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González R, Pons-Duran C, Piqueras M, Aponte JJ, ter Kuile FO, Menéndez C. Mefloquine for preventing malaria in pregnant women. *Cochrane Database of Systematic Reviews* 2018, Issue 3. Art. No.: CD011444. DOI: 10.1002/14651858.CD011444.pub2.

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[Intervention Review]

Mefloquine for preventing malaria in pregnant women

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Editorial group: Cochrane Infectious Diseases Group. Publication status and date: New, published in Issue 3, 2018.

Citation: González R, Pons-Duran C, Piqueras M, Aponte JJ, ter Kuile FO, Menéndez C. Mefloquine for preventing malaria in pregnant women. *Cochrane Database of Systematic Reviews* 2018, Issue 3. Art. No.: CD011444. DOI: 10.1002/14651858.CD011444.pub2.

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ABSTRACT

Background

The World Health Organization recommends intermittent preventive treatment in pregnancy (IPTp) with sulfadoxine-pyrimethamine for malaria for all women who live in moderate to high malaria transmission areas in Africa. However, parasite resistance to sulfadoxine-pyrimethamine has been increasing steadily in some areas of the region. Moreover, HIV-infected women on cotrimoxazole prophylaxis cannot receive sulfadoxine-pyrimethamine because of potential drug interactions. Thus, there is an urgent need to identify alternative drugs for prevention of malaria in pregnancy. One such candidate is mefloquine.

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; and
- the impact of HIV status, gravidity, and use of insecticide-treated nets on the effects of mefloquine.

Search methods

We searched the Cochrane Infectious Diseases Group Specialized Register, the Cochrane Central Register of Controlled Trials (CENTRAL) in the Cochrane Library, MEDLINE, Embase, Latin American Caribbean Health Sciences Literature (LILACS), the Malaria in Pregnancy Library, and two trial registers up to 31 January 2018. In addition, we checked references and contacted study authors to identify additional studies, unpublished data, confidential reports, and raw data from published trials.

Selection criteria

Randomized and quasi-randomized controlled trials comparing mefloquine IPT or mefloquine prophylaxis against placebo, no treatment, or an alternative drug regimen.

Data collection and analysis

Two review authors independently screened all records identified by the search strategy, applied inclusion criteria, assessed risk of bias, and extracted data. We contacted trial authors to ask for additional information when required. Dichotomous outcomes were compared using risk ratios (RRs), count outcomes as incidence rate ratios (IRRs), and continuous outcomes using mean differences (MDs). We have presented all measures of effect with 95% confidence intervals (CIs). We assessed the certainty of evidence using the GRADE approach for the following main outcomes of analysis: maternal peripheral parasitaemia at delivery, clinical malaria episodes during pregnancy, placental malaria, maternal anaemia at delivery, low birth weight, spontaneous abortions and stillbirths, dizziness, and vomiting.

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Main results

Six trials conducted between 1987 and 2013 from Thailand (1), Benin (3), Gabon (1), Tanzania (1), Mozambique (2), and Kenya (1) that included 8192 pregnant women met our inclusion criteria.

Two trials (with 6350 HIV-uninfected pregnant women) compared two IPTp doses of mefloquine with two IPTp doses of sulfadoxinepyrimethamine. Two other trials involving 1363 HIV-infected women compared three IPTp doses of mefloquine plus cotrimoxazole with cotrimoxazole. One trial in 140 HIV-infected women compared three doses of IPTp-mefloquine with cotrimoxazole. Finally, one trial enrolling 339 of unknown HIV status compared mefloquine prophylaxis with placebo.

Study participants included women of all gravidities and of all ages (four trials) or > 18 years (two trials). Gestational age at recruitment was > 20 weeks (one trial), between 16 and 28 weeks (three trials), or \leq 28 weeks (two trials). Two of the six trials blinded participants and personnel, and only one had low risk of detection bias for safety outcomes.

When compared with sulfadoxine-pyrimethamine, IPTp-mefloquine results in a 35% reduction in maternal peripheral parasitaemia at delivery (RR 0.65, 95% CI 0.48 to 0.86; 5455 participants, 2 studies; *high-certainty evidence*) but may have little or no effect on placental malaria infections (RR 1.04, 95% CI 0.58 to 1.86; 4668 participants, 2 studies; *low-certainty evidence*). Mefloquine results in little or no difference in the incidence of clinical malaria episodes during pregnancy (incidence rate ratio (IRR) 0.83, 95% CI 0.65 to 1.05, 2 studies; *high-certainty evidence*). Mefloquine decreased maternal anaemia at delivery (RR 0.84, 95% CI 0.76 to 0.94; 5469 participants, 2 studies; *moderate-certainty evidence*). Data show little or no difference in the proportions of low birth weight infants (RR 0.95, 95% CI 0.78 to 1.17; 5641 participants, 2 studies; *high-certainty evidence*) and in stillbirth and spontaneous abortion rates (RR 1.20, 95% CI 0.91 to 1.58; 6219 participants, 2 studies; *l²* statistic = 0%; *high-certainty evidence*). IPTp-mefloquine increased drug-related vomiting (RR 4.76, 95% CI 4.13 to 5.49; 6272 participants, 2 studies; *high-certainty evidence*) and dizziness (RR 4.21, 95% CI 3.36 to 5.27; participants = 6272, 2 studies; *high-certainty evidence*).

