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Full Length Research Paper

Protective response to Sulfadoxine-pyrimethamine during intermittent presumptive treatment of malaria in pregnant women in Sagamu, Nigeria

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We study the protective response to sulfadoxine-pyrimethamine (SP) during intermittent presumptive treatment (IPT) of malaria in pregnant women. Pregnant women attending the antenatal service of the primary health centre in Sagamu, Nigeria were enrolled into the study. In addition to the usual treatment with haematinics, participants were randomized into two treatments; SP treated (SPTG) and no SP treated (NSPTG) groups. Information on methods of protection against malaria infection and previous use of IPT was obtained from the participants. All participants were followed up for eight weeks and monitored for peripheral parasitaemia using microscopy. Of the 242 pregnant women enrolled 165(68.2%) pregnant women used at least one form of anti-vector measure; insecticide spray was most common. 186 (76.9%) of these participant had no knowledge of the IPT. Parasite Suppression and malaria pigment-clusters clearance were similar in the two groups. Although knowledge of IPT among pregnant women in the area remains low, use of high anti-vectors in pregnant women population may complement, but blur, the effect of IPT on malaria parasite.

Key words: Intermittent presumptive treatment, malaria, pregnant women, sulfadoxine-pyrimethamine, insecticide.

INTRODUCTION

Malaria is a public health problem of global concern. Over one million people, mostly children and pregnant women, die annually from the infection. In pregnant women, *falciparum* malaria has been responsible for maternal anaemia, intrauterine growth retardation, intrauterine death, still birth, premature delivery, low birth weight (LBW), perinatal and neonatal morbidity and mortality (Breman et al., 2004; Schellenberg et al., 2003; Shulman et al., 1996; Steketee et al., 1996). Most malaria infections, however, in the pregnant women, who reside in high and moderate transmission regions, are asymptomatic and infected women rarely present for treatment (Valleyl et al., 2007). Therefore, the World Health Organization (WHO) recommends a combination of interventions to prevent malaria in pregnancy, including insecticides treated bednets (ITN), intermittent presumptive treatment in pregnancy (IPTp) and effective case management and treatment (WHO, 2004). The knowledge about the current malaria prevention strategies during pregnancy remain poor amongst health workers in the primary health care settings in Nigeria (Fawole et al., 2008), despite clear Federal government policy support efforts (FMOH, 2005), which may have impact on malaria control efforts in the pregnant women.

Following the reports on the application of the IPTp in few African Countries, for example, randomized controlled trials in Kenya (Parise et al., 1998; Shulman et al., 1999) and Malawi (Schultz et al., 1994; Verhoeff et al., 1998;) which showed that sulfadoxine - pyrimetamine (SP) was efficacious, safe and cost effective, many nations in sub-Saharan Africa subsequently introduced

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SP - IPTp into national malaria control programme (EANMAT, 2003; Newman et al., 2006). Recent reports on use of SP from both southern (Ibadan) and northern (Jos) Nigeria (Falade et al., 2007; Tukur et al., 2007) demonstrate the advantage of use of SP on pregnancy outcome. However, more information is needed on the situation of the pregnant women who will have no access amidst poor implementation of the strategy.

In areas of full implementation of IPTp, the increasing resistance to SP is a growing challenge. Presently, in Nigeria, SP resistance is increasing (Sowunmi et al., 2004; Falade et al., 1997) and may compromise the use of IPTp. Already in part of Africa and Southeast Asia, the effectiveness of SP in IPTp is being threatened by increasing levels of resistance to SP (EANMAT, 2003; Plowe et al., 2004; White, 2004; Ringwald, 2004; Jima et al., 2005; Campbell et al., 2006; van den Broek et al., 2005), and has created the need to evaluate more antimalarial drugs, especially, combination antimalarial for IPTp. In Nigeria, baseline information of comparative effectiveness of SP in those who use and those who do not among the pregnant women is needed for determination of possible threats of poor practice of the current intervention policy and parasite resistance. It is for these reasons that the present study is designed to evaluate the use of IPT and extent of protection against parasite of use and non use of SP in pregnant women residing in an endemic area in southwest Nigeria.

