Protecting Pregnant Women from Malaria in Areas of High HIV Infection Prevalence

Steven R. Meshnick, Victor Mwapasa, and Stephen J. Rogerson

Departments of Epidemiology and Microbiology, University of North Carolina, Chapel Hill; Department of Community Health, College of Medicine, Blantyre, Malawi; Department of Medicine, University of Melbourne, Parkville, Victoria, Australia

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In the early 19th century, much of the map of Africa consisted of blank spaces—regions uncharted by Europeans. Now, 200 years later, our geographical knowledge of Africa is superb, but there are many uncharted regions in our knowledge of diseases that are endemic there.

The HIV and malaria epidemics overlap in sub-Saharan Africa. These are also particularly serious reproductive-health problems, imperiling the 18 million women who become pregnant each year in this region [1]. Up to 66% of pregnant women will become infected with *Plasmodium falciparum* [2, 3], leading to poor obstetrical outcomes such as low birth weight. The median reported prevalence of HIV infection in 21 sub-Saharan African countries was 11.4% in 2002–2003 [4]. Thus, many pregnant women will be coinfected with malarial parasites and HIV. Each disease exacerbates the other: malarial parasite–infected pregnant women have increased HIV loads [5], whereas HIV-infected pregnant women have reduced antimalarial immunity [6] and higher prevalences of malaria [7–9]. Nevertheless, there is a paucity of evidence on which to base policies to protect HIV-infected pregnant women from malaria and other opportunistic infections.

Intermittent preventive treatment during pregnancy (IPTp) for malaria is clearly effective. The World Health Organization (WHO) recommends at least 2 treatment doses of sulfadoxine-pyrimethamine (SP) for all pregnant women during the course of their pregnancy [10]. However, a study by Parise et al. in 1998 [11] suggested that 2 doses might be inadequate for HIV-infected women. The article by Filler et al. [12] in this issue of the *Journal of Infectious Diseases* tests the hypothesis that monthly doses of SP might be more effective than 2 doses of SP for the prevention of malaria in both HIV-uninfected and -infected pregnant women.

In this article, the US Centers for Disease Control and Prevention malaria group and their Malawian colleagues describe a randomized, controlled study of monthly SP versus 2-dose SP in of 266 HIV-positive and 432 HIV-negative pregnant women. Importantly, only 195 HIV-infected and 303 HIV-uninfected women could be evaluated for the primary outcome, placental parasitemia. Women who received monthly SP had a lower incidence of placental parasitemia than women who received the 2-dose SP standard of care, and the reduction in relative risk was similar for HIV-infected and -uninfected women. No significant impact was seen on birth outcome or maternal anemia, but the study was not powered to examine these end points.

However, there is a caveat to the study that needs to be stated. Women in the monthly treatment arm received their last dose of SP an average of 15 days before delivery, whereas women in the 2-dose arm received their last dose of sulfadoxine an average of 58 days before delivery (Filler et al., unpublished data). Because sulfadoxine has a half-life of 8 days [13], women in the monthly arm would have had significant concentrations of sulfadoxine in their plasma at the time of delivery, whereas women in the 2-dose arm would not have. Therefore, the absence of parasites in blood smears from women in the monthly arm could simply have been due to the concurrent presence of sulfadoxine. Although placental parasitemia is usually a good surrogate for the effects of malaria on pregnant women, it may not be so under these circumstances. Thus, a reason why monthly SP had no effect on birth outcome might be that SP was simply masking placental parasitemia. To this end, it would have been helpful if the investigators had also collected placental biopsy samples at delivery, because histological testing is more sensitive at revealing...
low-density infection, and it can also reveal hemozoin (malaria pigment), a marker of past infection [14].

