Back to chloroquine for malaria prophylaxis in pregnancy?

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Malaria is among the most common preventable causes of adverse pregnancy outcomes. WHO recommends intermittent preventive treatment in pregnancy with sulfadoxine-pyrimethamine for HIV-negative women; however, parasite resistance now threatens the effectiveness of this approach. Over the past decade, researchers have investigated alternative strategies, including screen-and-treat approaches and drugs for intermittent use to replace sulfadoxine-pyrimethamine, but results were mostly disappointing.[1] Apart from dihydroartemisinin-piperaquine,[2,3] all other options— including low-dose mefloquine, amodiaquine, and a fixed dose-combination of chloroquine-azithromycin[1-4]— were too poorly tolerated for intermittent treatment in pregnancy. It is unclear in the trial of chloroquine azithromycin whether poor tolerability resulted from the high dose of azithromycin (3 g per course), chloroquine, or their combination. A planned interim analysis showed no differences in suboptimum pregnancy outcomes relative to intermittent sulfadoxine-pyrimethamine, and the trial was terminated early on grounds of futility.[4] As a result, the study was underpowered to test whether the degree of chloroquine resistance, which varied widely between the five participating countries, modified the effect. Thus, a key question remained unanswered: could chloroquine be reconsidered for preventive use in countries with high-grade sulfadoxine-pyrimethamine resistance and where chloroquine susceptibility had returned?

Malawi was the first country in Africa to report renewed parasite sensitivity to chloroquine, about 8 years after withdrawing its use in 1993 in favour of sulfadoxine-pyrimethamine.[5] Chloroquine for antenatal chemoprevention, rather than dihydroartemisinin-piperaquine, would have the advantage of allowing the latter, an artemisinin-based combination therapy, to be reserved for first-line and second-line case management. Furthermore, chloroquine has well established dosing and safety profiles for treatment and chemoprophylaxis, including in the first trimester when sulfadoxine-pyrimethamine is contraindicated but when malaria is an important risk factor for adverse pregnancy outcomes.[6]

In *The Lancet Infectious Diseases*, Titus Divala and colleagues[7] report the results of a three-arm randomised trial undertaken in 900 HIV-uninfected women in Malawi. Chloroquine monotherapy was given either as two-course intermittent preventive treatment or as weekly prophylaxis and compared with two-course intermittent sulfadoxine-pyrimethamine, which was the standard treatment at the time of the study. Despite well-documented high-grade sulfadoxine-pyrimethamine resistance in the study area, intermittent chloroquine was no better than sulfadoxine-pyrimethamine in preventing

placental malaria confirmed by histopathology (relative risk [RR] 1·00, 95% CI 0·67–1·50). When provided as weekly prophylaxis, the prevalence of placental malaria by histopathology was 25% lower in univariate analysis (RR 0·75, 95% CI 0·48–1·17; p=0·24), and 34% lower after adjusting for confounding (RR 0·66, 0·46–0·95; p=0·027). The risk of clinical malaria was also 78% lower with chloroquine prophylaxis compared with intermittent sulfadoxine-pyrimethamine (two vs nine cases; RR 0·22, 95% CI 0·05–0·90; p=0·063). This reduction in clinical malaria is similar to that seen in the two trials of intermittent preventive treatment in pregnancy with dihydroartemisinin-piperaquine, but the 25% reduction in placental malaria is much more modest than the 65% achieved with three courses of dihydroartemisinin-piperaquine.[1-3] The absence of any difference between intermittent preventive treatment with sulfadoxine-pyrimethamine and intermittent chloroquine, and the relatively modest superior effect of weekly prophylaxis, is surprising, because a loading dose was given, each dose was supervised, and all infections at enrolment were chloroquine susceptible.

Similar to previous studies with mefloquine, amodiaquine, and chloroquine-azithromycin, intermittent chloroquine was poorly tolerated, with 94 (31%) of 300 women reporting at least one treatment-related adverse event, compared with four (1%) of 300 assigned sulfadoxine-pyrimethamine. Dizziness (n=57) and vomiting (n=50) were reported most frequently. Low tolerance of the two-course intermittent regimen precludes assessing a strategy of more frequent monthly dosing with chloroquine. As prophylaxis, however, chloroquine was much better tolerated, consistent with findings of older trials,[8] although the number reporting at least one adverse event was still higher than with intermittent sulfadoxine-pyrimethamine (RR 6·5, 95% CI 2·4–17·7; 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 intermittent sulfadoxine-pyrimethamine. One possible explanation is the potential protective effect of sulfadoxine-pyrimethamine against non-malarial causes of adverse pregnancy outcomes. Sulfadoxine-pyrimethamine has broad-spectrum antibacterial activity against Gram-positive bacteria.[9] Furthermore, sulfadoxine is from the group of agents used to treat *Neisseria gonorrhoeae*, *Chlamydia trachomatis*, *Trichomonas vaginalis*, and *Gardnerella vaginalis*, a bacterium associated commonly with bacterial vaginosis. Although sulfadoxine-pyrimethamine is unlikely to be curative of sexually transmitted infections or reproductive tract infections, it might reduce pathogen loads and maternal inflammatory responses.[10] The performance of intermittent preventive treatment in pregnancy with sulfadoxine-pyrimethamine is noteworthy because chloroquine has well-known anti-inflammatory properties, which could have improved pregnancy outcomes in the trial without altering non-malarial pathogen loads.

Although there is a need for more effective malaria chemoprevention strategies in pregnancy in east and southern Africa, evidence from the trial by Divala and colleagues is unlikely to swing the pendulum back in favour of chloroquine prophylaxis. Nevertheless, with the return of chloroquine susceptibility in many parts of Africa, use of chloroquine in the first trimester might be worth investigating further. Future studies are needed to ascertain if intermittent preventive treatment in pregnancy with dihydroartemisinin-piperaquine in the second and third trimesters is better than sulfadoxine-pyrimethamine at

reducing adverse pregnancy outcomes. If we can learn anything from this study and other trials, it is to temper our expectations.

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References

1. Desai M, Hill J, Fernandes S, et al. Prevention of malaria in pregnancy. *Lancet Infect Dis.* 2018.
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;386(10012):2507-2519.
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. 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.
5. Laufer MK, Thesing PC, Eddington ND, et al. Return of chloroquine antimalarial efficacy in Malawi. *N Engl J Med.* 2006;355(19):1959-1966.
6. 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. *Lancet Infectious Diseases.* 2018.
7. Divala TH, Mungwira RG, Mawindo PM, et al. Chloroquine as chemoprophylaxis every week or intermittent treatment to prevent malaria in pregnancy in Malawi: a randomised controlled trial. *Lancet Infect Dis.* 2018;S1473-3099(18)30415-8.(http://dx.doi.org/10.1016/).
8. 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. *Am J Trop Med Hyg.* 1996;55(1 Suppl):50-56.
9. 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. *Malar J.* 2010;9:303.
10. 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.