METHODOLOGY

Location

The study was carried out in three Primary Health Facilities (PHF), located in Makun. Sabo and Ogijo in the Sagamu Local government (SLG) area, Ogun State, Nigeria. The areas are located in the malaria endemic regions in Southwest Nigeria. Makun, Sabo and Ogijo are local Districts with estimated population of 89,000 inhabitants. The PHFs have provision for maternity health services with capacity for admission and delivery.

Patients

The pregnant women investigated were recruited from those presenting at the antenatal clinic of the PHF, between January 2008 and May 2008. The enrolment criteria include pregnancy with gestation age between 4 - 9 month, no fever or history of fever or symptoms compatible with acute *P. falciparum* malaria in the last one week before presentation, no microscopic parasitaemia in peripheral blood, no history of antimalarial drug administration in the 2 weeks preceding enrolment; absence of pregnancy related abnormalities, for example pre-eclampsia, informed consent; continuous residence in area of study > 1 year before the time of study.

In addition, any pregnant woman found malaria parasite positive were treated by the physician or the clinic nurse with antimalarial drug but were not included in the studies. Pregnant women on admission in the health center, or with concomitant illness, receiving treatment with other drugs, for example HIV mothers or had received IPT previously, were excluded for the study. A pregnant woman was withdrawn from the study if she violates drug protocol or use any other antimalarial other than the studied drugs, has complications developing during the studies, withdraw consent to participate further. Before a participant is enrolled, consent was taken and the participant was also informed of that she was free to withdraw consent if she wishes. The participant were made to know that two cohorts will be enrolled with all treated with the normal drug supplements and those not falling in the SP treatment group were encouraged to report to the clinic physician any sign of inconveniency and would be treated if malaria infection is established.

The day of enrolment and start of treatment was considered to be week 0, with clinical and parasitological follow-up for another 7 weeks. The pregnant women enrolled for the purpose of this study were openly randomized into two groups: those who received three tablets of SP containing 500 mg sulphadoxine and 25 mg pyrimethamine per tablet (Melarich™, Medreich PLC England); administered under supervision of midwives at the antenatal clinic (SP treated group-SPTG), and those who did not take SP (No SP group treated group- NSPTG). Enquiries about untoward effects were made during the next clinic visit and were recorded. An investigator assisted questionnaire was administered to enrolled pregnant women to collect information on socio-demographic factors, malaria chemoprophylaxis, prevention method and occurrence of fever and malaria symptoms as well as anti-malaria drug use during pregnancy. Clinical evaluation consisted of a general obstetric examination by the Physician including measurement of weight, fundus height, blood pressure, foetal breath, axillary temperature, a physical examination.

Assessment of parasitaemia and haematocrit level

On enrolment and for each weekly parasitological follow-up, a finger prick sample of blood was collected and used to make thick and thin blood smears. The smears were Giemsa-stained and were examined by light microscopy, under an oil-immersion objective, at x 1000 magnification, by two independent assessors. The level of L blood) was estimated from the thick parasitaemia (asexual stages/ smears by counting asexual forms against 1000 leucocytes or leucocytes against 500 asexual forms (whichever occurred first) and L of blood. Assuming that each pregnant woman had 6000 leucocytes/ Haematocrit was measured collecting blood from finger prick into 100 µL heparinized tube using microhaematocrit centrifuge and read off on the microhaematocrit reader. Anaemia was defined as a haematocrit < 30%.

Simple quantification of malaria pigment (Haemozoin) in peripheral blood (haemozoinaemia) of the pregnant women enrolled in the study

The determination of density of malaria pigment in peripheral blood of the pregnant women was done by estimating from the thick smears, counting the malaria pigment clusters irrespective of size against 500 leucocytes or leucocytes against 200 malaria pigment clusters (MPC), under an oil-immersion objective, at x1000 magnification, by two independent assessors. When pigments lies side by side with clearly distinct outside cluster layers or boundary, they are counted separately, otherwise counted as one.

Patients' evaluation

Patients were evaluated as follows

1. Parasite suppression time (PST), defined as the time elapse between drug administration and appearance of detectable parasite in peripheral blood for at least one week.
2. Malaria pigment-clusters clearance time (MPCT) is the time

lapse between drug administration and clearance of detectable pigment-clusters in the pregnant woman peripheral blood and remained so for two weeks.

