**Towards intermittent preventive therapy in pregnancy with dihydroartemisinin-piperaquine?**

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**Introduction:** Malaria is a major cause of adverse pregnancy outcomes in sub-Saharan Africa, but resistance to sulfadoxine-pyrimethamine, the only antimalarial recommended by the World Health Organisation for intermittent preventive therapy, is threatening the gains made in the last two decades. In this issue, Mlugu and colleagues present the results of a trial of dihydroartemisinin-piperaquine as an alternative to sulfadoxine-pyrimethamine. The results are impressive but raise the question why they differ so much from three previous trials.

**Main text:** The World Health Organisation (WHO) recommends intermittent preventive therapy for the control of malaria in pregnancy (IPTp) in malaria-endemic countries. Sulfadoxine-pyrimethamine (SP) is currently the only antimalarial recommended by WHO for IPTp. Approximately 33 African countries have adopted this strategy. However, its efficacy is threatened by high-grade resistance of the malaria parasite *Plasmodium falciparum* to SP. This is a particular challenge in East and Southern Africa, especially in two resistance hotspots in the northeast and northwest of Tanzania, where about half the parasites carry the sextuple *dhfr/dhps* mutant haplotype containing the *Pfdhps* A581G mutations, which are highly resistant to SP.1 Even in areas with less mutated parasites, were the quintuple-mutant haplotype is highly prevalent, SP fails to clear existing infections in about 30 to 45% of pregnant women who are parasitaemic when they receive their first course of SP for IPTp,2 resulting in the persistence of placental infections and associated harm. This level of resistance also results in a significant shortening of the duration of post-treatment prophylaxis, placing women at risk of new infections before the next monthly dose of SP is due.

To address these concerns, Tanzania introduced a national policy combining IPTp-SP with screen-and-treat approaches. As part of this hybrid strategy, all women, regardless of symptoms, are screened for malaria infection by rapid diagnostic tests (RDTs) at the first antenatal clinic visit. RDT-positive women then receive first-line case management drugs, such as artemether-lumefantrine, an artemisinin-based combination therapy (ACT). The first course of IPTp with SP is then provided at the subsequent scheduled visit.3 The efficacy of this hybrid strategy is unknown but is likely to be more effective than IPTp-SP alone because most existing infections should be cleared by artemether-lumefantrine. Furthermore, the sensitivity of the current generation of RDTs to detect PCR-positive malaria infections exceeds 80% in primigravidae during these first antenatal visits (mostly in the 2nd trimester), when the malaria parasite prevalence and densities tend to be highest.4

Concerns about IPTp-SP efficacy have led to a series of IPTp trials exploring alternative long-acting antimalarials, including chloroquine, amodiaquine, mefloquine, and piperaquine (as dihydroartemisinin-piperaquine [DP]). These showed that none were suitable for IPTp due to their poor tolerability when given at full treatment doses to asymptomatic women. The exception is DP, which is currently the only promising alternative candidate for use as IPTp. To date, three trials conducted in high-resistance areas in Kenya and Uganda have shown that IPTp-DP is much more effective than IPTp-SP in reducing malaria during pregnancy,5,6,7 especially when given monthly,7 resulting in 60 to 90% fewer malaria infections than IPTp-SP. However, no differences were detected in clinical outcomes such as preterm delivery or low birth weight.8 An individual patient data (IPD) meta-analysis involving 1,617 women showed that the birthweights were 69 grams (95% CI 26-112) higher in the SP arms, even though these newborns were born to pregnancies exposed to much more malaria, suggesting that SP has potent non-malaria effects on fetal growth.8 In 2015, WHO recommended that further trials were needed to compare the effect of IPTp-DP versus SP on adverse pregnancy outcomes.

In this issue, Mlugu and colleagues present the results of the fourth trial comparing monthly IPTp-SP vs monthly IPTp-DP. The trial took place in southeast Tanzania in an area with moderate malaria transmission and a high prevalence of the quintuple mutant parasites but a low prevalence of the sextuple mutants (e.g. <5%). This degree of resistance was similar to those documented in the study sites of the three published trials in Kenya and Uganda.5,6,7

Consistent with these previous trials, the investigators found that DP was much more effective than SP at reducing the risk of malaria. The prevalence of placental malaria (active or past infection detected by histopathology) (primary endpoint) was 69% lower with DP. The incidence of clinical malaria and any malaria infection during pregnancy was also reduced by 86% and 65%, respectively. However, contrary to the previous trials, IPTp-DP was also more effective in preventing adverse pregnancy outcomes, a secondary endpoint consisting of the composite of LBW, premature birth, spontaneous abortion, or stillbirth. These occurred in 13.2% of participants receiving monthly SP versus 5.4% in those receiving DP, a relative risk reduction of 59% (95% CI 36-73, P<0.001). The effect was observed in primigravidae (58%) and multigravidae (59%). This effect on the adverse pregnancy outcomes primarily reflected a 51% reduction in LBW (95% CI 22-73, p=0.003), the most common component of the composite. In contrast to the previous trials, newborns weighed on average 55 grams more (rather than less) in the DP arm than the SP arm.

