Efficacy of Mefloquine Intermittent Preventive Treatment in Pregnancy Against Schistosoma haematobium Infection in Gabon: A Nested Randomized Controlled Assessor-Blinded Clinical Trial

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Background. Urogenital schistosomiasis is a major public health problem in sub-Saharan Africa, and routine programs for screening and treatment of pregnant women are not established. Mefloquine—currently evaluated as a potential alternative to sulfadoxine-pyrimethamine as intermittent preventive treatment against malaria in pregnancy (IPTp)—is known to exhibit activity against Schistosoma haematobium. In this study we evaluated the efficacy of mefloquine IPTp against S. haematobium infection in pregnant women.

Methods. Pregnant women with S. haematobium infection presenting at 2 antenatal health care centers in rural Gabon were invited to participate in this nested randomized controlled, assessor-blinded clinical trial comparing sulfadoxine-pyrimethamine with mefloquine IPTp. Study drugs were administered twice during pregnancy with a 1-month interval after completion of the first trimester.

Results. Sixty-five pregnant women were included in this study. Schistosoma haematobium egg excretion rates showed a median reduction of 98% (interquartile range [IQR], 70%–100%) in the mefloquine group compared to an increase of 20% (IQR, −186% to 75%) in the comparator group. More than 80% of patients showed at least 50% reduction of egg excretion and overall cure rate was 47% (IQR, 36%–70%) 6 weeks after the second administration of mefloquine IPTp.

Conclusion. When used as IPTp for the prevention of malaria, mefloquine shows promising activity against concomitant S. haematobium infection leading to an important reduction of egg excretion in pregnant women. Provided that further studies confirm these findings, the use of mefloquine may transform future IPTp programs into a 2-pronged intervention addressing 2 of the most virulent parasitic infections in pregnant women in sub-Saharan Africa.

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Keywords. schistosoma; praziquantel; mefloquine; pregnancy; bilharziosis.

Schistosoma haematobium, the causative agent of urogenital schistosomiasis, is estimated to affect 120 million people in sub-Saharan Africa [1]. Children and women are at highest risk for schistosomiasis-related morbidity owing to frequent exposure to freshwater when doing domestic chores [2]. Anemia, bladder fibrosis, obstruction of the urinary tract, and an
increased risk for bladder cancer are classic complications of *S. haematobium* infection. However, other pathologies caused by the chronic granulomatous inflammation of the genitourinary tract including vaginal fibrosis, dyspareunia, and pelvic inflammatory disease are only recently being appreciated [3–5]. Importantly, *S. haematobium* infection has also been associated with an increased risk for human immunodeficiency virus (HIV) transmission, most likely due to chronic genital ulceration [6, 7].

The World Health Organization (WHO) estimates that only 33.5 million people among the 230 million people requiring treatment for schistosomiasis receive effective therapy each year [2]. At present, treatment of *Schistosoma* species relies entirely on the single drug praziquantel. Although no clinically relevant resistance to the drug has been confirmed so far, some studies report lower than expected cure rates, raising concerns about the continued usefulness of this drug [8]. There is therefore a broad consensus that new drugs with unrelated modes of action urgently need to be developed.

Mefloquine, an aryl-amino-quinoline antimalarial, is used for the treatment and prophylaxis of malaria on a large scale for >25 years. It is active against *Plasmodium* species resistant to common antimalarials including chloroquine and sulfadoxine-pyrimethamine. Tolerability of mefloquine is known to be limited by dose-dependent neuropsychiatric side effects and gastrointestinal disorders. It is, however, considered to be a particularly safe drug in pregnancy [9–12]. Mefloquine was shown to exert considerable activity against *Schistosoma mansoni* and *Schistosoma japonicum*—the causative agents of intestinal schistosomiasis—in rodent models [13–15]. Recently, a first exploratory trial evaluating mefloquine alone and in artemisinin combination therapy against *S. haematobium* infection in schoolchildren provided evidence for a clinically relevant effect in humans [16].

Pregnant women are thought to be at an increased risk for adverse pregnancy outcome owing to chronic inflammation and blood loss caused by urogenital schistosomiasis [17]. It is estimated that >10 million pregnant African women each year have *S. haematobium* infections [18]. However, because of a lack of established screening, treatment, or prevention programs, schistosomiasis is rarely diagnosed or treated during pregnancy.