Statistical analysis

Data were analysed using version 6 of the Epi-Info software (Anon., 1994), and the statistical program SPSS for Windows version 10.01 (SPSS, 1999). Normally distributed, continuous data were compared by Student's t-tests and analysis of variance (ANOVA). Data not conforming to a normal distribution were compared by the Mann-Whitney U-test and the Kruskal-Wallis test (or by Wilcoxon rank sum test). The association between two continuous variables was assessed by Spearman's rank correlation coefficient. P-values of < 0.05 were taken to indicate significant differences.

RESULTS

Between January and May 2008, a total of 242 pregnant women aged 18-51years (mean + standard deviation [SD] = 28.1 + 5.5) were enrolled into the study. The mean (SD) age of gestation at enrolment was 26.4(6.4) weeks. Seventy four pregnant women of the 242 enrolled were primigravidae (30.6%). The median Blood Pressure in the subjects enrolled was 110/70 mm of Hg. Table 1 showed the clinical presentation of the pregnant women enrolled in the study. Except for gestation age at enrolment, there was no significant difference in the clinical characteristics between the SP treated group (SPTG, n= 124) and the non-SP treated group (NSPTG, n= 118). One hundred and sixty five pregnant women (68.2%) of study participants admitted use at least one form of anti-vector measure. Insecticide spray (knock-down insecticide) was the most commonly used (55.8%) followed by insecticide treated bednets (ITNs- 10.3%) and coils (2.1%). Seventy seven (31.8%) of the participant used no anti-vector measure; only fifty-six of 242 (23.1%) of these participant had some knowledge of the IPTp.

Clinical response

The clinical response is presented in Table 2. The mean Parasite Suppression Time (PST), was similar in the SPTG and NSPTG (mean + standard deviation [SD] = 7.99 + 5.5 vs. 7.94 + 5.5, F: 0.02; P= 0.89). The malaria parasite pigment-clusters clearance times were similar, in the two groups (NSPTG, mean + standard deviation [SD] = 2.4 + 1.1, range 1-4, vs. SPTG, (2.3 + 1.6, range 1-7 weeks, F stat: 0.21; P=0.6).

Haematocrit changes

The median value of packed cell volume at enrolment were similar in the women enrolled in the SPTG and NSPTG (33%, range 21 - 40, versus 32%, range 17 -43, respectively, P = 0.2) and at follow-up (34%, range 31 - 41, versus 35%, range 30 - 40, respectively, P = 0.9).

Carriage of malaria pigment in peripheral blood

Eighty of 242 pregnant women enrolled were carriers of malaria pigment in peripheral blood at enrolment. Of these, 4 eventually develop parasitaemia between week 5-7 (1 of 39 (2.6%) and 3 of 41 (7.3%) in SPTG and NSPTG respectively, P value = 0.64). Table 3 showed the distribution of pregnant women with malaria pigments at enrolment. Of those with first time pregnancy, malaria pigment carrier in peripheral blood were less than 20% compared to those with second, third, fourth and fifth pregnancies. The proportion with malaria pigments cluster in peripheral blood at enrolment was similar. In two participants treated with SP, there was a prolonged malaria pigment carriage beyond the third week and cleared by weeks four and five, respectively.

DISCUSSION

The intervention with sulfadoxine-pyrimethamine for intermittent therapy has several success reports in Africa (Valley et al., 2007, WHO, 2004; Fawole et al., 2008; FMOH, 2005; Parise et al., 1998; Newman et al., 2006; Falade et al., 2007). Our experience on the field in the present study reflects same. Although the findings from this study showed no significant difference in parasite suppression times after eight weeks of follow-up in the two cohorts involved in the study, the low or no peripheral parasitaemia in the cohorts studied indicate some level of protection from malaria in the pregnant women. The protective effect against peripheral malaria parasitaemia will contribute to low morbidity of malaria in the period of study. It further emphasizes the advantage in ensuring that all pregnant women in the second and third trimester gain access to the IPTp intervention programme of the government. Albeit, the government need to ensure regular supply of the antimalarial drug to the primary health care centres.

The access and delivery on the programme by the government can be enhanced by adequate knowledge of the pregnant women population on the IPTp and its effectiveness. The level of knowledge and previous use of IPT assessed in the participating pregnant women in this study is low. Despite the acclaimed much effort from the government, the presumptive treatment seems not practically available to every pregnant woman and the programme appear largely poorly sustained. What must have gone wrong midway is not clear. Surprisingly, in another study, evaluation of the knowledge and practice of attending doctors and other health care providers in the southern Nigeria showed practices or management, inconsistent with the current WHO malaria prevention strategies in the pregnant women, or poor implement-tation, even from Obstetricians (Fawole et al., 2008; Omo

Table 1. Clinical presentation of the pregnant women enrolled in the study.

