

1 **Original Research Article**
2 **Effectiveness of sulphadoxine pyrimethamine in intermittent**
3 **preventive treatment of malaria in pregnancy at Federal medical**
4 **centre, Abeokuta.**

5
6 **Abstract**

7
8 **Objective:** To determine the effectiveness of sulphadoxine – pyrimethamine
9 (SP) in intermittent preventive treatment of malaria in pregnancy at Federal
10 medical centre, Abeokuta.

11
12 **Design:** Randomized controlled trial

13
14 **Setting:** Antenatal Clinic, Department of Obstetrics and gynaecology, Federal
15 Medical Centre, Abeokuta.

16
17 **Population:** Pregnant women presenting for antenatal booking that met the
18 inclusion criteria for the study

19
20 **Methods:** Patients were randomized into two groups. Blood film for malaria
21 parasite was collected from all the patients before administering sulphadoxine
22 – pyrimethamine to the first group. A repeat sample for malaria parasite was
23 collected from all the patients after two weeks before administering SP to the
24 second group. The maternal biodata, Pre and Post SP blood film analysis
25 results were compared within the two groups.

26
27 **Main outcome measure:** Prevalence of malaria parasitaemia and parasite
28 reduction or clearance rate with use of SP.

29 **Result:** The result of 358 patients were analysed; 203 in the case group and
30 155 in the control group. The prevalence of malaria in pregnancy in the study
31 population was 43.9%. The mean parasite density at booking was 1049.7
32 parasites/ μ l in the case group and 1183.4 parasites/ μ l in control group.

Prevalence of parasitaemia in the case group reduced by 67.4% and in the control group by 32.4% ($P=0.015$). The mean parasite density reduction was 59.3% and 37.9% in the case and control group respectively ($P=0.021$).

Conclusion: The study findings revealed that sulphadoxine-pyrimethamine is effective for the intermittent preventive treatment of malaria in pregnancy.

Keywords Sulphadoxine-pyrimethamine, intermittent preventive treatment, Malaria parasitaemia, Pregnancy.

Introduction

Malaria remains a major challenge in Africa where 45 Countries with the population of about 588 million people are within the endemic zone ¹. Pregnant women are the main adult vulnerable group and in Nigeria 11% of maternal mortality is attributable to malaria ². In areas of Africa with stable malaria transmission, *Plasmodium falciparum* infection is estimated to cause as many as 10,000 maternal deaths each year, 8% to 14% of all low birth weight babies, and 3% to 8% of all infant deaths³.

Each year, approximately 25-30 million African women become pregnant in malaria endemic areas and are at risk of *P. falciparum* infection during pregnancy. Most of these women are in the region of high and moderate(stable) transmission of malaria with majority having asymptomatic parasitaemia, which is associated with maternal anaemia (potentially responsible for maternal death when severe) and low birth weight ^{4,5}.

High and moderate or stable malaria transmission area is characterized by constant predisposition to infection with plasmodium parasite throughout the year. Women in this region acquire immunity to malaria and become partially immune to the infection. There is however a dramatic breakdown of the acquired immunity in pregnancy, especially in primigravida, making pregnant women more susceptible to malaria infection compared to non

64 pregnant women in the same location⁶. Low (unstable) transmission is
65 characterized by sporadic transmission of infection. Women in this region do
66 not acquire immunity to the infection and death may result from direct effect of
67 severe malaria or indirectly from malaria related severe anaemia^{7,8}.

68 Nigeria is in the region of stable malaria transmission and has been
69 noted, by the world malaria report, to account for a quarter of all malaria cases
70 in the endemic countries of Africa¹. This constitutes immense malaria burden
71 with its associated effects on the country. The prevalence of malaria in
72 pregnancy has been quoted by various studies as ranging from 19.7% to 72%
73^{9,10}. The study by Agomo *et al* showed a prevalence of 7.7%¹¹, with increased
74 incidence in **primigravida** and women less than 20 years of age. The WHO
75 recommends a package of interventions for the prevention and control of
76 malaria during pregnancy. This comprises intermittent preventive treatment
77 (IPT), use of insecticide treated nets (ITN) and access to effective case
78 management of malaria illness and anaemia¹².

