Effect of sulfadoxine-pyrimethamine resistance on the efficacy of intermittent preventive therapy for malaria control during pregnancy: a systematic review

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CRD summary
This review concluded that in areas of high sulfadoxine-pyrimethamine resistance, two doses of preventive treatment with sulfadoxine-pyrimethamine are effective for malaria control in HIV-negative pregnant women, but more frequent dosing is needed for HIV-positive women. Although the review was generally well-conducted, the conclusions are based on very few studies and the estimation of background resistance may not be reliable.

Authors' objectives
To evaluate the effect of sulfadoxine-pyrimethamine resistance on the efficacy of intermittent preventive therapy (IPT) with sulfadoxine-pyrimethamine for malaria control during pregnancy.

Searching
MEDLINE, EMBASE, Scopus, LILACS, the Cochrane CENTRAL Register, and the trial register and bibliographic database of the Malaria in Pregnancy Library were searched without language restrictions; the search terms were reported. In addition, reference lists were screened and experts in the field contacted for further primary studies.

Study selection
Study designs of evaluations included in the review
Randomised controlled trials (RCTs) were eligible for inclusion.

Specific interventions included in the review
Studies of sulfadoxine-pyrimethamine therapy were eligible for inclusion. The comparators were placebo, case management (treatment of incident malaria cases only; no preventive treatment), standard care (weekly chloroquine prophylaxis), or different sulfadoxine-pyrimethamine regimens (monthly versus 2-dose during pregnancy). Most of the included studies used a standard 2-dose sulfadoxine-pyrimethamine therapy as the intervention group; however, two based the number of doses given on the gestational age at enrolment, with the majority of participants given two doses. One study also assessed the use of insecticide-treated nets co-concomitantly with sulfadoxine-pyrimethamine.

Participants included in the review
Studies of pregnant women in sub-Saharan Africa were eligible for inclusion. The included studies mostly restricted inclusion to women during their first or second pregnancy. One study only recruited women who had at least one previous pregnancy, and one included human immunodeficiency virus (HIV)-positive women only.

Outcomes assessed in the review
No inclusion criteria were specified for the outcomes. The primary outcome used in the review was placental malaria. The secondary outcomes were maternal peripheral parasitaemia at delivery, low birth weight, mean birth weight, all-cause maternal anaemia and mean haemoglobin level.

How were decisions on the relevance of primary studies made?
The authors did not state how the papers were selected for the review, or how many reviewers performed the selection.

Assessment of study quality
The methodological quality of the studies was assessed by considering the methods used to generate the allocation sequence and concealment, the degree of blinding, and the level of loss to follow-up. Each study was given an overall score out of 9 based on a modified version of the Jadad score; a score of 6 or more was considered high quality. It is not clear how many reviewers performed the quality assessment.
Data extraction

Two reviewers independently extracted the data.

Primary and secondary outcomes were reported as the relative risk (RR) or weighted mean difference (WMD). For each IPT group, the reduction in the proportion of women with peripheral parasitaemia at delivery compared with that at enrolment was also calculated. Adverse events data were also extracted from the studies.

Methods of synthesis

How were the studies combined?

RR and WMD, alongside 95% confidence intervals (CIs), were calculated according to type of comparator using a fixed-effect model in the first instance. Where significant heterogeneity was detected, a random-effects model was then used. The overall percentage reduction in peripheral parasitaemia from enrolment to delivery for women given IPT was calculated by combining the results from all studies, irrespective of the comparator used.

How were differences between studies investigated?

Statistical heterogeneity was assessed using the I-squared test; values over 50% were considered to represent significant heterogeneity. Where detected, heterogeneity was investigated further by considering differences between the trials. The effect of differing background sulfadoxine resistance was investigated by matching each study with a study of treatment in children from the same country and during the same time period (within 2 years); matches for chloroquine resistance were also found for trials that used chloroquine as a comparator. Further factors of interest were the number of previous pregnancies and HIV status, and the influence of these factors on study results was investigated through subgroup analysis and stratification. Sensitivity analyses were also performed for study quality where possible.

Results of the review

Nine studies involving 5,631 women in total were included.

Two studies were considered poor quality with scores of 1; the remaining studies all scored 6 or more.

IPT 2-dose compared with chloroquine (2 studies, 831 participants): there was a statistically significant reduction in low birth weight (less than 2,500 g) with IPT compared with chloroquine (RR 0.77, 95% CI: 0.61, 0.97, p=0.02; I-squared 0%); although malarial infection (placental malaria and maternal parasitaemia at delivery) was also reduced, the effect was not statistically significant. The effect was greater in the study carried out against a background of high chloroquine resistance.