In contrast to this situation, intermittent preventive treatment against malaria is an established prevention strategy in most sub-Saharan African regions [19–21]. Due to increasing drug resistance of *Plasmodium falciparum* against sulfadoxine-pyrimethamine, mefloquine is currently investigated in a large multicenter randomized controlled trial for its efficacy, tolerability, and safety as intermittent preventive treatment of malaria during pregnancy (IPTp) in Africa. Since malaria and urogenital schistosomiasis show coendemicity in large parts of Africa, a shared prevention strategy against both malaria and schistosomiasis during pregnancy would therefore be particularly advantageous and a practicable public health intervention for these underserved populations [22].

This randomized controlled clinical trial was hence designed as a proof of concept study to evaluate whether mefloquine IPTp exerts clinically relevant activity against *S. haematobium* infection in pregnant women in Gabon when compared to sulfadoxine-pyrimethamine, which served as comparator without known antischistosomal activity. This study was set out to test whether mefloquine leads to an at least 50% reduction in egg excretion compared to sulfadoxine-pyrimethamine IPTp.

**MATERIALS AND METHODS**

This study was conducted at the Centre for Medical Research of Lambaréné, the Albert Schweitzer Hospital, and the Ngounié Medical Research Centre in Fougamou, Gabon [23]. This semirural region is situated within the equatorial rain forest and is known to be highly endemic for *S. haematobium* and *P. falciparum* infections [22, 24–26]. *Plasmodium falciparum* is known to show high levels of resistance against chloroquine, whereas mefloquine and quinine have retained high activity against clinical field isolates [27–29].

This study was designed as a nested randomized controlled, assessor blinded, clinical trial embedded in an open-label multicenter randomized controlled trial assessing the efficacy, tolerability, and safety of mefloquine IPTp against malaria (MIPPA-D [Malaria in Pregnancy Preventive Alternative Drugs]; NCT 00811421). All pregnant women attending an antenatal clinic before the 28th week of pregnancy were screened for *S. haematobium* infection and in case of positivity, participation in this nested trial was proposed after written informed consent was obtained. Exclusion criteria consisted of intake of anthelmintic or antimalarial drugs within 2 months or serologic evidence for HIV infection. At initial presentation, presence of hematuria was assessed semiquantitatively by a urine dipstick test (Combur, Roche Diagnostics, Switzerland). Infection with *S. haematobium* was determined by using 10 mL of urine passed through a 12-μm polycarbonate N-filter (Millipore, Billerica) followed by a subsequent microscopic examination for the detection of eggs as previously described [30]. Urine analysis was performed for each time point on at least 2 consecutive days and the arithmetic mean of available counts was used for further statistical analysis. Cure was defined as the examination of 3 consecutive urine samples without the presence of eggs.

Women were randomly allocated to either mefloquine or sulfadoxine-pyrimethamine treatment in a 2:1 allocation ratio. The randomization list was computer generated and provided...
by the independent MIPPAD Trial Management Team (Barcelona Centre for International Health Research, Spain), which was not involved in the recruitment of participants. Study assignment was concealed via sealed opaque envelopes, which were opened only after enrollment of a patient by a study investigator. The assigned study treatment was administered twice during pregnancy. The first dose was administered between the 13th and 28th weeks of gestation. The second dose was scheduled at least 1 month apart from the previous dose. Mefloquine was administered either as a single full dose (15 mg/kg bodyweight) or as a split dose of 2 doses (7.5 mg/kg each) on 2 consecutive days (Lariam, Roche, Basel, Switzerland). Drugs were administered under the supervision of a study investigator. The rationale for the evaluation of these 2 mefloquine treatment schedules was to evaluate potential differences in tolerability for mefloquine. The study design was chosen based on the assumption of comparable pharmacodynamics owing to mefloquine’s long half-life of 12–17 days. This assumption will further be elaborated in rich- and population-pharmacokinetic studies, which are still ongoing. Sulfadoxine-pyrimethamine was given as single-dose treatment following current WHO recommendations (3 tablets of 500/25 mg sulfadoxine-pyrimethamine; Malastop, Laboratoires STEROP, Brussels, Belgium). Sulfadoxine-pyrimethamine, a sulfa-type antimalarial, is known not to exert activity against S. haematobium and served as a control group in this randomized controlled trial to account for natural variations in egg excretion. In order to minimize potential bias in the microscopic assessment of Schistosoma egg excretion, laboratory technicians were blinded to the treatment allocation and the time point of sampling by labeling of urine samples with numbers.