79 The most promising preventive approach using antimalaria drugs is
80 intermittent preventive treatment¹². IPT is based on the use of antimalaria
81 drugs given in treatment doses at predefined intervals after quickening. WHO
82 recommends that in area of stable transmission IPT with an effective,
83 preferably one dose, antimalaria drug should be provided as part of antenatal
84 care, starting after quickening¹². Sulphadoxine- pyrimethamine (SP) is
85 currently the most effective single dose antimalaria drug for prevention of
86 malaria during pregnancy in areas of Africa where transmission of **P.**
87 **falciparum** malaria is stable and where resistance to SP is low. WHO
88 recommends that SP **be** given during regularly scheduled antenatal visits after
89 first trimester **until time of delivery, provided the doses are given at least 1**
90 **month apart**¹². Studies have shown SP to effectively reduce severe anaemia,
91 peripheral and placental malaria and **Low Birth Weight**⁶.

92 The prospect of this promising result with the use of SP is however
93 being eroded by recent evidence of an increasing incidence of treatment

94 failure with the use of SP in children under the age of five years, thus raising
95 questions about its effectiveness in IPT in the same environment^{13,14}.

96 Point mutations in the genes of the two enzymes important in the
97 parasite's folate biosynthetic pathway, Dihydrofolate reductase (*DHFR*) and
98 Dihydropteroate synthetase (*DHPS*) confer resistance to pyrimethamine and
99 sulfadoxine, respectively, with decreasing in vitro *P. falciparum* susceptibility
100 related to the number of mutations in each gene¹³. Quintuple and lately
101 sextuple mutant haplotypes of *P. falciparum* have been described^{15,16}.

102 However, recent evidence suggests that IPT with SP remains effective in
103 preventing the adverse consequences of malaria on maternal and fetal
104 outcomes in areas where a high proportion of *P. falciparum* parasites carry
105 quintuple mutations associated with treatment failure. Therefore, IPT with SP
106 should still be administered to women in such areas^{12,15,16}. WHO recommends
107 at least 3 doses during each pregnancy¹⁵.

108 The World Health Organisation has recommended a regular evaluation of the
109 efficiency of the drug in IPT as well as safety of repeated doses of SP to
110 facilitate evidence based practice¹².

111 This study was aimed at determining the effectiveness of Sulphadoxine
112 – pyrimethamine (SP) in intermittent preventive treatment of malaria in
113 pregnancy using changes in the level of parasitaemia as an indicator of
114 therapeutic response following the administration of a single dose of SP in a
115 cohort of asymptomatic pregnant women presenting at the antenatal clinic of
116 the Federal medical centre, Abeokuta.

117

118 **Methods**

119 The study is a randomized controlled trial conducted among patients attending
120 the ANC at the FMC, Abeokuta between 1st of August 2011 and 31st of
121 December 2011 (5 months). Ethical approval for the study was obtained from

122 the hospital health research ethics committee. The study involved patients
123 who booked after quickening and before 32weeks gestation. They had no
124 treatment for malaria within two weeks of presentation and no features of
125 malaria at presentation. Patients who booked at or beyond 32weeks gestation,
126 had malaria illness at presentation or previous treatment for malaria within two
127 weeks of presentation and patients with history of adverse reaction to any of
128 the components of the medication were excluded. Also, patients with
129 immunosuppressive illness such as HIV positive patients were excluded.

130

131 All consenting patients were scheduled for blood film for malaria parasite in
132 the first routine ANC clinic and two weeks (day 14) after the first visit. The
133 patients were randomized into two groups using randomly chosen numbers.
134 The first dose of IPT in the two groups was separated by the two weeks study
135 period. The study group (Cases) had IPT at first presentation after the initial
136 blood film for malaria parasite while the second group, the control group, had
137 the first dose of IPT after the Day 14 blood film for malaria parasite had been
138 obtained. All the patients eventually had the recommended minimum of two
139 IPT doses. Feature suggestive of malaria illness within the two week study
140 period were treated and the patients that had such presentation were
141 excluded from the study. The laboratory scientist collecting and analysing the
142 samples was blinded to the grouping of patients.