IPT 2-dose compared with case management or placebo (5 studies, 3,943 participants): the 4 studies that enrolled only women in their first or second pregnancy were pooled (1,941 participants) and IPT was found to significantly reduce placental malaria (RR 0.48; 95% CI: 0.35, 0.68, p<0.001; I-squared 52.1%), peripheral parasitaemia (RR 0.45, 95% CI: 0.36, 0.56, p<0.001; I-squared 21.6%), anaemia (RR 0.90, 95% CI: 0.81, 0.99, p=0.02; I-squared 59.9%) and low birth weight (RR 0.71, 95% CI: 0.55, 0.92, p=0.008; I-squared 27.2%), and to significantly increase haemoglobin (WMD 0.38 g/dL, 95% CI: 0.24, 0.51, p<0.001; I-squared 11%)and birth weight (WMD 79.05 g, 95% CI: 13.23, 144.77, p=0.02; I-squared 50.5%) compared with control. One further study (2,002 participants) did not include women in their first pregnancy; this study found IPT to reduce maternal parasitaemia at delivery compared with control, but there was no significant difference in the effects on other outcome measures.

IPT 2-dose compared with IPT monthly (3 studies, 1,529 participants): all 3 studies included HIV-positive women (2 included both HIV-positive and HIV-negative women). They found that monthly IPT gave greater reduction in placental malaria (RR 0.34, 95% CI: 0.18, 0.64, p<0.01; I-squared 0%), peripheral parasitaemia (RR 0.24, 95% CI: 0.14, 0.44, p<0.01; I-squared 0%) and greater increase in mean birth weight (WMD 112 g, 95% CI: 19, 205, p=0.02; I-squared 0%) compared with 2-dose IPT in HIV-positive women in their first and second pregnancies. This difference in effect...
was not observed for HIV-positive women with multiple previous pregnancies (1 study). For HIV-negative women, one study performed against a high background resistance to sulfadoxine-pyrimethamine found no difference in the efficacy of the two IPT regimens, while a second study performed against low background resistance found monthly dosing to have a significantly greater effect in reducing peripheral parasitaemia than 2-dose IPT.

Reduction in peripheral parasitaemia (7 studies): in HIV-negative women or those with unknown HIV status, the proportional reduction in peripheral parasitaemia with 2-dose IPT became lowered as the level of background sulfadoxine-pyrimethamine resistance increased, although it remained greater than 60% across the range of resistances studied. This effect of background resistance on 2-dose IPT appeared to be greater in HIV-positive women in their first or second pregnancy (one study found a proportional reduction of only 21% against high background resistance); in contrast, the monthly IPT regimen did not appear to be affected by background resistance.

Adverse events (9 studies): adverse events were not common and rates did not appear to differ between treatment and control groups or between treatment groups. One study reported a higher rate of adverse effects in HIV-positive women than HIV-negative women, whereas another study found no difference. There was one report of a death due to severe reaction to sulfadoxine-pyrimethamine in an HIV-positive woman.

Authors' conclusions
In areas of high sulfadoxine-pyrimethamine resistance (where 1 in 4 treatments in children fail by day 14) 2-dose IPT is effective for HIV-negative semi-immune pregnant women, but more frequent dosing is needed for HIV-positive women not using cotrimoxazole prophylaxis.

CRD commentary
The review question and inclusion criteria were clear. The search for primary studies was thorough: a wide range of databases was searched without language restrictions and efforts were made to obtain unpublished studies. The quality of the included studies was assessed, and the results of this assessment considered within the analysis of the study results. It was not reported whether steps were taken to minimise the introduction of errors and bias during the study selection, quality assessment and data extraction, for example, through the use of two independent reviewers.

The studies were combined using appropriate methods and possible sources of heterogeneity, in this case the focus of the review was background resistance to the treatments, were investigated. Although this review was generally well-conducted, there are some limitations to be considered when interpreting the authors' conclusions. First, the conclusions were drawn from only one or two of the included studies, those conducted in high resistance areas. Second, the level of background resistance was not taken from the included studies but was estimated from treatment studies that were matched to them, and the accuracy of this estimation is unknown. Therefore, the conclusions may not be reliable.

Implications of the review for practice and research
Practice: The authors stated that increasing the frequency of IPT with sulfadoxine-pyrimethamine for pregnant women to three or more doses, particularly in areas with high number of HIV-positive women, may be beneficial.

Research: The authors stated that further studies are needed to clarify whether there is a difference between 2-dose IPT and monthly dosing for HIV-negative women in areas of very high sulfadoxine-pyrimethamine resistance. In addition, high priority must be given to research into safe and affordable alternatives to sulfadoxine-pyrimethamine.

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