Clinical follow-up and repeated urine examinations were performed 4 weeks after the first intake of IPTp, coinciding with the second IPTp administration, and 6 weeks after the second dose of IPTp (Figure 1). The primary outcome measure was the parasitological urine examination 6 weeks after the second administration of IPTp, which was used to calculate the primary outcome as relative reduction of egg excretion in the mefloquine arm when compared to sulfadoxine-pyrimethamine. All women were offered a therapeutic course of praziquantel at 1 month after delivery. Pregnant women were further followed up until 6 weeks postdelivery and infants were followed up until their first birthday.

This proof of concept study was set out to test the primary hypothesis whether mefloquine IPTp leads to an at least 50% reduction in egg excretion compared to the inactive comparator drug sulfadoxine-pyrimethamine when evaluated 6 weeks after the second dose of IPTp (Wilcoxon signed rank test). To allow for loss to follow-up and incomplete parasitological assessments, 65 patients were included in this study ($\beta = 0.8$ and $\alpha = 0.05$). The secondary hypothesis was to evaluate whether mefloquine IPTp may lead to an adequate cure rate for S. haematobium infection of >80%. Efficacy analysis was performed, including participants contributing outcome measurements at the end of study visit. Because the sample size of this substudy was too low to draw any conclusions about the tolerability and safety of the trial medication, these analyses will be presented in the publication of the MIPPAD trial, which is powered to provide clinically significant information on this important issue. The study was granted ethical approval by the Institutional Review Board of the Medical Research Unit at the Albert Schweitzer Hospital in Lambaréné.

Data were recorded on dedicated paper record forms. Data entry was performed by 2 data clerks independently, and automated and manual verification of the database was performed. A commercially available software package was used for statistical analysis (JMP 5.0, SAS Institute). Descriptive characteristics were computed depicting median and interquartile ranges, and treatment outcomes were compared by nonparametric tests as appropriate.

**RESULTS**

From September 2009 to December 2011, 902 pregnant women participating in the MIPPAD study were screened at first presentation at the study centers for the presence of urogenital schistosomiasis (Figure 1); of these, 79 individuals (9%) were infected with S. haematobium and 65 (82%) provided written informed consent to participate in this study. Among these participants, 48 and 17 patients were randomized to the mefloquine and sulfadoxine-pyrimethamine treatment groups, respectively (Figure 1). Median gestational age at initial presentation was 21 and 20 weeks for the mefloquine and sulfadoxine-pyrimethamine groups, respectively. Both treatment groups had comparable baseline characteristics including age (median, 21 years), weight (median, 56 kg) and hemoglobin (median, 100 and 95 g/L for the mefloquine and sulfadoxine-pyrimethamine groups, respectively; Table 1). Thirty-seven and 28 patients were enrolled at the study centers in Lambaréné and Fougamou, respectively. There were no important differences in patient characteristics between the 2 sites (data not shown).

Thirty and 14 patients in the mefloquine and sulfadoxine-pyrimethamine groups, respectively, were successfully followed up for the primary outcome measure. Reasons for nonadherence to the full treatment course included loss to follow-up, withdrawal from the study, migration, delivery before second dose of IPTp, abortion, and refusal of second dose of IPTp (Figure 1).

Median egg excretion rates of S. haematobium decreased from 18 eggs/mL in urine (interquartile range [IQR], 4–177 eggs/mL) at baseline to 7 eggs/mL (IQR, 1–34 eggs/mL) and 2 eggs/mL (IQR, 0–10 eggs/mL) 4 weeks after the first administration of mefloquine-IPTp and 6 weeks after the second
administration, respectively. In the sulfadoxine-pyrimethamine treatment arm, respective egg excretion rates were 26 eggs/mL (IQR, 15–199 eggs/mL), 33 eggs/mL (IQR, 15–181 eggs/mL), and 62 eggs/mL (IQR, 5–174 eggs/mL) (Table 2). Hematuria was present in all participants at initial presentation (3+). Semi-quantitative detection of hematuria decreased in the mefloquine treatment arm (2+) and increased in the control group (4+).

