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A COMPARISON OF SULFADOXINE-PYRIMETHAMINE WITH CHLOROQUINE AND PYRIMETHAMINE FOR PREVENTION OF MALARIA IN PREGNANT NIGERIAN WOMEN

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Abstract. Few studies have documented the effectiveness in west Africa of intermittent preventive treatment of malaria with sulfadoxine-pyrimethamine (SP) in pregnancy. Pregnant Nigerian women were assigned to receive either SP given twice or presumptive chloroquine (CQ) treatment followed by weekly pyrimethamine (CQ + P); 250 were enrolled in each group. Of those completing follow-up, 4 (1.8%) in the SP group and 22 (9.8%) in the CQ + P groups had a febrile illness ($P = 0.005$). None in the SP group but 11 (4.9%) in the CQ + P group had peripheral parasitemia prior to or during delivery ($P = 0.002$). Two (1.2%) in the SP group and 9 (5.0%) in the CQ + P group were anemic at delivery ($P = 0.04$). There were six low birth weight infants in the SP group and eight in the CQ + P group ($P = 0.21$). Intermittent preventive treatment with SP is superior to CQ + P for prevention of malaria and anemia in pregnant women in Nigeria.

INTRODUCTION

Because the placenta is a site of preferential parasite sequestration and development, pregnant women have increased susceptibility to *Plasmodium falciparum* infection, with more frequent episodes of malaria and higher density of parasitemia than non-pregnant women.[1] This increased susceptibility is particularly evident in the first pregnancy and appears to decrease with subsequent pregnancies. Malaria infection during pregnancy increases the risk of maternal anemia, maternal mortality, abortion, prematurity, intrauterine growth retardation, intrauterine death, and low birth weight.[2–4] Low birth weight is the greatest risk factor for neonatal mortality. In Nigeria, malaria accounts for up to 11% of maternal deaths.[5] Malaria is one of the few conditions that cause low birth weight that is amenable to intervention during pregnancy. Given the adverse effects of malarial infection during pregnancy, pregnant women residing in malaria-endemic regions have been targeted for antimalarial prophylaxis.[6]

Intermittent preventive treatment (IPT) for malaria with sulfadoxine-pyrimethamine (SP) has been recommended for pregnant women living in malaria-endemic areas where *P. falciparum* is resistant to chloroquine (CQ) and sensitive to SP.[7–9] Intermittent preventive treatment with SP has been rapidly adopted in west Africa, despite the paucity of information on its effectiveness in the region.[10] Use of SP for IPT has been most extensively evaluated in east Africa. However, similar data are lacking from west Africa, where antimalarial drug resistance is not as widespread and infection with human immunodeficiency virus (HIV) is less prevalent.[11] Infection with HIV appears to interfere with the maintenance of malarial immunity acquired during infection in the first pregnancy,[12,13] and heavy placental malaria infection increases the risk of perinatal mother-to-child transmission of HIV.[14]

Emergence of CQ resistance in Nigeria[15,16] and problems of compliance have limited the effectiveness of weekly chemoprophylaxis with CQ. Weekly pyrimethamine is still widely used in antenatal clinics throughout Nigeria.[17] Presumptive treatment with CQ followed by weekly pyrimethamine (CQ + P) was standard practice at the time this study was conducted. Chemoprophylaxis with CQ during pregnancy may have a protective effect, even in certain areas where chloroquine-resistant *P. falciparum* is endemic and residents have partial immunity.[18] A recent report of the Disease Control Priorities Project estimated that IPT with CQ was more cost-effective than with SP.[19]

No study has demonstrated the superiority of IPT with SP over CQ + P in pregnant women in Nigeria, the most populated nation in Africa. We conducted a controlled trial to compare presumptive CQ treatment followed by weekly pyrimethamine (CQ + P) with IPT with SP.

METHODS

We hypothesized that SP would be more effective than CQ + P in preventing malaria in pregnancy among Nigerian women. The primary outcomes were episodes of acute uncomplicated or severe malaria during pregnancy, infants born with congenital malaria parasitemia, and infants with low birth weight.

Enrollment. The study was conducted from April to December 2002 in Jos, Nigeria, an urban center located in north-central Nigeria. Malaria is endemic and transmission occurs throughout the year with greater transmission during the rainy season from May to October. Consequently, most adults have partial immunity to malaria.

