**The pendulum of chloroquine chemoprophylaxis for malaria in pregnancy:**

**New evidence from Malawi**

R Matthew Chico and Feiko O ter Kuile

R Matthew Chico, London School of Hygiene & Tropical Medicine, London WC1E 7HT, UK

Feiko O ter Kuile, Liverpool School of Tropical Medicine, Liverpool, L3 5QA, UK

Words = 754
References = 13

Malaria is among the most common preventable causes of adverse pregnancy outcomes. WHO recommends intermittent preventive treatment (IPTp) with sulphadoxine-pyrimethamine (SP) for HIV-negative women, however, parasite resistance now threatens its effectiveness. Over the past decade, researchers have investigated alternative strategies using screen and treat approaches, and using alternative drugs to replace SP, but results were mostly disappointing.1 Apart from dihydroartemisinin-piperaquine,2,3 all other options, including low-dose mefloquine,4,5 amodiaquine,6 and a fixed dose-combination of chloroquine-azithromycin,7 were too poorly tolerated for IPTp. It is unclear in the latter trial whether poor tolerability resulted from the high dose of azithromycin (3g/course), from chloroquine, or from their combination. A planned interim analysis showed no differences in sub-optimal pregnancy outcomes relative to IPTp-SP, and the trial was terminated early on grounds of futility.7 Consequently, it was underpowered to test whether the degree of chloroquine resistance, which varied widely between the five participating countries, modified the impact. Thus, a key question remained unanswered: Could chloroquine be re-considered for preventive use in countries with high-grade SP resistance and where chloroquine susceptibility had returned? Malawi was the first country in Africa to report renewed parasite sensitivity to chloroquine about eight years after withdrawing its use in 1993 in favour of SP.8 The same phenomenon has since been observed elsewhere in the region. Chloroquine for antenatal chemoprevention, rather than dihydroartemisinin-piperaquine, would allow artemisinins to be reserved for first- and second-line case management. Furthermore, chloroquine has well-established dosing and safety profiles for treatment and chemoprophylaxis, including in the first trimester when SP is contra-indicated, but when malaria is an important risk factor for adverse pregnancy outcomes.9

In this issue, Divala and colleagues[ref] report the long-awaited results of a three-arm trial conducted among 900 HIV-uninfected women in Malawi. Chloroquine monotherapy was given either as two-course IPTp, or as weekly chloroquine chemoprophylaxis, and compared against two-course IPTp-SP, which was the standard at that time of the study. Despite well-documented high-grade SP resistance in the study area, IPTp-chloroquine was no better than SP in preventing placental malaria, the primary outcome (RR=1.00). However, when provided as weekly chemoprophylaxis, the prevalence was 25% lower (*P*=0.24), and 36% lower (*P*=0.01) when qPCR was considered. The risk of clinical malaria was also 78% lower. This reduction in clinical malaria is similar to that observed in the two recent trials with IPTp-dihydroartemisinin-piperaquine, but the 36% reduction in placental malaria is much more modest than the 65% achieved with three courses of dihydroartemisinin-piperaquine.1-3 The lack of any difference between IPTp-SP and IPTp-chloroquine and the relatively modest superior effect of weekly dosing is surprising as each dose was supervised and all infections at enrolment were chloroquine-susceptible.

Like previous studies with mefloquine, amodiaquine and chloroquine-azithromycin, IPTp-chloroquine was poorly tolerated with 31% of women reporting at least one treatment-related adverse event, compared to 1% in the SP arm. Dizziness and vomiting were reported most frequently. Pruritus, a common side-effect of chloroquine therapy in dark-skinned people, was not reported on the list of adverse events. Low tolerance of the two-course regimen precludes evaluating more frequent monthly dosing with chloroquine as IPTp. As chemoprophylaxis however, chloroquine was much better tolerated, consistent with older trials,10 although the number reporting at least one adverse event was still 6.5 times higher than with IPTp-SP (*P*<0.0001).