143

144 Thick and thin film for malaria parasite was collected on a slide. Peripheral
145 parasitaemia was determined by the presence of ring form of the *P falciparum*
146 with the reddish chromatin dot and a purple or blue cytoplasm, having been
147 stained with 10% Giemsa stain solution at pH 7.2 and examined using x100 oil
148 immersion objective lens¹⁷.

149 The proportion of women with peripheral parasitaemia in the two groups was
150 compared using the blood film for malaria parasite at the start of the study and
151 at Day 14. The parasite density was calculated by counting the number of
152 asexual Plasmodium parasites against 200 white blood cells (WBC).Mean

153 parasite densities (MPD) was calculated on the assumption that each subject
154 had 8000 WBC/ μ l blood.

155 Analysis of data was performed using SPSS version 17 statistical
156 software package. The findings focused on the prevalence of malaria
157 parasitaemia which was assessed using the absolute figures, percentages,
158 mean and further assessed using cross tabulation with associated variables
159 and significance determined using the chi-square. The effectiveness of SP in
160 parasite clearance was assessed with the determination of the parasitaemia at
161 booking and at day 14 in the study group which was compared with the control
162 for significance using the t- test.

163

164 **Results**

165 A total of 385 pregnant women were recruited. Twenty patients (5.2%)
166 did not present for follow up visit. Seven patients (1.8%) presented with
167 clinical features of malaria in pregnancy before the follow up appointment and
168 were treated. These 27 patients were excluded from the result analysis.

169 The result analysis involved a total of 358 patients; 203 patients in the
170 case group and 155 patients in the control group. The two groups had similar
171 socio-demographic characteristics as outlined in Table 1. The mean age of the
172 study population was 30.34yrs [Case group – 30.37yrs, Control group –
173 30.31yrs]. Primiparous patients had the highest percentage in both groups
174 [37.4% in both groups]. Most of the patients in both groups had tertiary
175 education (74.9% in Case group, 79.4% in Control group).

176 One hundred and fifty seven patients (43.9%) had positive film for
177 malaria parasite at the booking clinic (Table 2). The distribution of
178 parasitaemia in the case and control group was similar at booking (43.8% vs
179 43.9% respectively) (Table 2). There was a significant reduction in
180 parasitaemia in the case group compared to the control group at the follow up
181 visit (67.4% vs 32.4%, $P=0.015$) (Table 2). There was also a significant
182 reduction in the mean parasite density between case and control group
183 (59.3% vs 37.9%; $P=0.021$) (Table 3).

184 All patients in the case group with initial parasitaemia at booking had
 185 either parasite clearance or reduction while 3 patients in the control group had
 186 increased parasite density between booking and follow up appointment and all
 187 the 7 patients with clinical symptoms of malaria before the follow up visit were
 188 in the control group.

189

190

191 **Table 1: Socio-Demographic Characteristics of Both Case and**
 192 **Control Groups**

	CASE - 203 (%)	CONTROL - 155 (%)
Mean Age [yrs]	30.37	30.31
Age Group [n(%)]		
20-24	18(8.9)	18(11.6)
25-29	72(35.5)	60(38.7)
30-34	80(39.4)	49(31.6)
>= 35	33(16.2)	28(18.1)
Parity [n(%)]		
Nullipara	59 (29.1)	51 (32.9)
Primipara	76 (37.4)	58 (37.4)
Multipara	68 (33.5)	46 (29.7)
Educational Status [n(%)]		
Primary	20 (9.9)	6 (3.9)
Secondary	31 (15.2)	26 (16.7)
Tertiary	152 (74.9)	123 (79.4)
TOTAL	203 (100)	155 (100)