Parameter	Sulfadoxine-pyrimethamine treated group (n = 124)	No sulfadoxine-pyrimethamine treated group (n = 118)	P values
Age (yrs)			
Mean (SD)	28.3 (5.6)	27.9 (5.3)	0.57
Range	19-43	18-51	
Weight (kg)			0.64
Mean (SD)	64.8 (11.5)	63.1 (12.7)	
Range	46-111	45-110	
Temperature (℃)			0.80
Mean (SD)	36.1 (0.6)	36.1 (0.7)	
Range	35.4-37.1	35.7- 37.3	
Packed Cell Volume (%)			0.2
Mean	33	32	
range	17-43	21-403	
No. with < 25%	5		
Age of gestation (weeks)			0.01
Mean (SD)	27.2 (6.0)	25.2 (6.4)	
Range	16-36	16-36	
Age of pregnancy at booking (weeks)			
Mean (SD)	19.2 (7.2)	20.4 (6.4)	0.17
range	12-36	3-9	
Number of Primigravidae	38	36	
Number of Multigravidae	86	82	
Malaria pigment in peripheral blood (cluster count/ul of blood)	93*	98	
	28-420 (n=39)	29-802 (n=41)	0.49

*Geometric mean.

Table 2. Clinical outcome following intermittent presumptive treatment with or without sulfadoxine-pyrimethamine of the pregnant women enrolled in the study.

Parameter	Sulfadoxine-pyrimethamine treated group (n = 124)	No sulfadoxine-pyrimethamine treated group (n = 118)	P values
Proportion parasitaemic			
Week 0	0	0	
Week 1	1	2	
Week 2	0	0	
Week 3	0	1	
Week 4	0	0	
Week 5	0	0	
Week 6	0	0	
Week 7	0	0	
Parasite suppression time (week)			
Mean (sd)	7.99 (0.3)	7.94 (0.4)	
Range	0-7	0-7	
Proportion with malaria pigment			0.25

Table 2. Continued.

Week 0	39	41	
Week 1	6	5	
Week 2	3	4	
Week 3	1	2	
Week 4	1	1	
Week 5	1	1	
Week 6	1	1	
Week 7	4	1	
Malaria pigment cluster clearance time (week)			0.65
Mean (sd)	2.30 (1.6)	2.44 (1.1)	
Range	1-7	1-7	

Table 3. Distribution of pregnant women with pigment carriage in peripheral blood at enrolment.

No. of pregnancies (n)	No. with pigment in peripheral blood (%)
0 (73)	13 (17.8)
1 (62)	27 (43.5)
2 (49)	19 (38.7)
3 (37)	15 (40.5)
4 (13)	5 (38.5)
5 (7)	1 (14.3)

-Aghoja et al., 2008). Is our training offered through seminars and workshops to health workers not adequate? Is it possible that both the doctors and care givers do not believe that the strategy can work on the field, and thus little engage in its promotion? Whatever may be the case, there is the need to evaluate what would be the fate of those who still lack IPTp care in the local suburb and the urban settings, and are in their second and third trimester; We attempted, in the presents study, to evolve an index of measure of parasite suppression by using simple malaria pigment observation of clearance over time following drug administration.- Malaria pigment cluster clearance from peripheral blood, MPCC.

This is designed to provide a quick monitor of effect of drug on suppression on parasite development or none microscopically detectable parasite activities that will be readily adaptable in the local settings where microscopy is available but handled by a poorly trained microscopist. Malaria pigment which initially is deposited in vacuoles within the erythrocytes during infection is known to subsequently release into suspension in plasma on rupture of parasitized erythrocytes, from where it is scavenged by leukocytes (Bohle et al., 1998; Metzger et al., 1995) and the detection in blood or tissue is positively indicative of malarial infection, with a number of biological effects. Should our participants harbour non-microscopically detectable parasitaemia, it will be expected that those treated with antimalarial should have low pigments concentration in plasma over time compared to those who did not take the antimalarial. In the present study, the reason(s) for the prolonged pigment carriage in two SP treated participants is not clear from our present study. More studies may in the future find application for
the proposed index as it lend itself conspicuous for use within available but limited capacity formicroscopy in poor endemic settings.