There was one other beneficial effect of monthly SP seen in the study: women in the monthly arm had significantly fewer episodes of malaria than women in the 2-dose arm. There were 66% and 50% reductions in risk observed in HIV-positive and -negative women, respectively. But this was a secondary outcome, and it might also have been the result of increased plasma drug levels at the time of antenatal clinic visits. Also, although symptomatic malarial infections during pregnancy may be significantly more common than previously realized [15], the adverse consequences of these infections for fetal development require characterization.

The relative merit of the monthly regimen is even less certain in light of the results of a recent Zambian study. Hamer et al. [16] compared monthly and 2-dose SP IPTp in HIV-positive women. In that study, the 2-dose and monthly dose groups did not differ in terms of the incidence of malaria or poor birth outcomes. Thus, more research is needed before a monthly regimen can be recommended to policy makers.

In addition to efficacy under controlled conditions, probable effectiveness should be considered. Filler et al. [12] make the important point that a successful preventive regimen must be easily understood to be effectively implemented. We and others working in Malawi have shown that the uptake of SP was poor [17, 18], in part because most antenatal clinic staff did not understand the policy (available at: http://www.cdc.gov/malaria/pdf/MIPESA_Newsletter.pdf; J. Ngoma and S.J.R., unpublished data). Monthly SP is operationally easier to understand and (provided that drug supplies are available) can result in significantly increased uptake of SP.

There are other important lacunae in our understanding of how to best prevent malaria during pregnancy. One is the role of insecticide-treated bed nets (ITNs). In the study by Filler et al., ~15% of women used ITNs at enrollment. There is strong evidence that ITNs successfully decrease the impact of malaria in pregnancy and are beneficial [19, 20]. However, one study suggested little additive benefit from the combination of IPTp and ITNs [21]. Furthermore, there is a paucity of evidence about whether social marketing or the free distribution of ITNs achieves superior coverage [22–24].

HIV-infected pregnant women are also susceptible to opportunistic infections. Another important gap in our knowledge is whether and when they should receive cotrimoxazole (trimethoprim/sulfamethoxazole) prophylaxis. A recent WHO report recommended cotrimoxazole for all HIV-infected adults, including pregnant women, with CD4+ cell counts below a certain threshold (200, 350, or 500 cells/mL, depending on circumstances) [25]. The report recommends that pregnant women receive cotrimoxazole prophylaxis “since the risk of life-threatening infection … outweighs the theoretical risk of congenital abnormalities.” It also recommends that these women should not receive SP IPTp concurrently with cotrimoxazole prophylaxis.

There is some evidence that cotrimoxazole is also an effective antimalarial [26]. However, the risks of cotrimoxazole prophylaxis are far from theoretical. Short-term treatments with cotrimoxazole (10–14 days) have been clearly associated with birth defects when it is administered during the first trimester [27]. Cotrimoxazole administered during the second and third trimester might also have deleterious effects. Antifolates such as trimethoprim cause folate deficiency during pregnancy [28], and dietary folate deficiency during the last 2 trimesters has been linked to preterm delivery and maternal anemia [29–31]. Surprisingly, there have been no studies on the effects that daily prophylaxis with cotrimoxazole has on birth outcomes in pregnant women. Because this agent is now recommended for daily use by >1.5 million women each year, this lack of knowledge is an urgent, critical omission. Would the policy have ever been approved for developed countries?

One final area of uncertainty is whether SP and cotrimoxazole will remain effective against malaria in light of the increasing prevalence of antifolate-resistant parasites [32, 33]. There are no clear-cut replacement candidates for either SP or cotrimoxazole presently in the pipeline.

In sum, current evidence suggests that ITN and IPTp can benefit all pregnant African women exposed to malaria. HIV-infected women are at a particularly high risk of placental malaria, but clear evidence is lacking that cotrimoxazole is safe (especially during early pregnancy) or that more frequent IPTp results in better pregnancy outcomes. Studies such as the one discussed here are far from easy to conduct. Operational and funding hurdles can be enormous. Yet many lives—both of mothers and their unborn children—are at stake. More research is urgently needed.

References