193

194 **Table 2: Prevalence of malaria parasite at booking clinic.**

	Positive	Negative	Total
At Booking Clinic			
Case [n (%)]	89 (43.8)	114 (56.2)	203 (100)

Control [n (%)]	68 (43.9)	87 (56.1)	155 (100)
Total	157 (43.9)	201 (56.1)	358 (100)
At follow up Clinic			
Case [n (%)]	29 (14.3)	174 (85.7)	203 (100)
Control [n (%)]	46 (29.7)	109 (70.3)	155 (100)
Total	75	283	358

Table 3: Mean Parasite Density [MPD] Distribution in Case and Control Group.

	MPD at booking [no. parasites/ μ l]	MPD follow up [no. parasites/ μ l]	MPD difference [n (%)]
Case	1049.7	427.2	622.5 (59.3%)
Control	1183.4	734.9	448.5 (37.9%)

Discussion

The study revealed a prevalence of malaria parasitaemia of 43.9%. This value is higher than the 7.7% observed by Agomo et al in Lagos¹¹, 29% by Nwonwu et al in Abakaliki¹⁸ and some other studies^{19,20}. The prevalence was lower than what was reported by Nnaji et al, among antenatal booking patients at the Nnamdi Azikwe university teaching hospital, Nnewi²¹, Adefioye et al in Osogbo¹⁰ and Mockenhaupt et al in southern Ghana also reported higher prevalence²². The prevalence is however comparable to that described by Anorlu et al, among pregnant women at booking in a primary health care facility in a peri-urban community in Lagos²³. It is slightly higher than the 35.6% described earlier in the same environment by Idowu et al²⁴.

There was a significant reduction in parasitaemia in the case group with a 67.4% reduction in prevalence of parasitaemia compared with a 32.4%

216 reduction observed in the control group ($P=0.015$). This reduced risk of
217 parasitaemia is comparable with the findings of Gies et al ²⁵. This response is
218 lower than that described by Kayantao H et al where only 1.8% of the patient
219 who used SP did not have parasite clearance ²⁶. The parasite density also
220 reduced significantly in the case group showing a reduction of 59.3% from a
221 mean density of 1049.7 parasites/ μ l to 622.5 parasites/ μ l compared with the
222 control group showing a parasite reduction of only 37.9% from a mean density
223 of 1183.4 parasites/ μ l to 734.9 parasites/ μ l ($P=0.021$).

224 During the study period, 7 patients presented with features of malaria in
225 pregnancy and they were all in the control group. This is at variance with the
226 findings by Kayantao et al, who had 14.13% of the patients in the study group
227 (IPTp-SP), compared to 21.7% and 22.5% in the control groups (IPTp with
228 chloroquine and weekly chloroquine respectively) presenting with clinical
229 illness at follow up and were treated ²⁶. In the study by Kayantao et al, all the
230 patients were followed up at 2 weeks initially and subsequently, at 4 weekly
231 intervals till delivery, whereas in our study, patients were evaluated for clinical
232 malaria within 2 weeks of enrolment into the study.

233 ²⁶. Also, 3 patients in the control group showed increase in parasite density at
234 follow up in contrast to the patients in the study group who had no increase in
235 their parasite density at follow up visit. A patient in the study group with
236 negative blood film at the booking clinic had parasitaemia at the follow up
237 clinic compared to 3 patients in the control group. These findings are
238 consistent with a significant difference between the case and control group in
239 parasitaemic parameters and in keeping with an effective intermittent
240 preventive treatment role of sulphadoxine – pyrimethamine. The effectiveness
241 of sulphadoxine – pyrimethamine in the intermittent preventive treatment of
242 malaria in pregnancy was also documented by Falade et al in Ibadan ²⁷ and
243 other studies ^{28,29}. However, the development of parasitaemia in a patient that
244 had negative blood film at booking in the study group further highlights the
245 need for repeat doses of SP in IPTp as is currently recommended by WHO
246 and Federal Ministry of Health ^{15,16}.