When compared with cotrimoxazole, IPTp-mefloquine plus cotrimoxazole probably results in a 48% reduction in maternal peripheral parasitaemia at delivery (RR 0.52, 95% CI 0.30 to 0.93; 989 participants, 2 studies; *moderate-certainty evidence*) and a 72% reduction in placental malaria (RR 0.28, 95% CI 0.14 to 0.57; 977 participants, 2 studies; *high-certainty evidence*) but has little or no effect on the incidence of clinical malaria episodes during pregnancy (IRR 0.76, 95% CI 0.33 to 1.76, 1 study; *high-certainty evidence*) and probably no effect on maternal anaemia at delivery (RR 0.94, 95% CI 0.73 to 1.20; 1197 participants, 2 studies; *moderate-certainty evidence*), low birth weight rates (RR 1.20, 95% CI 0.89 to 1.60; 1220 participants, 2 studies; *moderate-certainty evidence*), and rates of spontaneous abortion and stillbirth (RR 1.12, 95% CI 0.42 to 2.98; 1347 participants, 2 studies; *very low-certainty evidence*). Mefloquine was associated with higher risks of drug-related vomiting (RR 7.95, 95% CI 4.79 to 13.18; 1055 participants, one study; *high-certainty evidence*) and dizziness (RR 3.94, 95% CI 2.85 to 5.46; 1055 participants, 1 study; *high-certainty evidence*).

Authors' conclusions

Mefloquine was more efficacious than sulfadoxine-pyrimethamine in HIV-uninfected women or daily cotrimoxazole prophylaxis in HIVinfected pregnant women for prevention of malaria infection and was associated with lower risk of maternal anaemia, no adverse effects on pregnancy outcomes (such as stillbirths and abortions), and no effects on low birth weight and prematurity. However, the high proportion of mefloquine-related adverse events constitutes an important barrier to its effectiveness for malaria preventive treatment in pregnant women.

PLAIN LANGUAGE SUMMARY

Mefloquine for preventing malaria in pregnant women

What is the aim of this review?

The aim of this Cochrane Review was to find out whether the antimalarial drug mefloquine is efficacious and safe for prevention of malaria in pregnant women living in stable transmission areas. We found six relevant studies to help us answer this question.

Key messages

The antimalarial drug mefloquine is efficacious for malaria prevention in pregnant women. The drug has been found to be safe in terms of adverse pregnancy outcomes, such as low birth weight, prematurity, stillbirths and abortions, and congenital malformations. However, it is worse tolerated than other antimalarial drugs.

What was studied in the review?

Pregnant women are vulnerable to malaria infection, especially if they are living with HIV. The consequences of malaria during pregnancy can be severe and include poor health outcomes for both women and their children. For this reason, in malaria-endemic areas of stable transmission, women are recommended to prevent malaria infection by sleeping under mosquito bed-nets and by taking effective drugs (such as sulphadoxine-pyrimethamine or cotrimoxazole in case of HIV infection) as chemoprevention against malaria throughout pregnancy.

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This Cochrane Review looked at the effects of mefloquine for prevention of malaria in both HIV-uninfected and HIV-infected pregnant women.

What are the main results of the review?

We found five relevant studies conducted in sub-Saharan Africa and one in Thailand between 1987 and 2013. These studies compared mefloquine with placebo or other antimalarial drugs currently recommended for prevention of malaria in pregnant women. The review shows the following:

• Compared with sulfadoxine-pyrimethamine, mefloquine chemoprevention in HIV-uninfected women:

•reduces risks of maternal peripheral parasitaemia (presence of malaria parasites in the blood of women) and anaemia at delivery;
• makes no difference in the prevalence of adverse maternal outcomes (such as low birth weight, prematurity, stillbirths and abortions, and congenital malformations) and in the incidence of clinical malaria episodes during pregnancy; and
• increases risks of drug-related adverse events including vomiting, fatigue/weakness, and dizziness.

• Compared with cotrimoxale prophylaxis alone, mefloquine chemoprevention plus cotrimoxazole in HIV-infected women:

• reduces the risk of maternal peripheral parasitaemia at delivery and the risk of placental malaria;

makes no difference in the prevalence of adverse pregnancy outcomes (such as low birth weight, prematurity, stillbirths and abortions, and congenital malformations) and in the incidence of clinical malaria episodes during pregnancy; and
increases the risk of drug-related adverse events such as vomiting and dizziness.

Overall, the high proportion of mefloquine-related adverse events constitutes an important barrier to its effectiveness for malaria preventive treatment in pregnant women.

How up-to-date is this review?

The review authors searched for studies up to 31 January 2018.