We offered enrollment to pregnant women who came to Jos University Teaching Hospital for antenatal care between 12 and 28 weeks of gestation and who intended to deliver at the teaching hospital. Women were excluded from the study if they were currently using malaria prophylaxis, had a history of allergies to sulfa drugs or intolerance to CQ, or had sickle cell disease. The ethical committee of Jos University Teaching Hospital reviewed and approved the study, and written informed consent was obtained from all subjects.

Women were alternately assigned to receive CQ + P or SP. Women in the CQ + P group were presumptively treated with CQ, 600 mg base on days one and two, followed by 300 mg base on day 3. This was followed by weekly pyrimethamine,

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25 mg, until delivery. Repeated full treatment with CQ was given to those in the CQ + P group who developed malaria during pregnancy. In the event of CQ failure, women were treated with SP. Women with a history of pruritus from CQ were given oral promethazine, 25 mg, with each dose of CQ.

Women in the SP group were given SP (sulfadoxine, 1,500 mg and pyrimethamine, 75 mg) at the initial visit. Women were given a second dose of SP in the third trimester a minimum of 4 weeks after the first dose but not after 34 weeks gestation. Those in the SP group who were infected with HIV were given SP monthly until 34 weeks gestation. Any patient in the SP group who developed malaria was given a repeat dose of SP.

Daily ferrous sulfate, 200 mg, and folic acid, 5 mg, were routinely prescribed to each woman from enrollment to delivery. Ferrous sulfate was given twice a day to women with a hematocrit < 30%.

Follow-up. Between 12 and 28 weeks gestation, antenatal visits were scheduled every 4 weeks; between 29 and 35 weeks gestation, visits were every 2 weeks; and from 36 weeks until delivery, visits were weekly. At each visit, symptoms and signs were recorded, with special attention to fever and self-reported drug adherence. Subjects were instructed to return if they had any febrile illness.

Maternal blood samples were collected for malaria parasite examination at enrollment and on the occasion of any febrile illness between enrollment and delivery. A trained laboratory technician and one of the authors (IUT) independently examined Giemsa-stained thick and thin blood films. Discrepancies were resolved by consensus after re-examining the blood films. Thick films were used to identify malaria parasites and determine parasite density, and thin films were used for species identification. Malaria parasite densities were recorded as 1+ = 1–10 parasites per 100 fields, 2+ = 11–99 parasites per 100 fields, 3+ = 1–10 parasites per field; and 4+ = 11–100 parasites per field.

Uncomplicated malaria was defined as fever, headache, or myalgias without any other cause and malaria parasites present in the blood film. Severe complicated malaria was defined as malaria parasitemia and any of the following: respiratory distress, a hematocrit < 20%, impaired consciousness, multiple convulsions, a temperature ≥ 39.8°C, prostration, circulatory collapse, a blood glucose level < 30 mg/dL, pulmonary edema, abnormal bleeding, jaundice, or hemoglobinuria.

At delivery maternal and cord blood was collected, and infants were weighed to the nearest 50 g. Congenital malaria was defined as malaria parasites in cord blood. Anemia in pregnancy was defined as a hematocrit < 30%. Low birth weight was defined as a birth weight < 2.5 kg.

Assuming a birth weight SD of 700 g, a sample size of 171 in each group was calculated to provide 95% confidence and 80% power to detect a difference in birth weight between the two groups of 150 g. To allow for attrition, 250 subjects were recruited for each group. Data analysis was performed using Epi-Info 2000 (Centers for Disease Control and Prevention, Atlanta, GA). Mean values of normally distributed variables were compared using the *t*-test. Frequencies were compared between groups with the chi-square statistic. The Mantel-Haenszel test was used to determine if the effect of treatment group assignment on outcome differed between primigravid and multigravid women.

RESULTS

A total of 500 pregnant women were enrolled: 250 in the CQ + P group and 250 in the SP group (Figure 1). Of those enrolled, 218 (87.2%) in the SP group and 224 (89.6%) in the CQ + P group completed four or more follow-up visits, and 173 (69.2%) in the SP group and 180 (72%) in the CQ + P group delivered at Jos University Teaching Hospital. Cord blood samples were collected from 47.6% in the SP group and 49.6% in the CQ + P group.

Clinical and laboratory characteristics of the study subjects at baseline did not differ significantly between the two groups (Table 1). One-third (35.5%) of the women were primiparous. A total of 97 (19.5%) women used bed nets, but only one used insecticide-treated bed netting. Most women (66.9%) used insecticide. Only 57 (11.4%) did not use any protective measure. At baseline, 104 women (20.9%) had anemia and 30 (6.0%) had malaria parasitemia.