247

248 **Conclusion:**

249 Sulphadoxine – pyrimethamine is effective in the intermittent preventive
250 treatment of malaria in pregnancy and its continued use for the purpose is
251 therefore recommended.

252 **References**

- 253 (1) World Health Organization. World Malaria Report 2008. Geneva: World
254 Health Organization 2008, p99-101.
- 255 (2) Federal Ministry of Health. Malaria situation analysis document. Federal
256 ministry of Health, Nigeria. 2000, p14.
- 257 (3) Malaria in pregnancy. Roll Back Malaria Partnership: malaria in
258 pregnancy in
259 <http://www.rollbackmalaria.org>
- 260 (4) Steketee RW, Nahlen BL, Parise ME, Menendez C. The burden of
261 malaria in pregnancy in malaria - endemic areas. Am j Trop Med Hyg
262 2001, 64 (1-2 Suppl) : 28-35.
- 263 (5) Shulman CE, Dorman EK, Cutts F, Kawuondo K, Bulmer JN, Pesliu N,
264 Marsk K. Intermittent Sulphadoxine – Pyrimethamine to prevent severe
265 anaemia secondary to malaria in pregnancy: a randomised placebo-
266 controlled trial. Lancet, 1999, 353 (9153): 632-636.
- 267 (6) Kakkilaya BS. Malaria and pregnancy in <http://www.malariasite.com>.
268 June 2009
- 269 (7) Luxenburger C, Ricci F, Nosten F, Raimond D, Bathet S, White NJ. The
270 epidemiology of severe malaria in an area of low transmission in
271 Thailand. Trans R Soc Trop Med Hyg 1997, 91 (3): 256-262.
- 272 (8) Hammerich A, Campbell OM, Chandramohan D. Unstable malaria
273 transmission and maternal mortality-experiences from Rwanda. Trop
274 Med Int Health 2002, 7 (7): 573-576.
- 275 (9) Kagu MB, Kawuma MB, Gadzama GB. Anaemia in pregnancy: cross
276 sectional study of pregnant women in a Sahalian tertiary hospital in
277 North-eastern Nigeria. J Obstet Gynaecol 2007; 27: 676- 679.

- 278 (10) Adefioye OA, Adeyeba OA, Hassan WO, Oyeniran OA. Prevalence of
279 malaria parasite infection among pregnant women in Osogbo,
280 Southwest, Nigeria. American- Eurasian J Sci Res 2007; 2: 43-45.
- 281 (11) Agomo CO, Oyibo WA, Anorlu RI, Agomo PU. Prevalence of malaria in
282 pregnancy in Lagos, South-West Nigeria. Korean J. Parasitol. Vol. 47,
283 No 7: June 2009, 179-183.
- 284 (12) WHO policy brief for the implementation of intermittent preventive treatment
285 of malaria in pregnancy using sulfadoxine-pyrimethamine (IPTp-SP) April
286 2013 (Revised January 2014)
- 287 (13) Gatton ML, Laura BM, Cheng Q. Evolution of resistance to
288 Sulphadoxin-Pyrimethamine in *Plasmodium falciparum*. Antimicrobial
289 agents and Chemotherapy. June 2004; 2116-2123
- 290 (14) Mbugi EV, Mutayoba BM, Malisa AL, Balthazary ST, Nyambo TB,
291 Mshinda H. Drug resistance to sulphadoxine-pyrimethamine in
292 *Plasmodium falciparum* in Mlimba, Tanzania *Malaria Journal* 2006; 5: 94
- 293 (15) WHO Malaria Policy Advisory Committee and Secretariat *Malar J* (2016)
294 15:117
- 295 (16) Federal Ministry of Health, Nigeria. National Guidelines and Strategies
296 for Malaria Prevention and Control during Pregnancy, 2nd Edition,
297 February 2014.
- 298 (17) WHO. Basic Malaria Microscopy Part 1 Learners' guide. Second edition.
299 World Health Organization, 2010
- 300 (18) Nwonwu EU, Ibekwe PC, Ugwu JI, Obarezi HC, Nwagbara OC.
301 Prevalence of malaria parasitaemia and malaria related anaemia
302 among pregnant women in Abakaliki, South East, Nigeria. Niger J Clin
303 Pract, 2009 Jun; 12(2): 182 – 6.
- 304 (19) Verhoeff FH, Brabin BJ, Chimsuka L, Kazembe P, Russell WB,
305 Broadhead RL. An evaluation of the effects of intermittent Sulfadoxine-
306 Pyrimethamine treatment on parasite clearance and risk of low birth
307 weight in rural Malawi. Ann Trop Med Parasitol 1998, 92(2): 141-150.

