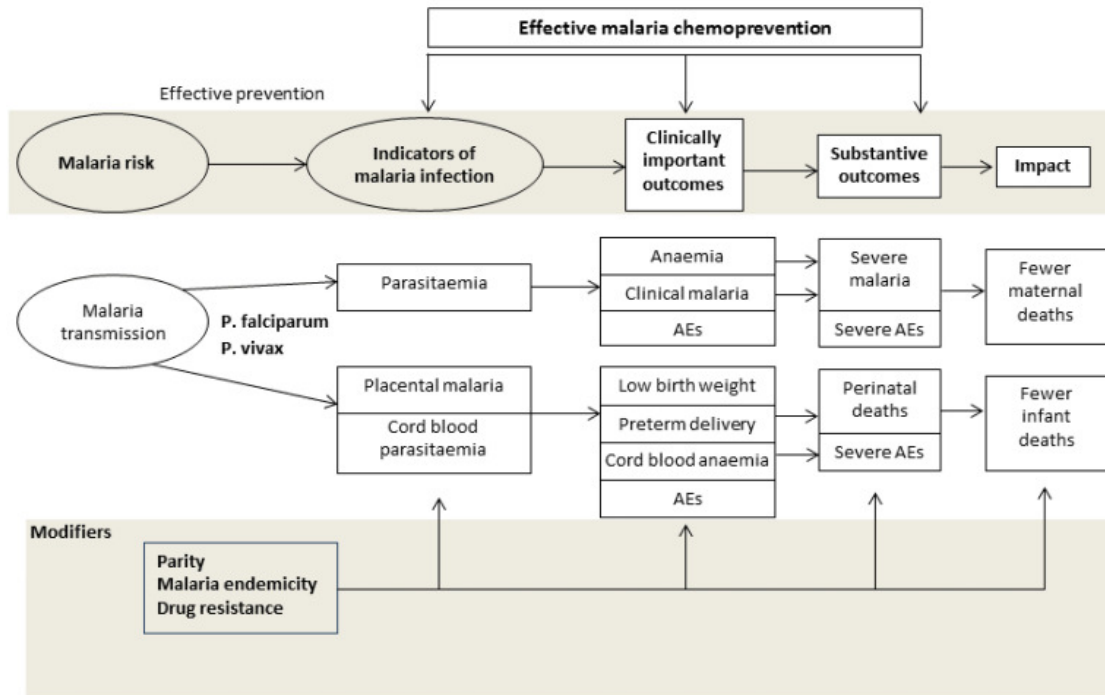
Placebo, no intervention, or an alternative drug regimen.

Types of outcome measures

- Maternal:
 - Maternal peripheral parasitaemia during pregnancy
 - Maternal peripheral parasitaemia at delivery
 - Placental malaria*
 - Mean haemoglobin and maternal anaemia (as defined in the original studies) during pregnancy
 - Mean haemoglobin and maternal anaemia at delivery

- Clinical malaria episodes during pregnancy
 - Fetal/infant:
 - Cord blood parasitaemia
 - Cord blood haemoglobin and anaemia (as defined in the original studies)
 - Mean birth weight
 - Low birth weight prevalence (< 2500 g)
 - Prematurity prevalence (<37 weeks of gestation)
 - Neonatal morbidity in first 28 days of life
 - Morbidity in first year of life
 - Safety:
 - Serious Adverse Events (SAEs)
 - ◇ Illnesses that were life threatening or required hospitalization during pregnancy
 - ◇ Adverse pregnancy outcomes: spontaneous abortions, stillbirths, congenital malformations
 - ◇ Maternal mortality
 - ◇ Perinatal, neonatal, infant mortality
 - Tolerability
 - ◇ Frequency and severity of reported all-cause and drug-related adverse effects
- *Placental malaria diagnosed by histology, microscopy or any method used in the included study. [Figure 2](#) shows the relation between the different outcomes.

Figure 2. Reproduced under the terms of a Creative Commons Licence from Radeva-Petrova 2014: Radeva-Petrova D, Kayentao K, ter Kuile FO, Sinclair D, Garner P. Drugs for preventing malaria in pregnant women in endemic areas: any drug regimen versus placebo or no treatment. Cochrane Database of Systematic Reviews 2014, Issue 10. Art. No.: CD000169. DOI: 10.1002/14651858.CD000169.pub3.



Search methods for identification of studies

We will attempt to identify all relevant trials regardless of language or publication status (published, unpublished, in press, and in

progress).

Electronic searches

We will search the following databases using the search terms and

strategy described in Appendix 1: Cochrane Infectious Diseases Group Specialized Register; Central Register of Controlled Trials (CENTRAL), published in The Cochrane Library; MEDLINE; EMBASE; and LILACS. We will also search the Malaria in Pregnancy (MiP) Library (<http://www.mip-consortium.org/resources/index.htm>), the WHO clinical trial registry platform, and the metaRegister of Controlled Trials (mRCT) using 'mefloquine', 'malaria', and 'pregnan*' as search terms.

Searching other resources

We will contact researchers working in the field for unpublished data, confidential reports, and raw data of published trials. We will also check the citations of all trials identified by the above methods.

Data collection and analysis

Selection of studies

Two authors will independently screen all trials identified by the search strategy (Appendix 1). Full text copies will be retrieved for all trials deemed potentially relevant. Two authors will then independently assess eligibility using a form based on the inclusion criteria. Disagreements will be resolved through discussion or by consulting a third author. Any author that has participated in trials that could be potentially meeting the inclusion criteria of the review will not participate in the procedure to select studies for inclusion.