Of the women who completed at least four antenatal visits, 26 (5.9%) had a febrile illness during follow-up: 4 (1.8%) in the SP group and 22 (9.8%) in the CQ + P group ($P = 0.005$). None of the women in the SP group developed severe malaria, but 3 (1.3%) in the CQ + P group had severe malaria ($P = 0.25$). One woman with severe malaria had prostration, and the other two had anemia with respiratory distress and signs of heart failure. Of those who completed at least four antenatal visits, no woman in the SP group but 11 women (4.9%) in the CQ + P group had peripheral parasitemia prior to or during delivery ($P = 0.002$). Uncomplicated malaria was no more likely to occur in women in their first or second pregnancies than in women with two or more prior pregnancies ($P = 0.60$).

Of those who completed at least four visits, five (2.3%) in the SP group had minor reactions to the drug, most commonly vomiting and dizziness. Eleven (4.9%) in the CQ + P group had minor reactions, most commonly pruritus and vomiting. No woman discontinued prophylaxis because of side effects. Nine (4.1%) women in the SP group did not receive the sec-

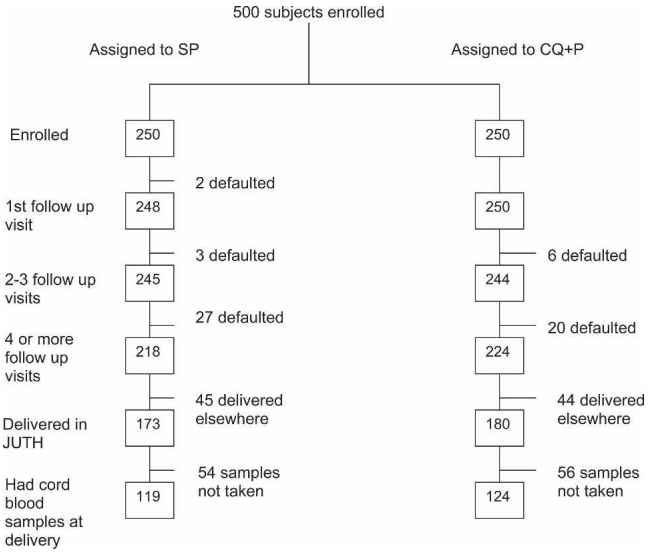

FIGURE 1. Flow chart of study. SP = sulfadoxine-pyrimethamine; CQ + P = chloroquine plus pyrimethamine; JUTH = Jos University Teaching Hospital.

TABLE 1
Baseline characteristics of pregnant Nigerian women*

Characteristic	SP group	CQ + P group
Mean ± SD age (years)	27.3 ± 5.6	26.9 ± 5.4
Mean ± SD height (meters)	1.6 ± 0.1	1.6 ± 0.1
Mean ± SD weight (kg)	65.9 ± 10.9	63.8 ± 11.7
Parity		
Primiparous	86 (34.7)	91 (36.4)
Multiparous	148 (59.7)	145 (58.0)
Grand multiparous	14 (5.6)	14 (5.6)
Other anti-malarial methods		
Insecticide	165 (66.5)	168 (67.5)
Bed net	45 (18.1)	52 (20.9)
ITN	1 (0.4)	0 (0.0)
Bed net plus insecticide	7 (2.8)	3 (0.9)
None	30 (12.1)	27 (10.8)
Hematocrit		
< 30%	53 (21.4)	51 (20.4)
≥ 30%	195 (78.6)	199 (79.6)
Malaria parasitemia		
+	16 (6.5)	10 (4.0)
++	2 (0.8)	2 (0.8)
Negative	230 (92.7)	237 (95.2)

* Values are no. (%) unless otherwise indicated. SP = sulfadoxine-pyrimethamine; CQ = chloroquine; P = pyremethamine; ITN = insecticide-treated bed net.

ond dose of SP, and 27 (12.1%) in the CQ + P group missed two or more doses of weekly pyrimethamine. However, these women had no significant increased frequency of malaria compared with women with full adherence.

By delivery, the proportion of women with anemia decreased in both treatment groups (Table 2). Significantly fewer women in the SP group had anemia (1.2%) than in the CQ + P group (5.0%; $P = 0.04$). The mean hematocrit at delivery was 34.4% in the SP group compared with 33.7% in the CQ + P group ($P = 0.02$).