- 308 (20) Schultz LJ, Steketee RW, Macheso A, Kazembe P, Chitzulo L, Wirima
309 JJ. The efficacy of antimalarial regimens containing Sulfadoxine-
310 Pyrimethamine and/or Chloroquine in preventing peripheral and
311 placental *Plasmodium falciparum* infection among pregnant women in
312 Malawi. *Am J Trop Med Hyg* 1994, 51 (5): 515-522.
- 313 (21) Nnaji GA, Okafor CI, Ikechebelu JI. An evaluation of the effect of parity
314 and age on malaria parasitaemia in pregnancy. *J Obstet Gynaecol* 2006
315 Nov; 26(8): 755-8.
- 316 (22) Mockenhaupt FP, Badu – Addo G, Von Gaertner C, Boye R, Fricke K,
317 Hannibal I et al. Detection and clinical manifestation of placental malaria
318 in southern Ghana. *Malar J* 2006;5:119.
- 319 (23) Anorlu RI, Odum CU, Essien EE. Asymptomatic malaria parasitaemia in
320 pregnant women at booking in a primary health care facility in a
321 periurban community in Lagos, Nigeria. *Afr J. med sci* 2001; 30:39-41.
- 322 (24) Idowu OA, Mafiana CF, Sotiloye D. Anaemia in pregnancy: a survey of
323 pregnant women in Abeokuta, Nigeria. *Afr Health Sci.* 2005 Dec;
324 5(4):295-9.
- 325 (25) Gies S, Coulibaly SO, Quattara FT, D’Alessandra U. Individual efficacy
326 of intermittent preventive treatment with sulfadoxine – pyrimethamine in
327 primi- and secondgravidae in rural Burkina Faso. Impact on
328 parasitaemia, anaemia and birth weight. *Trop Med Int Health* 2009;
329 14(2):174 -182.
- 330 (26) Kayantao K, Kodio M, Newman RD, Maiga H, Doumtabe D, Ongoiba A
331 et al. Comparison of intermittent preventive treatment with
332 chemoprophylaxis for the prevention of malaria during pregnancy in
333 Mali. *J infect Dis.* 2005; 191(1):109 – 116.
- 334 (27) Falade CO, Yusuf BO, FAdero FF, Mokuolu A, Hamer DH, Salako LA.
335 Intermittent preventive treatment with sulphadoxine – pyrimethamine is
336 effective in preventing maternal and placental malaria in Ibadan, south-
337 western Nigeria. *Malar J* 2007;6:88.

- 338 (28) Parise ME, Ayisi JG, Nahleu BL, Schultz LJ, Robers JM, Misore A,
339 Muga R, Oloo AJ, Steketee RW. Efficacy of Sulphadoxine –
340 Pyrimethamine for the prevention of placental malaria in an area of
341 Kenya with a high prevalence of malaria and human immunodeficiency
342 virus infection. *Am J Trop Med Hyg* 1998, 59(5): 813-822.
- 343 (29) Van Eijk AM, Ayisi JG, ter kuile FO, Otieno JA, Misore AO, Odondi JO,
344 Rosen DH, Kager PA, Steketee RW, Nahlen BL. Effectiveness of
345 intermittent preventive treatment with Sulphadoxine – Pyrimethamine
346 for control of malaria in pregnancy in western Kenya: a hospital based
347 study. *Trop Med Int Health* 2004, 9, 351-360.