



Published in final edited form as:

Clin Infect Dis. 2012 October ; 55(8): 1103–1105. doi:10.1093/cid/cis604.

Intermittent Preventive Treatment in Pregnancy With Sulfadoxine–Pyrimethamine: The Controversy Continues

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Each year, approximately 32 million pregnancies occur in malaria-endemic areas of Africa [1]. Malaria in pregnancy (MiP) is a serious condition that contributes to both maternal and infant morbidity and mortality. It is estimated that up to 200 000 infant deaths occur annually as a result of MiP (<http://www.who.int/features/2003/04b/en/>). In order to decrease the risk of *Plasmodium falciparum* infection in pregnancy and subsequent morbidity and mortality, the World Health Organization (WHO) recommends intermittent preventive treatment in pregnancy (IPTp) with at least 2 doses of sulfadoxine-pyrimethamine (SP) 1 month apart after quickening. As resistance of *Plasmodium falciparum*, the most important malaria species in MiP, to SP has increased in the past 2 decades with a concomitant decrease in the efficacy of SP for treatment of children <5 years of age, the continued benefit of providing IPTp-SP has been questioned [2]. IPTp-SP continues to provide benefit to mothers and infants in areas where the rate of treatment failure in children is up to 39% [3]; however, where treatment failure rates are higher, and when coverage with insecticide-treated bednets is high, IPTp-SP appears to provide less benefit [4, 5]. More worrisome are data from Muheza, Tanzania, suggesting that IPTp-SP may be harmful, exacerbating placental malaria and contributing to fetal anemia [6, 7]. If this finding is replicated in other areas, it will have significant implications, as it would suggest that the practice of providing IPTp-SP to women in areas with high levels of SP resistance should be discontinued immediately, rather than continuing this practice until an alternate drug for prophylaxis in pregnancy is found.

In this issue of *Clinical Infectious Diseases*, Rogawski et al provide reassuring data from a large retrospective delivery cross-sectional study in Malawi that IPTp-SP is not associated with fetal anemia or cord hemoglobin concentration [8]. There was no evidence that this lack of association changed over time as SP resistance increased. Furthermore, their data suggest that IPTp-SP continues to provide some beneficial effect, as evidenced by the finding that malaria parasitemia at delivery had the largest effect on fetal anemia among primigravid women who did not take SP and no significant effect among multigravid women whether or not they took SP. This is consistent with what has been reported

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Potential conflicts of interest. Author certifies no potential conflicts of interest.

The author has submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

previously; IPTp-SP has been shown to be beneficial in primigravid and secundigravid women, but it remains unclear whether there is a benefit to women of higher gravidity [9]. The fact that IPTp-SP may still confer some benefit to primigravid women in Malawi is an important finding, especially in light of the fact that Malawi has high levels of molecular resistance to SP, with nearly 100% saturation of quintuple mutants, although mutations such as *dhps* 581 or *dhfr* 164, which are associated with higher level SP resistance, are still rare [10]. This suggests that although it is necessary to explore alternative therapies to IPTp-SP, it need not be abandoned yet.

It is important to note that other studies that have examined the issue of fetal anemia following maternal SP use have also found that IPTp-SP decreases, not increases, the prevalence of fetal anemia [5, 11]. The reason for the discrepancy between these studies and the study conducted in Muheza may have to do with the extremely high level of resistance found in the Muheza area, with 14-day treatment failure rates in children of 68% (no recent studies in children have been done in Malawi to compare with this) or with the relatively higher proportion of *dhps* 581 mutations in Muheza than can be found in other study sites. The data from Muheza suggesting that SP is responsible for the fetal anemia are convincing: cord sulfa concentration was found to inversely correlate with cord hemoglobin levels. However, of the 880 women studied, cord samples for sulfa analysis were available from 847 and IPTp-SP history was available from 826, but only 685 are used in the analysis of fetal hemoglobin. It is unclear how this subset was identified for analysis, and whether this could have affected the results.

Another issue to consider in future studies examining the effectiveness of IPTp-SP is which women should be included. Initial studies of IPTp-SP focused on primigravid and secundigravid women, as they have the least pregnancy-specific malaria immunity, and so are at the greatest risk [12]. As insecticide-treated bednet coverage and other malaria interventions are scaled up and transmission declines, it is likely that the effects of MiP will increasingly be seen in women of higher gravidity. However, if we really want to evaluate whether IPTp-SP continues to reduce the burden of MiP, we should choose the women most likely to benefit and exclude multigravid women, otherwise we run the risk of diluting our ability to observe an effect.

It is clear that in areas of high level SP resistance, IPTp-SP no longer provides the same degree of benefit that it once did, and that it is imperative to search for alternatives to prevent MiP [4, 5]. SP can be given as a single dose, it is extremely cost-effective, and there is a long experience of its use in pregnancy showing it to be safe. As the currently available best options (mefloquine, dihydroartemisinin-piperaquine, and azithromycin-chloroquine) are certainly much more expensive than SP, it remains to be seen how feasible it will be to implement any of these at scale across sub-Saharan Africa. In addition, of these options, only mefloquine can possibly be given as a single dose (and it is unclear whether mefloquine as a single dose will be tolerated by the majority of pregnant women), thus directly observed therapy administered at antenatal clinics will no longer be a practical option. Given the difficulties with the other options, IPTp-SP should be continued as long as it provides benefit, ideally with 3 doses delivered during the course of pregnancy [13]. Countries where

SP is used for IPTp should prioritize monitoring SP resistance using the standardized protocol, to allow for a change in policy when IPTp-SP ceases to be beneficial.

Despite the fact that most sub-Saharan African countries have high antenatal clinic attendance and have had a written policy recommending IPTp-SP since 2004, coverage of 2 doses remains woefully inadequate (<60% in the majority of countries) [14]. Various factors have been proposed to explain this, including stock-outs of SP, confusion among healthcare workers about when SP is safe and when to give it, and multiple versions of guidelines in countries indicating different recommendations. It is likely that the continued debate over the safety and efficacy of IPTp-SP contributes to a lack of political will and traction for promoting what ought to be a very simple intervention.

Intermittent screening and treatment during pregnancy (ISTp) is an alternative strategy comprising a rapid diagnostic test at each antenatal clinic visit and treatment of only those women who test positive. This has the benefit of exposing only those women who actually have malaria to a drug, thus limiting the risks of adverse effects. An initial study in Ghana which looked at ISTp-SP and ISTp with amodiaquine plus artesunate compared with IPTp-SP suggests that this may be a promising strategy, but further studies looking at additional drugs and settings are needed before this can be widely recommended [15]. Until such a time as a feasible alternative to IPTp-SP exists, and as long as there is evidence of some beneficial effect, a clarification of the guidelines with a change to recommend provision of IPTp-SP at each antenatal clinic visit could go a long way toward increasing coverage of this intervention.

Acknowledgments

Disclaimer. The findings and conclusions in this report are those of the author and do not necessarily represent the official position of the Centers for Disease Control and Prevention.

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