Data extraction and management

Two authors will independently extract data using a data extraction form. We will extract data on trial characteristics, including trial site, year, local malaria transmission estimates, antimalarial resistance pattern of mefloquine and the comparator drug (where possible), trial methods, participants, interventions, doses and outcomes.

We will extract the number of participants randomized and the number analysed in the experimental and control arms for each outcome. For dichotomous outcomes, we will extract the number of participants experiencing the event and the number assessed in each treatment group. For continuous outcomes, we will extract the arithmetic means, standard deviations for each treatment group (where provided), and the number of participants assessed in each group. We will also extract medians and ranges where provided.

Any author who has participated in any of the trials included in the review will not participate in the data extraction or risk of bias assessment.

Assessment of risk of bias in included studies

Two authors will independently assess the risk of bias for each trial using the Cochrane Collaboration's tool for assessing the risk of bias (Higgins 2011). This approach assesses the risk of bias across six domains: sequence generation, allocation concealment, blinding, incomplete outcome data, selective outcome reporting, and other potential biases (Higgins 2011). For each domain, we will assign a judgment of low risk of bias, high risk of bias, or unclear risk of bias. For observational studies, the risk of selection, performance, attrition, detection and selective reporting biases will be evaluated, following the guidelines of the Agency for Healthcare Research and Quality (Viswanathan 2012).

Measures of treatment effect

Dichotomous outcomes will be presented using risk ratios (RR), count outcomes will be presented as rate ratios (Rate R), and continuous outcomes will be presented as the mean difference (MD). All measures of effect will be presented with 95% confidence intervals (CI).

Unit of analysis issues

Trials including more than two comparison groups will be split and analysed as individual pair-wise comparisons. When conducting a meta-analysis, we will ensure that participants and cases in the placebo group are not counted more than once, by dividing the placebo cases and participants evenly between the intervention groups.

Dealing with missing data

We will aim to conduct the analysis according to the intention-to-treat principle. However, when there was loss to follow up (or if participants were excluded because they developed malaria parasitaemia after randomization and received antimalarial treatment), a complete-case analysis will be used, such that participants for whom no outcome was reported are excluded from the analysis. This analysis assumes that the participants for whom an outcome is available are representative of the original randomized patients. We will conduct a sensitivity analysis as described below to evaluate the robustness of this methodology. If data from the trial reports are insufficient, unclear or missing, we will attempt to contact the authors for additional information.

Assessment of heterogeneity

We will calculate the I^2 -statistic using values of 30% to 59%, 60% to 89%, and 90% to 100% to denote moderate, substantial and considerable levels of heterogeneity respectively.

Assessment of reporting biases

Where possible, we will assess the risk of publication bias by constructing funnel plots and looking for asymmetry.

Data synthesis

Data will be analyzed using Review Manager 5.3 ([Review Manager \(RevMan\)](#)). The primary analysis will be stratified by parity and HIV status where possible. In the absence of heterogeneity, we will use a fixed-effect model for the meta-analysis, and where moderate heterogeneity is detected we will use a random-effects model.

Subgroup analysis and investigation of heterogeneity

We will investigate heterogeneity by conducting pre-specified subgroup analysis to evaluate the contribution of differences in trial characteristics such as risk of bias, geographical region, malaria

transmission pattern, antimalarial resistance, drug regimen, use of ITNs, parity (para 0 to 1 versus multigravidae), HIV status (negative, positive, unknown), and trial methods.

Sensitivity analysis

We will conduct a sensitivity analysis to restore the integrity of the randomization process and test the robustness of our results.

ACKNOWLEDGEMENTS

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* Indicates the major publication for the study

APPENDICES

Appendix I. Detailed search strategies

Search set	CIDG Specialized register	CENTRAL	MEDLINE	Embase	LILACS
1	malaria	Malaria ti, ab, MeSH	Malaria ti, ab, MeSH	Malaria ti, ab, Emtree	malaria
2	Mefloquine OR Lariam	Mefloquine ti, ab, MeSH	Mefloquine ti, ab, MeSH	Mefloquine ti, ab, Emtree	Tafenoquine
3	Pregnan*	Lariam ti, ab	Lariam ti, ab	Lariam ti, ab	Lariam

(Continued)

4	1 and 2 and 3	2 or 3	2 or 3	2 or 3	2 or 3
5		1 and 4	1 and 4	1 and 4	1 and 4
6		Pregnan* ti, ab	Pregnan* ti, ab	Pregnan* ti, ab	Pregnan\$
7		Pregnancy [Mesh]	Pregnancy [Mesh]	Pregnancy [Emtree]	5 and 6
8		6 or 7	6 or 7	6 or 7	
9		5 and 8	5 and 8	5 and 8	

CONTRIBUTIONS OF AUTHORS

RG, DS, FtK, PG and CM designed the study. RG, RB, DS and FtK wrote the protocol. RG and RB will assess the trial eligibility and risk of bias. RG, RB and DS will extract the data. RG, RB, DS and JA will do the analyses. RG, RB and DS will write the first version of the review. All authors will interpret the results, and contribute and approve the final version of the review.

DECLARATIONS OF INTEREST

RG, JA, CM are all authors of a trial of mefloquine to prevent malaria in pregnancy published in 2014 which is a candidate for inclusion in this review.

SOURCES OF SUPPORT

Internal sources

- Barcelona Institute of Global Health (ISGlobal), Hospital Clínic- Universitat de Barcelona, Spain.

External sources

- No sources of support supplied