TABLE 2
Outcomes of malaria prophylaxis in pregnant Nigerian women*

Outcome	SP group	CQ + P group	RR (95% CI)†	*p*
Antenatal febrile illness				
Yes	4 (1.8)	22 (9.8)	0.30 (0.12–0.74)	0.005
No	214 (98.2)	202 (90.2)	1	
Peripheral malaria parasitemia				
+	0	9 (4.2)	0 (0.0–0.38)	0.002
++	0	2 (0.9)		
Negative	179 (86.1)	166 (78.3)	1	
Not done	29 (13.9)	35 (16.5)		
Hematocrit at delivery				
< 30%	2 (1.2)	9 (5.0)	0.36 (0.10–1.3)	0.04
≥ 30%	171 (98.8)	171 (95.0)	1	
Birth weight (kg)				
0.50–1.45	0 (0.0)	2 (1.1)	0.87 (0.47–1.6)	0.64
1.50–2.45	6 (3.5)	6 (3.3)		
≥ 2.5	167 (96.5)	172 (95.6)	1	
Cord blood parasitemia				
+	0 (0.0)	4 (3.2)	0 (0.0–1.1)	0.06
++	0 (0.0)	1 (0.8)		
Negative	119 (100)	119 (96.0)	1	

* RR = relative risk; CI = confidence interval. For definitions of other abbreviations, see Table 1.
† Value of 1 indicates referent group. Parasitemia and birth weight risk ratios were calculated for all categories of parasitemia or low birth weight combined.

Two women in the CQ + P group delivered very low birth weight infants (< 1,500 gm) at a gestational age of 30 weeks. Twelve subjects delivered low birth weight infants (< 2,500 gm) between 30 and 35 weeks of gestation, six (3.5%) in the SP group and six (3.3%) in the CQ + P group ($P = 0.63$). Low birth weight was not associated with maternal or cord blood parasitemia. The mean ± SD birth weight in the SP group was 3.12 ± 0.51 kg compared with 3.17 ± 0.56 kg in the CQ + P group ($P = 0.38$).

Five subjects in the CQ + P group and none in the SP group had cord blood malaria parasites ($P = 0.06$). None of the 11 mothers with HIV infection who had blood examined at delivery had parasitemia. No instance of neonatal mortality was recorded within the first 24 hours after delivery.

When outcomes were examined according to parity (Table 3), none differed significantly between primigravid and multigravid women. The effect of treatment group assignment on most outcomes did not differ between primigravid and multigravid women. However, compared with CQ + P, the effect of SP on low birth weight was significantly different between primigravid and multigravid women (risk ratio in primigravid women = 0.15, 95% confidence interval [CI] = 0.02–1.2 versus risk ratio in multigravid women = 5.1, 95% CI = 0.60–43, $P = 0.02$ for difference in risk ratios). We found no significant interaction of treatment group with bed net use for any outcome.

DISCUSSION

Our study is important in that it confirms the effectiveness of SP in Nigeria, the most populated nation in Africa. In Nigeria, pyrimethamine continues to be frequently used alone for malaria prophylaxis in pregnancy, despite its demonstrated lack of efficacy in pregnant Nigerian women.[17,20] After completion of this study, the Nigerian Federal Ministry of Health released guidelines for malaria prevention in pregnancy in which IPT with SP was formally adopted.[5] Our study provides evidence to support the superiority of IPT with SP over CQ + P in Nigeria.

Published reports supporting the use of IPT with SP in west

TABLE 3
Outcomes in pregnant Nigerian women by gravidity*

Outcome	Primigravid no. (%)	Multigravid no. (%)	RR (95% CI)	*p*
Antenatal febrile illness				
Yes	9 (5.3)	17 (6.2)	0.90 (0.52–1.6)	0.70
No	160 (94.7)	256 (93.8)		
Peripheral malaria parasitemia				
Yes	5 (3.4)	6 (2.2)	1.3 (0.66–2.5)	0.53
No	122 (96.6)	223 (97.8)		
Hematocrit at delivery				
< 30%	2 (1.7)	9 (3.8)	0.54 (0.15–1.9)	0.35
≥ 30%	116 (98.3)	226 (96.2)		
Birth weight (kg)				
< 2.5	8 (6.8)	6 (2.5)	1.8 (1.1–2.8)	0.08
≥ 2.5	110 (93.2)	229 (97.5)		
Cord blood parasitemia				
Yes	2 (2.5)	3 (1.8)	1.2 (0.42–3.7)	0.66
No	77 (97.5)	161 (98.2)		

* RR = relative risk; CI = confidence interval.