It is noteworthy that the outcome in the pregnant women without SP treatment was similar to those on the IPTp. The high use of anti-vector might have contributed to boosting the observed host response. The associated challenge for assessment of effectiveness of IPTp in the area of study is the blurring of outcome assumed to result from the effect of frequent use of vector control methods. However, the advantage is the use of combination of the IPTp and effective vector control measures. This will improve the outcome of pregnancy from women residing in malaria endemic regions.

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REFERENCES

Bohle DS, Debrunner P, Jordan PA, Madsen SK, Schulz CE (1998). Aggregated heme detoxification byproducts in malarial trophozoites: b-hematin and malaria pigment have a single S ¼ 5/2 iron environment in the bulk phase as determined by EPR and magnetic Mossbauer spectroscopy. J. Am. Chem. Soc., 120: 8255-8256.

Breman JG, Alilio MS, Mills A (2004). Conquering the intolerable burden of malaria: what's new, what's needed: a summary. Am. J. Trop. Med. Hyg., 7(2): 1-15.

Campbell P, Baruah S, Narain K, Rogers CC (2006). A randomized trial comparing the efficacy of four treatment regimens for uncomplicated falciparum malaria in Assam state, India.Trans. Res. Soc. Trop. Med. Hyg., 100(2): 108-118.

East Africa Network for Monitoring Anti-Malarial Treatment (EANMAT) (2003). The efficacy of antimalarial monotherapies, sulphadoxine-pyrimethamine and amodiaquine in East Africa: implications for sub-regional policy. Trop. Med. Int. Health, 8(10): 860-867.

Enato EFO, Okhamafe AO, Okpere EE, Oseji FI (2007). Prevalence of malaria during pregnancy and antimalarial intervention in an urban secondary health care facility in Southern Nigeria. Med. Princ. Pract., 16: 240-243.

Falade CO, Salako LA, Sowunmi A, Oduola AM. Larcier P (1997). Comparative efficacy of halofantrine, chloroquine and sulfadoxine-pyrimethamine for treatment of acute uncomplicated falciparum malaria in Nigerian children. Trans. Res. Soc. Trop. Med. Hyg., 91(1): 58-62.

Falade CO, Yusuf BO, Fadero FF, Mokuolu OA, Hamer DH, Salako LA (2007). Intermittent preventive treatment with sulphadoxine-pyrimethamine is effective in preventing maternal and placental malaria in Ibadan, south-western Nigeria. Malar J., 6: 88.

Fawole AO, Onyeaso NC (2008). Perception and practice of malaria prophylaxis in pregnancy among primary health care provider in Ibadan, Nigeria. West Afr. J. Med., 27(2): 92-96.

Federal Ministry of Health (FMOH) (2005). National Treatment guidelines for the treatment of malaria in Nigeria. Federal Ministry of Health.

Jima D, Tesfaye G, Medhin A, Kebede A, Argaw D, Babaniyi O (2005). Efficacy of sulfadoxine-pyrimethamine for the treatment of uncomplicated falciparum malaria in Ethiopia. East Afr. Med. J., 85(8): 391-395.

Metzger WG, Mordmuller BG, Kremsner PG (1995). Malaria pigment in leucocytes. Trans. Res. Soc. Trop. Med. Hyg., 89: 637-638.

Newman RD, Moran AC, Kayentao K, Kayentao K, Benga-De E, Yameogo M, Gaye O, Faye O, Lo Y, Moreira PM, Doumbo O, Parise ME, Steketee RW (2006). Prevention of malaria during pregnancy in West Africa: policy change and the power of subregional action.

Omo-Aghoja LO, Aghoja CO, Oghaghon K, Omo-Aghoja VW, Esume C (2008). Prevention and treatment on malaria in pregnancy in Nigeria: Obstetrician's knowledge of guideline and policy change- a call for action. J. Chin. Clin. Med., 3(2): 114-120

Parise ME, Ayisi JG, Nahlen BL, Schultz LJ, Roberts JM, Misore A (1998). Efficacy of sulfadoxine-pyrimethamine for prevention of placental malaria in an area of Kenya with a high prevalence of malaria and human immunodeficiency virus infection. Am. J. Trop. Med. Hyg., 59(5): 813-22.

