

THE EFFICACY OF SULFADOXINE-PYRIMETHAMINE AS A MALARIA PROPHYLACTIC DRUG AMONG PREGNANT WOMEN IN OSOGBO, SOUTHWESTERN NIGERIA

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ABSTRACT

Malaria in pregnancy is a major public health problem in Nigeria. A cross sectional study was carried out to determine the efficacy of sulfadoxine-pyrimethamine (SP) as a prophylactic drug against malaria among antenatal subjects in Osogbo, South Western Nigeria. A total of eighty-five pregnant women were recruited for the study. Thick blood film of the blood samples of the studied subjects were assessed for plasmodium falciparum at an interval for three consecutive times. Questionnaires were administered to assess adverse effect, knowledge, utilization and compliance with the drug regimen.

The overall mean parasite density before drug administration was 700 ± 221.3 , 629.3 ± 196.3 and 556.6 ± 165.8 , and after drug administration was 37.8 ± 25.6 , 39.2 ± 28.3 and 32.9 ± 32.6 in the primigravidae, secundigravidae and multigravidae respectively ($P < 0.001$). Based on dose(s) taken, the mean parasite density after drug administration in the study subjects that took two doses of SP was 35.0 ± 24.9 , 35.0 ± 30.5 and 10.9 ± 12.4 in primigravidae, secundigravidae and multigravidae respectively. The mean parasite density in those that took only one dose was 64.3 ± 16.8 , 63.9 ± 11.6 and 48.9 ± 33.8 in primigravidae, secundigravidae and multigravidae respectively.

Comparing the differences in mean parasite density among those that received one dose and those that received two doses shows statistical significance only for the secundigravidae ($P=0.016$). Eighty three (97.7%) of the recruited women knew SP as a malaria prophylactic drug during pregnancy and 70 (82.4%) knew correct timing of taking the drug. Mild adverse effects were reported in the study. Fifty eight (68.2%) of study subjects took recommended doses of SP. It is evident from our results that sulfadoxine-pyrimethamine is a reliable drug that is useful for prophylaxis among pregnant women in secundigravidae and multigravidae in this locality.

Key words: Maternal malaria, Sulfadoxine-pyrimethamine (SP), Primigravidae, Secundigravidae, Multigravidae.

1. INTRODUCTION

Malaria is a major public health problem worldwide most especially in African countries. Forty percent of the world's populations live in malaria endemic regions, and an estimated 25 million pregnancies are believed to occur annually in malaria endemic areas of sub-Saharan Africa [1]. High prevalence were recorded among pregnant women and children under five [2,3], while 48% of pregnant women were diagnosed with malaria in Nigeria according to the Federal Ministry of Health I 2005 [4]. In southwest Nigeria, past studies reported malaria parasite prevalence between 60% and 72% among pregnant women [4,5]. Malaria during pregnancy caused up to 10,000 maternal deaths each year and contributes to high rates of maternal morbidity including fever and severe anaemia, especially among first time mothers [6,7]. It is also a cause of low birth weight and placental parasitaemia [8,9], as between 75,000 to 200,000 infant deaths are attributable to malaria infection in pregnancy annually [1,10].

The harmful impact of malaria is most apparent in the first and second pregnancies of most pregnant women living in areas of relatively stable transmission [11]. The transient depression of immunity allowing for development of the allograft (foetus) is one of the reasons adduced for the increased susceptibility of the pregnant woman to malaria [9]. Other reasons adduced for this increase susceptibility to malaria infection include relative impairment of the immune system [12,13], cytoadherence to chondroitin sulphate A in the placenta [14], and an increased attractiveness of pregnant women to malaria vectors [15]. The outcomes of the invasion of the placenta by parasites, inflammatory cells and cytokines include abortion, premature labour, small-for-date babies and foetal or maternal death in some instances [9,10,16]. These unfavorable pregnancy outcomes are associated with sequestration of malaria parasites in the placental intervillous spaces attached to chondroitin-sulphate [17,18]. Pro-inflammatory cells and cytokines also

invade the placental bed, the net result is impairment of foetal blood and nutrient supply, which in turn predisposes to low birth weight as occurs in babies born prematurely.