These are impressive results that could have potential policy implications but raises the question why they differ so much from the three published trials that each failed to show an impact on birthweight? The study arms were well balanced for potential confounders of the effect on adverse pregnancy outcomes. However, as in all studies, residual confounding due to unmeasured factors cannot be excluded. Could SP have been even less effective at preventing malaria than in Kenya and Uganda? Unlikely because the study was conducted in southern Tanzania with similar degrees of SP resistance to those observed in Kenya and Uganda. Daily supplementation with high dose folic acid (e.g. with 5mg tablets, commonly used in Africa) counteracts the antimalaria effects of SP. However, the standard dose of folic acid was used (0.5 mg daily), which is known not to interact with SP. The SP used was also quality controlled and procured and stored by the Government’s Medical Stores Department in Tanzania.

A variation in treatment effect between studies is to be expected due to sampling variability (chance) and real differences in the treatment effect in each study, e.g., due to differences in background rates of malaria transmission or parasite resistance, or differences in study design, etc. Could these explain the observed differences? One would expect that the more malaria transmission, the greater the potential benefit of an effective malaria intervention like monthly DP. Malaria is one of the most important contributors to low birth weight in malaria-endemic Africa, especially in primigravidae. Thus, it would be tempting to conclude that the observed reduction in LBW reflects the notable reductions in malaria in the DP arm. However, it is unlikely that reductions in malaria alone explain a reduction in LBW of 51% overall, including a 65% reduction in primigravidae and a 45% in multigravidae. Even if DP prevented all malaria infections, this would exceed what can reasonably be expected based on the population attributable fraction of malaria as a cause of LBW in these moderate malaria transmission areas. Over 90% of trial participants used insecticide-treated nets during pregnancy, and only 21% of women in the SP arm had evidence of malaria infection at delivery detected by either placental histology, PCR, RDT or microscopy.

Furthermore, only 45 women (4.2%) of participants had patent malaria infection (detected by RDT) when screened for eligibility at enrolment, a good proxy of malaria transmission intensity.3 By contrast, 51% of pregnant women had patent malaria infections (detected by microscopy) in Uganda’s most recent IPTp trial that used the same monthly regimen.7 Mlugu and colleagues excluded these 45 women because they had received artemether-lumefantrine as part of Tanzania’s hybrid strategy. By doing so, the investigators likely excluded a sub-group of women most at risk of malaria for biological (e.g. primigravidae, age), environmental or behavioural reasons (e.g. malaria exposure). In this respect, the study design did differ notably from the previous studies. At least in part, it could provide a potential explanation of the observed difference in treatment effect on birthweight if patent malaria infections early in pregnancy (i.e. before enrolment) causes irreversible malaria-associated damage to placental function. There is increasing evidence that exposure to malaria in early pregnancy is associated with significant harm in later pregnancy, even after prompt treatment of the initial infection with effective antimalarials. For example, before 24 weeks gestation, malaria infection has been associated with dysregulation of essential regulators of angiogenesis, metabolism, and inflammation and an increased risk of preterm birth.9 Other studies found that these early infections also cause delayed effects on fetal growth in later pregnancy when nutrient requirements are highest.10 Thus, if a large proportion of participants is exposed to malaria earlier in pregnancy before they enrol in a trial, like the 51% in Uganda,7 it could reduce the impact of an intervention on fetal growth when compared to trials where all women with patent infection at enrolment are excluded from enrolment, like in the current trial by Mlugu and colleagues. This would be particularly true if catch-up growth is absent or only partially achieved10 despite the intervention being very effective at clearing existing infections and preventing reinfections. However, it is unlikely to fully explain these large observed differences as previous trials of ITNs or malaria chemoprophylaxis typically show the greatest benefits from malaria prevention are achieved in the sub-groups at highest risk of malaria, such as primigravidae and adolescents.

Although the differences in results with the previous trials are not easily explained, this trial by Mluge and colleagues provides an important contribution to the limited arsenal of available studies that assess the impact of DHA-PiP as an alternative to SP. It confirms that DP is well tolerated as IPTp and is the better antimalarial. However, the jury is still out whether IPTp with DP results in better birth outcomes than SP. Any switch away from IPTP with SP, which can be given monthly as a single-day dose of 3 tablets as directly observed therapy in the antenatal clinic, to more complex 3-day IPTp regimens with DP needs to be well justified. Hopefully, we should have more insight within the coming year as a further two trials were recently completed in East and Southern Africa (including in sites with a high prevalence of the highly SP resistant sextuple mutant parasites in northern Tanzania) (NCT03009526, NCT03208179). A further two trials in Nigeria may reach completion in 2022 (PACTR202002644579177, PACTR201808204807776). An IPD meta-analysis of these trials is planned (PROSPERO 2020 CRD42020196127). If the combined evidence suggests that SP has a potent non-malarial effect on fetal growth,8 then perhaps further IPTp studies of the combination of DP and SP are worth considering. Preliminary research to answer this question is ongoing (NCT04336189). The introduction by Tanzania of the current hybrid strategy that combines the clearance effects of ACTs at the first ANC visit in the second and third trimester with subsequent IPTp-SP seems like a sensible approach during the interim period.

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