The Use of Intermittent Preventive Treatment With Sulfadoxine-Pyrimethamine for Preventing Malaria in Pregnant Women

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(See the articles by Maiga et al, on pages 215–223, and Harrington et al, on pages 224–230.)

When a woman is pregnant, especially for the first and second times, she is susceptible to more frequent and severe malaria infections than when she was not pregnant. These infections are associated with maternal anemia, premature deliveries, and low birth weight infants. In areas where malaria is endemic, strategies to control malaria during pregnancy include preventive measures, such as the use of insecticide-treated mosquito nets (ITNs) and intermittent preventive treatment (IPTp), as well as case management as a curative measure.

With regard to IPTp in the African Region, the World Health Organization (WHO) recommends 2 or 3 doses of sulfadoxine-pyrimethamine (SP) that are given during the second and third trimesters, at least 1 month apart [1]. This policy has been accepted by most African countries, and SP is delivered at routine antenatal visits. IPTp is being scaled up through reproductive health programs, particularly with funds from the Global Fund for the fight against Tuberculosis, AIDS, and Malaria.

Results from other trials have shown that an additional dose of SP adds more benefit over the 2-dose regimen among human immunodeficiency virus (HIV)–infected women who are primi- and secundi-gravidæ [2]. Thus, the WHO recommends 2 or 3 doses of IPTp SP, with 3 doses being used where the prevalence of HIV infection among women is high. Some countries, such as Cameroon, have selected 3 doses of SP in their policy for all pregnant women, whereas some countries, such as Mali, chose 2 doses.

In this issue of the journal, Maiga et al [3] report on a randomized clinical trial performed in Mali, which shows the superiority of 3 over 2 doses of IPTp SP for the prevention of placenta malaria and associated low birth weight infants. Mali, as the authors describe, has highly seasonal malaria transmission, moderate levels of ITN use, and low levels of SP resistance. Mali had adopted a 2-dose strategy in 2003. A survey of 1696 pregnant women during 2005–2007 showed that women who completed IPT SP early during the third trimester had reinfections later during the third trimester, meaning that the 2 doses provided insufficient protection. Therefore, the study reported in this issue was undertaken. Results of this randomized clinical trial clearly showed that adding a third dose of SP halved the risk of placenta malaria and low birth weight in all gravidæ, compared with the standard 2-dose regimen. This study has therefore provided evidence that was needed in Mali, to move their policy from 2 to 3 doses.

In the study design, the use of ITNs was not considered as a factor, most likely because Mali has moderate levels of ITN use. Studies from Kenya and the Gambia [2] have shown that IPTp SP provides less benefit to pregnant women who are using ITNs. Thus, increased use of ITNs may overcome the need for a third dose of SP, which would result in less use of SP by the population and, consequently, put less drug pressure on the parasite. Increased drug use and its consequence of drug pressure is an important factor that drives the development of drug-resistant parasites.
Harrington et al [4] report the results of a study performed in Muheza in Tanzania, where they show that IPTp does not confer benefit in an area of widespread drug resistance. According to the WHO, IPTp remains effective in areas where SP treatment failure among children reaches 50%. Muheza is a hot spot for malaria drug resistance. Earlier work by the authors showed that IPTp may exacerbate placental malaria when it fails to prevent infection and, therefore, could worsen some delivery outcomes [5]. Thus, the study described in this issue of the journal was undertaken to explore this potential.

Results are reported from a cross-sectional comparative study on a prospective birth cohort of 718 women who reported having used IPTp and 108 women who reported no IPTp use [4]. Measured plasma sulfa levels were consistent with self-reported SP exposure. Results showed that IPTp was not associated with decreased odds of placenta malaria, mean maternal hemoglobin levels, or neonatal birth weight. They found that IPTp was unexpectedly associated with decreased cord hemoglobin levels and increased risk of fetal anemia. Therefore, IPTp treatment, which in Mali was efficient even with 2 doses and significantly improved with 3 doses, was very inefficient in Muheza. SP resistance is very low in Mali, whereas in Muheza, the 14-day treatment failure rate among children has increased over the past years from 41% to 68%. According to the WHO, IPTp remains effective in areas where SP treatment failure among children reaches 50%. However, in areas, such as Muheza, where it has reached 68%, there is evidence, as described here, that it is no longer effective for IPTp. The study showed that SP was not only ineffective but has been shown to have deleterious effects on cord blood hemoglobin and on fetal anemia, both of which are risk factors for infant mortality. The authors conclude in their abstract that “IPTp does not improve overall pregnancy outcome in Muheza where SP resistant parasites predominate, and may increase the odds of fetal anemia. As parasite resistance increases in a community, the overall effect of IPTp may transition from net benefit to neutral or net harm.” With parasite resistance fast spreading from the eastern to the western regions in Africa, it is important to follow WHO recommendations that appropriate monitoring of the efficacy of SP, as has been done in this study, should be performed to determine when SP needs to be replaced with a more effective antimalaria drug.