The effect of infection on the pregnancy is dependent on pre-pregnancy immunity. This acquired anti-malarial immunity depends on intensity of transmission and the number of previous pregnancies among others. In areas of stable malaria transmission, the ill health effects are particularly apparent in the primigravidae, and secundigravidae [19]. Previous studies have shown a higher prevalence and parasitaemia in the first trimester and primigravidae of pregnancy [19]. Also multigravidae with HIV infection are similar to primigravidae without HIV infection in terms of susceptibility to and negative consequences of malaria [20]. However, in areas of unstable transmission, exposure is infrequent and people of all ages are at risk of severe malaria and in such areas, pregnant women also suffer more severely than non-pregnant adults with about 3 to 4 times the risk of developing severe malaria and death [19].

With the numerous complications associated with malaria infections, the need to prevent malaria infections in pregnancy become imperative due to lack of malaria vaccine. Sulfadoxine-pyrimethamine is currently the recommended regimen for prevention of malaria in pregnancy in Nigeria [21]. The World Health Organization (WHO) currently recommends that each pregnant woman in malaria endemic areas should receive at least two doses of intermittent preventive treatment after quickening [1]. This objective of this study is to assess the efficacy of sulfadoxine pyrimethamine dosage regimen in different stages of pregnancy among antenatal subjects in order to ascertain the extent of its reliability.

2. MATERIAL AND METHOD

Study site: This cross-sectional study was conducted at the antenatal clinic of State general hospital, Asubiaro, Osogbo Osun-state Nigeria from June to September 2010. During the time of this study, the drugs were provided free to all the patients attending the hospital by the hospital management, courtesy of the state government free health programme.

Study design: Descriptive cross-sectional study among pregnant women.

Inclusion Criteria: Pregnant women who were SP eligible, with no history of allergy to SP and were willing to attend antenatal clinic, follow-up visits regularly and consent to participate in this study.

Sample size and sampling: A total of 85 antenatal subjects who were registered into ANC care in the hospital within the period were recruited for the study who are users of sulfadoxine-pyrimethamine. Registered pregnant women were stratified into two groups. The first were subjects in the first trimester and those above 38 weeks of gestation, as these were ineligible for SP, and were excluded from this study. The second group or the rest of the pregnant women were eligible and were recruited into the study.

Sample collection and processing: 2mls venous blood was collected into Ethylenediamine tetra acetic acid (EDTA) anticoagulant bottle to determine parasite load. Questionnaires used were semi-structured, interviewer-administered and pre-tested to assess adverse reaction to the drug, to assess compliance with the drug, knowledge and utilization of the drug, and to determine any other preventive measure being used by studied subjects. Blood samples were collected from each study subject, before and after drug administration to determine parasite density. Three blood samples were collected from each study subject, the first blood sample was collected before drug administration (basal sample), and the other two blood samples were collected from each subject at a month interval after respective drug administration.

Thick films were prepared to determine the parasite load and stained with 10% Giemsa stain, and the pH of the stain was maintained at 7.2. The parasite density in the thick film was determined using Greenwood and Armstrong method [22]. Efficacy of the drug was assessed by decreasing density of the parasitaemia in the thick film of blood samples, collected intermittently from the study subjects.

Drug provision: A general prescription script was written by the doctor, and this was used to obtain the drugs from the hospital pharmacy for the study subjects. The brands of sulfadoxine-pyrimethamine used in this hospital were Fansidar[®] and Amalar[®].

Drug administration : A sachet of Amalar[®] / Fansidar contains three tablets, each containing 500 mg sulfadoxine and 25 mg pyrimethamine which was taken as a single dose. The study subjects were instructed to come with their own drinking cup and water, though the researcher also provided bags of sachet water. Directly Observed Therapy (DOT) scheme was employed in drug administration. Each pregnant woman was provided with three tablets of

Sulfadoxine-pyrimethamine (SP) with a cup of water and observed by a nurse and the researcher to ensure tablets were swallowed. Each subject was administered with two therapeutic doses of sulfadoxine-pyrimethamine at monthly interval. The first dose was administered at 16 weeks or after sixteen weeks of pregnancy and the second dose was given four weeks later. Dates of first and subsequent treatment were recorded, subjects were told to report any feelings or reaction after treatment to the hospital or the nearest pharmaco-vigillant office. Study subjects were also advised not to self-administer any drug, because there are different brands of sulfadoxine-pyrimethamine (SP) in market and also to avoid drug–drug interaction.