Plowe CV, Kublin JG, Dzinjalamala FK, Kamwendo DS, Mukadam RA (2004). Sustained clinical efficacy of sulfadoxine-pyrimethamine for uncomplicated falciparum malaria in Malawi after 10 years as first line treatment: five year prospective study. BMJ., 6(328): 545-549.

Ringwald P (2004). Treatment failure and resitance in Malawi remain subject for debate. BMJ; 328: 1259-1259.

Schellenberg D, Armstrong-Schellenberg JRM, Mushi A, de Savigny D, Mgalula L, Mbuya C, Victora CG (2003). The silent burden of anemia in Tanzania children: a community based study. Bull. World Health Org., 81(8): 581-590.

Schultz LJ, Steketee RW, Macheso A, Kazembe P, Chitsulo L, Wirima JJ (1994). The efficacy of antimalarial regimens containing sulfadoxine-pyrimethamine and/or chloroquine in preventing peripheral and placental Plasmodium falciparum infection among pregnant women in Malawi. Am. J. Trop. Med. Hyg., 51(5): 515-522.

Shulman CE, Dorman EK, Cutis F, Kawuondo K, Bulmer JN, Peshu N, Marsh K (1999). Intermittent sulphadoxine-pyrimethamine to prevent severe anaemia secondary to malaria in pregnancy: a randomized placebo-controlled trial. Lancet., 353: 632-636.

Shulman CE, Graham WJ, Jilo H, Lowe BS, New L, Obiero J, Snow RW, Marsh K (1996). Malaria as an important cause of anemia in primigravidae: evidence from a district hospital in coastal Kenya. Trans. Res. Soc. Trop. Med. Hyg., 90: 535-553

Sowunmi A, Fehintola FA, Adedeji AA, Gbotosho GO, Falade CO, Tambo E, Fateye (2004). Open randomized study of pyrimethamine-sulfadoxine versus pyrimethamine-sulfadoxine plus probenecid for the treatment of uncomplicated Plasmodium falciparum malaria in children. Trop. Med. Int. Health, 9: 606-614.

Sowunmi A, Gbotosho GO, Adedeji AA, Fateye BA, Sabitu MF, Happi TC, Fehintola FA (2007). Effects of acute Plasmodium falciparum malaria on body weight in children in an endemic area. Parasitol. Res., 100: 343-349.

Steketee RW, Wirima JJ, Slutsker L, Khoromana CO, Heymann DL, Breman JG (1996). Malaria treatment and prevention in pregnancy: indications for use and adverse events associated with use of chloroquine or mefloquine. Am. J. Trop. Med. Hyg., 55(1): 50-56.

Tukur IU, Thacher TD, Sagay AS, Madaki JK (2007). A comparison of sulfadoxine-pyrimethamine with chloroquine and pyrimethamine for prevention of malaria in pregnant Nigerian women. Am. J. Trop. Med. Hyg., 76(6): 1019-1023.

Valleyl A, Valleyl L, Changalucha J, Greenwood B, Chandramohan D (2007). Intermmitent preventive treatment for malaria in pregnancy in Africa: What's new, what's needed? Malaria J. 6(16): 10. 1186/1475-2875-6-16.

van den Broek IV, Maung UA, Peters A, Liem L, Kamal M (2005). Efficacy of chloroquine + sulfadoxine--pyrimethamine, mefloquine + artesunate and artemether + lumefantrine combination therapies to treat Plasmodium falciparum malaria in the Chittagong Hill Tracts, Bangladesh. Trans. Res. Soc. Trop. Med. Hyg., 99(10): 727-35.

Verhoeff FH, Brabin BJ, Chimsuku L, Kazembe P, Russel WB, Broadhead RL (1998). An evaluation of intermittent sulfadoxine-pyrimethamine treatment in pregnancy on parasite clearance and risk of low birth weight in rural Malawi. Ann. Trop. Med. Parasitol., 92: 141-150.

White N (2004). Sulfadoxine-pyrimethamine is not working in Malawi. BMJ., 328: 1259.

World Health Organization (WHO) (2004). A Strategic Framework for Malaria Prevention and control during Pregnancy in the Africa Region. World Health Organization Regional Office for Africa.