Cure rates in the mefloquine and sulfadoxine-pyrimethamine groups were 47% (IQR, 36%–70%) and 7% (IQR, 1%–31%) at the end of the study in per protocol analysis, respectively. Intention to treat analysis using worst-case and best case-scenarios showed 29% (IQR, 18%–43%) and 67% (IQR, 53%–78%) for mefloquine and 6% (IQR, 1%–27%) and 24% (IQR, 10%–47%) for sulfadoxine-pyrimethamine, respectively. A >50% reduction in egg excretion at the end of the study was reached in 80% (IQR, 63%–90%) and 36% (IQR, 16%–61%) of participants in the mefloquine and sulfadoxine-pyrimethamine groups, respectively ($P = .004$; Table 2). The primary hypothesis—whether mefloquine IPTp shows an at least 50% reduction of egg excretion compared to sulfadoxine-pyrimethamine IPTp—showed a
statistically significant difference (2 vs 62 eggs/mL urine for mefloquine and sulfadoxine-pyrimethamine IPTp, respectively; \( P = .001 \); Table 2).

**DISCUSSION**

Our data show a marked reduction of egg excretion in pregnant women infected with *S. haematobium* when receiving mefloquine as intermittent preventive treatment against malaria. A rapid and marked antischistosomal effect was evident after the first dose of mefloquine IPTp, and this effect was further increased after the second dose of IPTp, leading to clinically important reductions in egg excretion. A high proportion of women (80%) showed a reduction by >50%. Importantly, 47% showed complete cessation of egg excretion at 6 weeks of follow-up, indicating parasitological cure from schistosomiasis after administration of mefloquine IPTp.

The activity of mefloquine against *S. haematobium* is significantly higher in our patient population than in a previously published clinical trial. In that study evaluating mefloquine in a pediatric patient population a cure rate of 21% was reported [16]. A number of reasons may explain this significantly improved outcome in our study. First, important differences in the therapeutic regimen of mefloquine may have led to a higher efficacy in our study population. Mefloquine was administered twice with a 1-month interval in our study as opposed to a single treatment course in the other reports. This repeated dose regimen of a slowly eliminated drug with an estimated half-life of 12–17 days ensures prolonged therapeutic serum concentrations over a >2-month period and therefore leads to sustained exposure of adult *S. haematobium* worms to the drug. This repeated dosing regimen may compensate for the lower dose of mefloquine per drug administration (15 mg/kg) as was used in this study compared to previous reports (25 mg/kg). These data may therefore indicate that the length of exposure to therapeutic drug concentrations of mefloquine may constitute a more important predictor for treatment outcome than peak plasma concentrations.

**Table 1. Baseline Characteristics of Study Participants**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>MQ</th>
<th>Range</th>
<th>SP</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. and %</td>
<td>24 MQf</td>
<td>74%</td>
<td>17</td>
<td>26%</td>
</tr>
<tr>
<td></td>
<td>24 MQs</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Age, y</td>
<td>21</td>
<td>19–25</td>
<td>21</td>
<td>19–25</td>
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<tr>
<td>Weight, kg</td>
<td>56</td>
<td>50–66</td>
<td>56</td>
<td>53–66</td>
</tr>
<tr>
<td>Height, cm</td>
<td>156</td>
<td>153–162</td>
<td>160</td>
<td>156–164</td>
</tr>
<tr>
<td>Gestational age at inclusion, wk</td>
<td>20</td>
<td>17–23</td>
<td>21</td>
<td>19–25</td>
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<tr>
<td>Hemoglobin, g/L</td>
<td>100</td>
<td>89–111</td>
<td>95</td>
<td>84–110</td>
</tr>
<tr>
<td>Median egg count V1/mL</td>
<td>18</td>
<td>4–177</td>
<td>26</td>
<td>15–199</td>
</tr>
<tr>
<td>Hematuriaa</td>
<td>3</td>
<td>2–4</td>
<td>3</td>
<td>2–4</td>
</tr>
<tr>
<td>Literacy, No. and %</td>
<td>38</td>
<td>81%</td>
<td>15</td>
<td>88%</td>
</tr>
<tr>
<td>MUAC, cm</td>
<td>23</td>
<td>19–25</td>
<td>24</td>
<td>21–25</td>
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</table>

Abbreviations: MQ, mefloquine; MQf, single full dose of 15 mg/kg mefloquine; MQs, split dose of 7.5 mg/kg mefloquine over 2 consecutive days; MUAC, mid-upper arm circumference; SP, sulfadoxine-pyrimethamine.  