Ethical issues and ethical clearance: Ethical clearance and approval was obtained from Osun state Ministry of Health and Ethical Committee of Ladoke Akintola University of Technology Teaching Hospital, Osogbo, Osun State. Informed consent was also sought and obtained from the State Hospital, Asubiario, Osogbo, Osun-state hospitals management board and subjects used for the study. Reasons as well as the procedures of the study were explained to the antenatal subjects and consent obtained before commencing the study.

Statistical analysis: All data were entered and analyzed with SPSS for window 15.0 (Chicago, USA). Data were summarized using frequency table, graph, mean and standard deviation. Analysis was done using the chi-square test to determine association between relevant categorical variables. P-Values were considered to be statistically significant if less than 0.05 and all analysis were done at 95% confidence interval.

3. RESULTS

Table 1 shows the general characteristics of study subjects. Age range of the subjects is from 19-46years and age bracket 25-35 years accounted for (65.9%) of the subjects. Fifty percent of the participants were gainfully employed while 15 (17.6%) were students. Forty-one (48.2%) had tertiary education while 5 (5.9%) were illiterates. Based on gravidity, 37(43.5%) were primigravidae, 29 (34.1%) were secundigravidae and 19 (22.4%) were multigravidae. Fifty-eight (68.2%) of the subjects were in the second trimester when recruited for this study. Only ten participants (11.8%) were herb users while seventy-five (88.2%) were non herb users. Majority 71 (83.5%) can afford to buy SP for use. All the pregnant women recruited were user of prophylactic folate.

Table 2 shows the efficacy of sulfadoxine-pyrimethamine based on gravidity. Among the 37 (43.5%) primigravidae recruited, the mean parasite density was 700 ± 221.3 before drug administration and 37.8 ± 25.6 after drug administration ($P=0.000$). Among the 29 secundigravidae, the mean parasitaemia was 629.3 ± 196.3 before drug administration and 39.2 ± 28.3 after drug administration, and the difference was statistically significant ($P=0.000$). In the 19 multigravidae, the mean parasite density was 556.6 ± 165.8 and 32.9 ± 32.6 before and after drug administration respectively, and the difference was also statistically significant ($P=0.000$).

Table 3 shows the frequency of parasitaemia before and after drug administration based on gravidity. Before drug administration, and among the primigravidae recruited, 28 (75.7%) had moderate parasitaemia, and 9 (24.3%) had high parasitaemia. Among the secundigravidae recruited, 26 (89.7%) had moderate parasitaemia and 3 (10.3%) had high parasitaemia. Among the multigravidae recruited, 18 (94.7%) had moderate parasitaemia and 1 (5.3%) had high parasitaemia. After drug administration and among the primigravidae, 6 (16.2%) had no parasite count, while 31 (83.8%) had low parasitaemia. Among the secundigravidae, 4 (13.8%) had no parasitaemia while 25 (86.2%) had low parasitaemia. Among the multigravidae recruited, 4 (21.1%) had no parasite count while 15 (78.9%) had low parasitaemia.

Table 4 shows the effect of sulfadoxine-pyrimethamine on parasitaemia based on dose received. The mean parasite density in the primigravidae that received two doses was 694.2 ± 234.0 before drug administration and 35.0 ± 24.9 after drug administration, and the difference was statistically significant ($P=0.000$). The mean parasite density in primigravidae that received one dose was 889.3 ± 116.2 before drug administration and 64.3 ± 16.8 after drug administration, and the difference was also statistically significant ($P=0.000$). When the difference in the mean parasitaemia among primigravidae that received two doses was compared with those who received only one dose, the difference was not statistically significant ($P=0.114$).