Information on ITN use was shown in the results but not discussed. ITN use was not very high in Muheza. In Mozambique, where there is widespread use of ITNs, IPTp had no effect on the prevalence of placenta malaria, maternal anemia, or low birth weight. Harrington et al [4] suggest that the lack of benefit could be attributed to the masking benefits of bed nets, but could equally have been attributable to the loss of SP efficacy in the area. If more of the women in the current study had used ITNs, perhaps fewer women would have had infection, because the masking benefits of ITNs that have been seen in the Gambia, Kenya, and Mozambique could have an effect in reducing numbers of women who become infected.

Harrington, et al [4] hypothesized that in utero SP exposure may suppress hematopoiesis in the fetus. In the study, an inverse relationship was observed between cord sulfa concentration and both cord hemoglobin level and red blood cell counts, supporting their hypothesis. It is very important that future studies be performed to verify this finding, because it could have serious consequences.

The study of Harrington et al [4] brought up a very important point. It is imminent that new and effective drugs and new IPTp regimens be available for use during pregnancy, in the face of increasing drug resistance as resistance to SP is spreading quite fast, and studies such as this one have demonstrated the limitations in the use of this drug. However, as the article reports, new interventions are evaluated against older interventions, which are the standard of care. Ongoing efforts to find effective new IPTp regimens would therefore be compared with SP, which as this study shows, will not be correct. This is an issue that should be studied.

We have seen in the 2 aforementioned articles the improved efficacy of IPTp SP in Mali by the addition of an additional dose of SP [3] and the inefficacy of IPTp SP in Muheza owing to the increased drug resistance in that area [4]. The good news is that SP is still efficacious in

Table 1. Comparison of Malaria Prevalence Before and After Implementation of Intermittent Preventive Treatment (IPTp) in Cameroon

<table>
<thead>
<tr>
<th>Location</th>
<th>IPTp</th>
<th>Percentage of women who were blood smear positive during pregnancya</th>
<th>Percentage of women positive for placental malaria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yaoundé Before</td>
<td></td>
<td>50.5</td>
<td>14.6</td>
</tr>
<tr>
<td>Yaoundé After</td>
<td></td>
<td>8.7</td>
<td>3.1</td>
</tr>
<tr>
<td>Rural Villages</td>
<td></td>
<td>86.8</td>
<td>43.6</td>
</tr>
<tr>
<td>Rural Villages</td>
<td></td>
<td>43.6</td>
<td>14.9</td>
</tr>
</tbody>
</table>

* Slide positive ≥ 1 time during pregnancy, based on at least 4 prenatal visits. Number of women followed-up through pregnancy: before IPTp implementation in Yaoundé (n = 93) and in the villages (n = 39); after IPTp implementation in Yaoundé (n = 409) and in the villages (n = 109).
many countries in Central and West Africa, where it provides substantial benefit to pregnant women. Here in Yaoundé, our National Institutes of Health–funded project observed pregnant women in the city and in 2 villages, before the introduction of IPTp SP, and is now observing women who are receiving IPT SP (2009 to present). Our results clearly show that the use of IPT SP is significantly reducing the prevalence of malaria during pregnancy (Table 1). SP is administered as a single dose, long acting, cost-effective, easy to use, and known to be safe. In many African countries, SP is used mainly for IPTp, resulting in less drug pressure on the parasite, and hopefully will delay the development of resistance. Where resistance has reached levels as in Muheza, well above the WHO threshold, a change of drug for IPTp should be considered. Therefore, there is an urgent need to explore alternative drugs that are safe for pregnant women and are affordable. Priority should be given to close monitoring of SP resistance in all countries where it is being used for IPTp, keeping in mind that drug resistance may vary in different parts of the same country.

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References