*a* Semiquantitative detection of hemoglobin by urine strip (scale: 0–4).

**Table 2. Posttreatment Schistosoma haematobium Egg Excretion and Cure Rates**

<table>
<thead>
<tr>
<th></th>
<th>MQ</th>
<th>Median</th>
<th>Range</th>
<th>SP</th>
<th>Median</th>
<th>Range</th>
<th>( P ) Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Follow-up 1 (4 wk)</td>
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<tr>
<td>No.</td>
<td>24</td>
<td>24</td>
<td></td>
<td></td>
<td>13</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Egg excretion, eggs/mL</td>
<td>7</td>
<td>1–34</td>
<td></td>
<td></td>
<td>33</td>
<td>15–181</td>
<td></td>
</tr>
<tr>
<td>Reduction in egg excretion, %</td>
<td>80</td>
<td>–22 to 99</td>
<td></td>
<td></td>
<td>–22</td>
<td>–85 to 28</td>
<td></td>
</tr>
<tr>
<td>Hematuriaa</td>
<td>3</td>
<td>1–4</td>
<td></td>
<td></td>
<td>3</td>
<td>2–4</td>
<td></td>
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<tr>
<td>Follow-up 2 (10 wk)</td>
<td></td>
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<td></td>
<td></td>
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<td></td>
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<tr>
<td>No.</td>
<td>30</td>
<td>30</td>
<td></td>
<td></td>
<td>14</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Egg excretion, eggs/mL</td>
<td>2</td>
<td>0–10</td>
<td></td>
<td></td>
<td>62</td>
<td>5–174</td>
<td></td>
</tr>
<tr>
<td>Reduction in egg excretion, %</td>
<td>98</td>
<td>70–100</td>
<td></td>
<td></td>
<td>–20</td>
<td>–186 to 75</td>
<td>.004&lt;sup&gt;b&lt;/sup&gt;</td>
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<tr>
<td>Hematuriaa</td>
<td>2</td>
<td>0–3</td>
<td></td>
<td></td>
<td>4</td>
<td>3–4</td>
<td></td>
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<tr>
<td>&gt;50% reduction</td>
<td>24</td>
<td>80% (63–90)</td>
<td></td>
<td></td>
<td>5</td>
<td>36% (16–61)</td>
<td>.004&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>&gt;80% reduction</td>
<td>21</td>
<td>70% (52–83)</td>
<td></td>
<td></td>
<td>2</td>
<td>14% (4–40)</td>
<td>.0004&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Cure rate</td>
<td>14</td>
<td>47% (36–70)</td>
<td></td>
<td></td>
<td>1</td>
<td>7% (1–31)</td>
<td>.01&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

Abbreviations: MQ, mefloquine; SP, sulfadoxine-pyrimethamine.  

*a* Semiquantitative measurement of hemoglobinuria: range 0–4.  

<sup>b</sup> \( \chi^2 \) test.  

<sup>c</sup> Fisher exact test.
Another reason for differences in treatment responses may constitute the fact that pregnant women—although an important population at risk for urogenital schistosomiasis—are typically excreting fewer eggs per milliliter of urine than pediatric patient populations, who harbor highest levels of infection [1, 31, 32]. Low rates of egg excretion, and a potentially lower number of reproducing adult worms, may therefore constitute an important explanation for higher cure rates in adult patients. Acquired specific immunity against S. haematobium in adults may act synergistically with the antelmithic effect of mefloquine, leading to more pronounced activity than in pediatric patient populations. Finally, less freshwater exposure and therefore a lower rate of reinfection leading to less diverse developmental stages may further explain improved outcomes in adults than in pediatric populations [33, 34].