The mean parasitaemia in secundigravidae that received two doses was 623.8 ± 206.9 before drug administration and 35.0 ± 30.5 after drug administration, and the difference was statistically significant ($P=0.000$). The mean parasitaemia in secundigravidae that received only one dose was 669.4 ± 160.5 before drug administration and 63.9 ± 11.6 after drug administration, and the difference was also statistically significant ($P=0.000$). When the difference in the mean parasite density of secundigravidae that took two doses was compared with those that took one dose, the difference was however found to be statistically significant ($P=0.016$).

The mean parasitaemia of the multigravidae that received two doses was 512.5 ± 216.3 before drug administration and 10.9 ± 12.4 after drug administration, and the difference was statistically significant ($P=0.000$). The mean parasitaemia in multigravidae that received only one dose before and after drug administration was 579.5 ± 121.4

and 48.9 ± 33.8 respectively and the difference was also statistically significant ($P=0.000$), When the difference in the mean parasitaemia between the multigravidae that received two doses was compared with those that received one dose, the difference was not statistically significant ($P=0.408$).

Table 5 shows the knowledge and utilization of SP as a malaria prophylactic drug. Out of the 85 study subjects recruited, 83 (97.7%) knew SP as a malaria prophylactic drug during pregnancy while 2 (2.4%) does not. Majority (92.9%) of the study subjects knew the timing when SP is safe while all respondents knew SP as an antimalarial drug. Eighty-two (96.5%) knew the number of tablets to be taken per dose while 3(3.5%) does not. Seventy (82.4%) knew the recommended dose to be taken during pregnancy while 15 (17.7%) does not. Also 70 (82.4%) knew the month interval before administration of the second dose while 15 (17.7%) does not.

Table 5 also shows that adverse effect reported by the study subjects were mild, 50(58.8%) of the subjects reported no adverse effects of the drug while 17(20%), 13(15.3%), 4(4.7%), and 1(1.2%) reported Nausea, Abdominal discomfort, slight itching and diarrhea respectively. Compliance of pregnant women with the drug shows that out of the 85 pregnant women recruited, 58 (68.2%) took the recommended doses (2 doses) while 27 (31.8%) pregnant women took only one dose. Fifteen (17.7%) of the pregnant women took their drug home for taking while 70 (82.4%) took their drug as Directly Observed Therapy (DOT).

4. DISCUSSION

In this study, there was a significant decreased in the mean malaria parasite density in all the study subjects recruited. This high efficacy of sulfadoxine-pyrimethamine (SP) as a malaria prophylactic drug irrespective of gravidity may be due to suppression of the asymptomatic infection and the long half life of the drug. This agrees with other studies [9,22-28] done within and outside Nigeria supporting SP as an effective malaria prophylactic drug in reducing maternal and placenta malaria during pregnancy

In this study, both two doses as well as one dose of SP were effective as malaria prophylactic drug, and this may be as a result of suppression in the existing asymptomatic malaria parasitaemia and long half-life of the drug, which prevent new infection. This supports another study [29]. However, mean parasitaemia in those that received two doses after drug administration was found to be more lower than those that received only one dose among the primigravidae, secundigravidae and multigravidae studied. This also agreed with other studies within and outside Nigeria [22-27].

Before drug administration, 5.3% of multigravidae recruited in this study had high parasitaemia, and this is lower compared to the frequency of high parasitaemia recorded for primigravidae (24.3%) and secundigravidae (10.3%) respectively. This was also in agreement with work of previous researchers [1,19,30], who reported that ill health effect are particularly apparent in primigravidae and secundigravidae than multigravidae whom may have acquired pre-pregnancy immunity. After drug administration in this study, it was found that 16.2% (primigravidae), 13.8% (secundigravidae) and 21.1% (multigravidae) had no parasite in their thick films while others had low parasite density in their thick films with little difference in their proportions 83.8% (primigravidae), 86.2% (secundigravidae) and 78.9% (multigravidae). This demonstration of suppressive effect of SP as a malaria prophylactic has been reported by yet other studies [25,29,30], and may play an important role in prevention of malaria related anaemia in pregnant women and preventing placenta parasitaemia. This is also supported by another study [9].

