Drugs for preventing malaria in pregnant women in endemic areas

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RHL Summary

Key findings

- Malaria chemoprophylaxis demonstrated clinically important benefits on anaemia and antenatal and placental parasitaemia in mothers, and on birthweight in infants.
- No conclusions due to small sample size or no information reported, on maternal mortality, spontaneous abortion, stillbirth, perinatal or neonatal death.

Evidence included in this review

Seventeen trials (RCTs and quasi-RCTs) were included in this review, comparing different regimens of chemoprophylaxis for malaria infection against placebo or no treatment, involving 14,481 pregnant women in endemic areas. Antimalarials used in included trials were chloroquine, pyrimethamine, proguanil, pyrimethamine-dapsone, mefloquine and sulfadoxine-pyrimethamine.

Quality assessment

Overall, trials were of moderate risk of bias. Six trials reported on allocation concealment and were considered at low risk of selection bias. Eleven trials used a placebo and four trials reported outcome assessors blinding. There was a high or unclear risk of attrition bias in most of trials due to incomplete outcome data.

Clinical implications

Maternal and neonatal benefits of malaria chemoprophylaxis were demonstrated in first or second pregnancies. There was a statistically significant reduction in maternal anaemia, antenatal and placental parasitaemia, as well as a reduction in low birthweight infants and an increase in mean birthweight. In multigravid women, effects on parasitaemia were similar, but no other differences were found.

Further research

Long term outcomes in infants, adverse events and alternative regimens for drug-resistant malaria should be investigated.

Cochrane review
Abstract

Pregnancy increases the risk of malaria and this is associated with poor health outcomes for both the mother and the infant, especially during the first or second pregnancy. To reduce these effects, the World Health Organization recommends that pregnant women living in malaria endemic areas sleep under insecticide-treated bednets, are treated for malaria illness and anaemia, and receive chemoprevention with an effective antimalarial drug during the second and third trimesters.

To assess the effects of malaria chemoprevention given to pregnant women living in malaria endemic areas on substantive maternal and infant health outcomes. We also summarised the effects of intermittent preventive treatment with sulfadoxine-pyrimethamine (SP) alone, and preventive regimens for *Plasmodium vivax*.

We searched the Cochrane Infectious Diseases Group Specialized Register, CENTRAL, MEDLINE, EMBASE, LILACS, and reference lists up to 1 June 2014.

Randomized controlled trials (RCTs) and quasi-RCTs of any antimalarial drug regimen for preventing malaria in pregnant women living in malaria-endemic areas compared to placebo or no intervention. In the mother, we sought outcomes that included mortality, severe anaemia, and severe malaria; anaemia, haemoglobin values, and malaria episodes; indicators of malaria infection, and adverse events. In the baby, we sought foetal loss, perinatal, neonatal and infant mortality; preterm birth and birthweight measures; and indicators of malaria infection. We included regimens that were known to be effective against the malaria parasite at the time but may no longer be used because of parasite drug resistance.

Two review authors applied inclusion criteria, assessed risk of bias and extracted data. Dichotomous outcomes were compared using risk ratios (RR), and continuous outcomes using mean differences (MD); both are presented with 95% confidence intervals (CI). We assessed the quality of evidence using the GRADE approach.

Seventeen trials enrolling 14,481 pregnant women met our inclusion criteria. These trials were conducted between 1957 and 2008, in Nigeria (three trials), The Gambia (three trials), Kenya (three trials), Mozambique (two trials), Uganda (two trials), Cameroon (one trial), Burkina Faso (one trial), and Thailand (two trials). Six different antimalarials were evaluated against placebo or no intervention; chloroquine (given weekly), pyrimethamine (weekly or monthly), proguanil (daily), pyrimethamine-dapsone (weekly or fortnightly), and mefloquine (weekly), or intermittent preventive therapy with SP (given twice, three times or monthly). Trials recruited women in their first or second pregnancy (eight trials); only multigravid women (one trial); or all women (eight trials). Only six trials had adequate allocation concealment.

For women in their first or second pregnancy, malaria chemoprevention reduces the risk of moderate to severe anaemia by around 40% (RR 0.60, 95% CI 0.47 to 0.75; three trials, 2503 participants, high quality evidence), and the risk of any anaemia by around 17% (RR 0.83, 95% CI 0.74 to 0.93; five trials, 3662 participants, high quality evidence). Malaria chemoprevention reduces the risk of antenatal parasitaemia by around 61% (RR 0.39, 95% CI 0.26 to 0.58; seven trials, 3663 participants, high quality evidence), and two trials reported a reduction in febrile illness (low quality evidence). There were only 16 maternal deaths and these trials were underpowered to detect an effect on maternal mortality (very low quality evidence).

For infants of women in their first and second pregnancies, malaria chemoprevention probably increases mean birthweight by around 93 g (MD 92.72 g, 95% CI 62.05 to 123.39; nine trials, 3936 participants, moderate quality evidence), reduces low birthweight by around 27% (RR 0.73, 95% CI 0.61 to 0.87; eight trials, 3619 participants, moderate quality evidence), and reduces placental parasitaemia by around 46% (RR
0.54, 95% CI 0.43 to 0.69; seven trials, 2830 participants, high quality evidence). Fewer trials evaluated spontaneous abortions, still births, perinatal deaths, or neonatal deaths, and these analyses were underpowered to detect clinically important differences.

In multigravid women, chemoprevention has similar effects on antenatal parasitaemia (RR 0.38, 95% CI 0.28 to 0.50; three trials, 977 participants, high quality evidence) but there are too few trials to evaluate effects on other outcomes.

In trials giving chemoprevention to all pregnant women irrespective of parity, the average effects of chemoprevention measured in all women indicated it may prevent severe anaemia (defined by authors, but at least < 8 g/L: RR 0.19, 95% CI 0.05 to 0.75; two trials, 1327 participants, low quality evidence), but consistent benefits have not been shown for other outcomes.

In an analysis confined only to intermittent preventive therapy with SP, the estimates of effect and the quality of the evidence were similar.

A summary of a single trial in Thailand of prophylaxis against *P. vivax* showed chloroquine prevented vivax infection (RR 0.01, 95% CI 0.00 to 0.20; one trial, 942 participants).

Routine chemoprevention to prevent malaria and its consequences has been extensively tested in RCTs, with clinically important benefits on anaemia and parasitaemia in the mother, and on birthweight in infants.

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