Whereas sulfadoxine-pyrimethamine IPTp is an established strategy to reduce malaria related morbidity and mortality in pregnant women, no such interventions exist for urogenital schistosomiasis [35]. Despite the fact that the use of praziquantel was encouraged by WHO for the treatment of schistosomiasis in pregnant women and that praziquantel is highly efficacious in this indication, neither active screening nor routine treatment programs are established in most endemic regions, indicating that most infections will remain undetected and untreated and an opportunity for intervention during antenatal care visits is missed. Since the therapeutic usefulness of sulfadoxine-pyrimethamine against falciparum malaria is limited by the continuing spread of drug resistance in sub-Saharan Africa, the search for second-generation IPTp drugs provides the opportunity for an informed decision on the most appropriate candidate drug [19, 36]. This decision may be based not simply on the antimalarial activity of a candidate drug, but may take the potentially significant collateral effect of any IPTp drug on other infectious diseases during pregnancy into account. Although it is well established that sulfadoxine-pyrimethamine is highly efficacious against a number of important gram-negative and gram-positive bacterial pathogens, little evidence exists on the clinical importance of this antibacterial activity when used as IPTp [37]. Similarly, potential risks for the selection and spread of drug-resistant bacterial pathogens by large-scale use of antifolate antimalarials is not well understood, despite the potential threat to health systems of low-income countries with limited alternatives for antibiotic drugs. The clinical development of any new second-generation IPTp drug should therefore evaluate its potential as antimalarial, but should similarly assess its impact on concomitant infectious and noninfectious diseases in pregnant women and the ecologic effect on common bacterial pathogens.

Our study adds important information on the collateral activity of mefloquine on one of the most important coendemic parasitic diseases infecting pregnant women. Although cure rates of mefloquine IPTp against S. haematobium are not comparable to current first-line treatment with praziquantel, a reduction of egg excretion and the associated granulomatous inflammation in pregnant women may lead to multiple beneficial consequences including reduced exposure of the newborn to inflamed or bleeding vaginal mucosa—therefore potentially reducing exposure to vertically transmitted infections including HIV and hepatitis B virus—and reduction of pathological consequences of chronic urogenital schistosomiasis including pelvic inflammatory disease and infertility [38–40]. Similarly, a cure rate of 47% as evidence in our study is an important improvement from a public health perspective compared to the current standard of care in many regions, leaving the majority of pregnant women unscreened and untreated for urogenital schistosomiasis during antenatal care.

Our study was designed as a proof of concept study with the aim to provide for the first time data on the use of mefloquine on urogenital schistosomiasis during pregnancy. Whereas the results show a striking activity against S. haematobium, the overall sample size of this clinical trial is limited and a proportion of participants did not completely adhere to the treatment and follow-up schedule. The small sample size of this study is a consequence of the primary hypothesis, which was set out to find a dramatic and therefore potentially clinically significant effect of mefloquine on egg excretion. Importantly, reinfection with S. haematobium due to continued freshwater exposure is likely to have occurred throughout the study period in our patient population. The true efficacy of mefloquine against urogenital schistosomiasis may therefore be underestimated in this clinical study. Much emphasis was laid on a rigorous trial methodology to minimize potential bias. The design as a nested randomized, placebo-controlled clinical trial provided the unique opportunity to assess the activity of mefloquine against the natural background variation in egg excretion over time. Assessor bias affecting the main pharmacodynamic outcome measure was minimized by blinding of urine microscopists, whereas tolerability measures may have been affected by the lack of blinding of the participants and the physicians. Future larger studies will be needed to confirm these findings in diverse geographical regions and patient populations.

In summary, urogenital schistosomiasis is a greatly under-appreciated health problem of pregnant women in sub-Saharan Africa. The search for second-generation IPTp regimens against malaria provides an important opportunity to evaluate and address their impact on other infectious diseases including S. haematobium infection. The activity of mefloquine IPTp as evidence in this randomized controlled clinical trial is likely to be of clinical importance. IPTp programs including mefloquine may therefore serve as a 2-pronged approach against 2 of the most important parasitic infections.
Notes

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Author contributions. A. B., G. M. N., and M. R. participated in the design and coordination of the study and drafted the manuscript; M. C., D. A. A., H. W., J. R. M. F., R. M. Z., R. G., and C. M. participated in study design and conduct of the study and reviewed the manuscript, participated in the recruitment and follow-up of study participants, collection of data, and review of the manuscript; A. A. A., P. G. K., and M. R. participated in the design of the study and performed the statistical analysis. All authors read and approved the final manuscript.

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Potential conflicts of interest. All authors: No reported conflicts.

All authors have 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.

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