Similar to trials with dihydroartemisinin-piperaquine and mefloquine, the reductions in placental malaria did not translate into fewer cases of low birthweight relative to IPTp-SP. One potential explanation is the potential protective effect of SP against non-malarial causes of adverse pregnancy outcome. SP has broad-spectrum anti-bacterial activity against Gram-positive bacteria.11 Furthermore, sulphadoxine is from the group of sulphonamides historically used to treat *Neisseria gonorrhoeae*, *Chlamydia trachomatis*, *Trichomonas vaginalis*, and *Gardnerella vaginalis*, a bacterium commonly associated with bacterial vaginosis. Although SP is unlikely curative of STIs/RTIs, it may reduce pathogen loads and maternal inflammatory responses.12 The performance of IPTp-SP is all the more interesting given that chloroquine has well-known anti-inflammatory properties,13 which may have improved pregnancy outcomes in the trial without altering non-malarial pathogen loads.

Although there is need for more effective malaria chemoprevention strategies in pregnancy in East and Southern Africa, the evidence from the current trial is unlikely to swing the pendulum back in favour of chloroquine chemoprophylaxis. Nevertheless, with the return of chloroquine susceptibility in many parts of Africa, its use in the first trimester may be worth exploring further. It remains to be determined if IPTp-dihydroartemisinin-piperaquine in the second and third trimester is better than SP at reducing adverse pregnancy outcomes. If we can learn anything from this and the recent series of trials it is to temper our expectations.

We declare no competing interests.

References

1. Desai M, Hill J, Fernandes S, et al. Prevention of malaria in pregnancy. *The Lancet Infectious diseases.* 2018;18(4):e119-e132.

2. Desai M, Gutman J, L'Lanziva A, et al. Intermittent screening and treatment or intermittent preventive treatment with dihydroartemisinin-piperaquine versus intermittent preventive treatment with sulfadoxine-pyrimethamine for the control of malaria during pregnancy in western Kenya: an open-label, three-group, randomised controlled superiority trial. *Lancet.* 2015.

3. Kakuru A, Jagannathan P, Muhindo MK, et al. Dihydroartemisinin-Piperaquine for the Prevention of Malaria in Pregnancy. *N Engl J Med.* 2016;374(10):928-939.

4. Briand V, Bottero J, Noel H, et al. Intermittent treatment for the prevention of malaria during pregnancy in Benin: a randomized, open-label equivalence trial comparing sulfadoxine-pyrimethamine with mefloquine. *The Journal of infectious diseases.* 2009;200(6):991-1001.

5. Gonzalez R, Mombo-Ngoma G, Ouedraogo S, et al. Intermittent preventive treatment of malaria in pregnancy with mefloquine in HIV-negative women: a multicentre randomized controlled trial. *PLoS Med.* 2014;11(9):e1001733.

6. Clerk CA, Bruce J, Affipunguh PK, et al. A randomized, controlled trial of intermittent preventive treatment with sulfadoxine-pyrimethamine, amodiaquine, or the combination in pregnant women in Ghana. *The Journal of infectious diseases.* 2008;198(8):1202-1211.

7. Kimani J, Phiri K, Kamiza S, et al. Efficacy and Safety of Azithromycin-Chloroquine versus Sulfadoxine-Pyrimethamine for Intermittent Preventive Treatment of Plasmodium falciparum Malaria Infection in Pregnant Women in Africa: An Open-Label, Randomized Trial. *PloS one.* 2016;11(6):e0157045.

8. Laufer MK, Thesing PC, Eddington ND, et al. Return of chloroquine antimalarial efficacy in Malawi. *N Engl J Med.* 2006;355(19):1959-1966.

9. Rogerson SJ, Desai M, Mayor A, Sicuri E, Taylor SM, van Eijk AM. Burden, pathology, and costs of malaria in pregnancy: new developments for an old problem. *The Lancet Infectious diseases.* 2018;18(4):e107-e118.

10. 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. *The American journal of tropical medicine and hygiene.* 1996;55(1 Suppl):50-56.

11. Capan M, Mombo-Ngoma G, Makristathis A, Ramharter M. Anti-bacterial activity of intermittent preventive treatment of malaria in pregnancy: comparative in vitro study of sulphadoxine-pyrimethamine, mefloquine, and azithromycin. *Malaria journal.* 2010;9(1):303.

12. Chico RM, Chaponda EB, Ariti C, Chandramohan D. Sulfadoxine-pyrimethamine exhibits dose-response protection against adverse birth outcomes related to malaria and sexually transmitted and reproductive tract infections. *Clinical Infectious Diseases.* 2017;64(8):1043-1051.

13. Savarino A, Boelaert JR, Cassone A, Majori G, Cauda R. Effects of chloroquine on viral infections: an old drug against today's diseases? *Lancet Infectious Diseases.* 2003;3(11):722-727.