Africa have appeared only recently.[21] A clinical trial in Mali demonstrated a lower risk of placental parasitemia and low birth weight infants among pregnant women given IPT with SP compared with IPT with CQ or weekly CQ.[21] An observational program assessment in Burkina Faso also found that IPT with SP was associated with reduced parasitemia rates and low birth weight infants.[22] Chemoprophylaxis with CQ in Burkina Faso was relatively ineffective in preventing malaria in pregnancy.[23] A study of only multigravidae from The Gambia reported that IPT with SP benefited only the subgroup of women who did not use a bed net.[24]

Episodes of antenatal febrile illness and peripheral malaria parasitemia were both significantly reduced by IPT with SP compared with CQ + P. However, the absolute proportion of women who benefited from SP was approximately 3% greater for antenatal febrile illness than for peripheral malaria parasitemia. This may reflect the additional antibacterial action of SP to suppress bacterial infections as well as malaria. The effectiveness of IPT with SP in preventing low birth weight could be due in part to prevention of bacterial infections known to precipitate preterm labor.

We found that 6% of pregnant women had asymptomatic malaria parasitemia when they came for antenatal care. This prevalence rate is low compared with similar studies from other areas in Africa. The prevalence of parasitemia at enrollment was 58.8% in Mali,[21] 29% in Burkina Faso,[23] 46% in Malawi,[12] and 45% in Kenya.[11] The low prevalence we observed could be related to the high proportion of pregnant women in Jos using insecticide or bed nets, prior use of antimalarial drugs, or relatively low endemicity of malaria.

Despite the low prevalence of peripheral parasitemia, the prevalence of anemia (hematocrit < 30%) at baseline was 20.9%. Although the prevalence of anemia decreased in both groups, women in the SP group were significantly less likely to be anemic at delivery (absolute risk reduction = 3.8%), which is consistent with the absence of peripheral parasitemia in the SP group. Intermittent preventive treatment with SP reduces the frequency of malaria parasitemia and severe anemia in pregnancy.[8] The clinical implications of reduced anemia and cord blood parasitemia are reduced risk from hemorrhagic complications of delivery and reduced rates of admission for sepsis evaluation of febrile neonates with congenital malaria.

Overall, only 4% of the women delivered an infant with a low birth weight, and the frequency of low birth weight in the SP group did not differ from that of the CQ + P group. Corresponding rates of low birth weight in other studies in west Africa have been much greater: 14.1% in Burkina Faso[23] and 29.7% in Mali.[21] The small number of infants with low birth weights in our study resulted in insufficient power to detect an effect of IPT with SP on this outcome measure. In an area of high malaria infectivity and HIV infection in Kenya, 8% of women who received either two doses or monthly SP gave birth to infants with low birth weights compared with 18% of women who were given SP only for episodes of fever and parasitemia.[11] Other studies have demonstrated reduced risk of low birth weight with IPT with SP.[9,21]

One of the limitations of our study was our use of alternate treatment group assignment and lack of allocation concealment, which could potentially introduce bias. However, the baseline characteristics of the two groups did not significantly differ, which indicated that selection bias was unlikely. Another limitation of our study was that some women delivered outside the hospital and follow-up was incomplete.

Since SP resistance increases in sub-Saharan Africa, further research is needed on antimalarial regimens that are both effective against resistant *P. falciparum* and safe in pregnancy. Treatment of malaria in pregnant women in Burkina Faso with SP was associated with a 12.9% late parasitologic failure rate, but no clinical failures, compared with an overall failure rate with CQ of 46.7%.[25] Restricted use of SP was suggested to curtail the spread of resistance. The combination of SP + CQ was superior to SP alone among outpatients with malaria in our institution, and the addition of CQ or other antimalarial drugs to SP may warrant further study in pregnant women.[26]

Compared with CQ + P, we confirmed that IPT with SP in pregnancy is associated with better adherence, less side effects, fewer febrile episodes, reduced peripheral parasitemia, and reduced risk of anemia in Nigerian women. These results support the adoption of IPT with SP for pregnant women in Nigeria.

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