It was found that about two-thirds of the women recruited received two doses of SP while about one-third received one dose of SP. This uptake of the recommended doses (two doses) of SP was similar to the study carried out in Tanzania [31], and Senegal [32] in which two thirds and almost three-quarter of the pregnant women studied respectively took two doses of SP. This is however in contrast to some studies within and outside Nigeria in which only a quarter to one third of pregnant women studied took 2 doses of SP [33-36].

The high uptake of the recommended doses of SP recorded in this study could be as a result of the fact that the drug is free or charge, the fact that directly observed therapy scheme was employed in this study, persistent inclusion of the subject matter in health talk by nurses during ANC, and early enrolment for antenatal care in the southwestern part of Nigeria Low uptake of SP could be due to late enrolment, fear of side effects, and unavailability of SP in stock as reported by previous researchers [25,31,37,38]

Adverse reactions reported by this study participant were mild. These mild adverse effects may not necessitate any treatment as they occur for short period of time and then disappear with time. This finding supports other studies [9,19,24,25,27,28]. Serious life threatening allergic reaction to SP (such as severe cutaneous reactions) as reported by a study [39], were said to be relatively rare and if such allergic reactions occurred, the drug must be withdrawn [21,40,41].

The fact that almost all pregnant women in this study recruited knew SP as a malaria prophylactic drug during pregnancy was in agreement with an East African study [38], but in contrast with another study in which only half of pregnant women studied have heard about SP as a malaria prophylactic drug during pregnancy. Increased awareness of SP as a malaria prophylactic drug during pregnancy recorded in this study could be because the use of

SP was included in routine antenatal health talk, where antenatal women were educated about the time to start and stop SP usage and other relevant information about the uptake of SP.

About four-fifth of the pregnant women in this study knew the recommended dose as well as the time interval for administration of the second dose. This was in contrast with other studies [33,38] in which one-fifth to one third of pregnant women studied knew the correct timing of SP. However the finding that almost all subjects in this study knew the number of tablets of SP to be taken per dose agreed with similar studies carried out by other researchers [31,33,38,41]. These two trends could be explained by the fact that many of our subjects most especially the secundigravidae and multigravidae might have patronized private hospitals in the past, and these private practice freely discuss drugs among other clinically oriented information. This coupled with increased emphasis on comprehensive health education in our focused antenatal care programme would afford pregnant women the opportunity to have correct and accurate information concerning their antenatal care drugs.

5. CONCLUSION

Sulfadoxine-pyrimethamine (SP) is effective as a malaria prophylactic drug during pregnancy in preventing maternal malaria, reducing morbidity and mortality rate in pregnant women and maintaining healthy pregnancy. While we advocate that the use of SP should be taken as directly observed therapy, its knowledge and utilization should be integrated into antenatal care services at all level of health care in Nigeria.

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Table I: Socio-demographic characteristics and Obstetrics history of respondents

Age group (years)	
≥ 19-24	11 (12.9)
25-35	56 (65.9)
36-46	18 (21.2)
Occupation	
No of employed	50 (58.8)
No of unemployed	20 (23.5)
No of students	15 (17.6)
Level of education	
No formal	5 (5.9)
Primary	12 (14.1)
Secondary	27 (31.8)
Tertiary	41 (48.2)
Gestational age of pregnancy at ANC booking	
First trimester	—
Second trimester	58 (68.2)
Third trimester	27 (31.8)
Month of pregnancy at recruitment.	
First trimester (1-3 months)	—
Second trimester (4-6 months)	58 (68.2)
Third trimester (7-9 months)	27 (31.8)
Using folic acid	85 (100)
Other preventive measure(s)	
Insecticide treated bed net	6 (7.1)
Untreated bed net	45 (52.9)
Spray	9 (10.6)
Mosquito coil	3 (3.5)
Non	22 (25.9)
Use native herb in pregnancy	10 (11.8)
Can afford to buy SP	71 (83.5)

Table II: Showing efficacy of sulfadoxine-pyrimethamine based on gravidity.

Gravidity	No examined	MPD _a (mean±SD)	MPD _b (mean±SD)	P value
Primigravidae	37 (43.5)	700±221.3	37.8±25.6	0.000
Secundigravidae	29 (34.1)	629.3±196.3	39.2±28.3	0.000
Multigravidae	19 (22.4)	556.6±165.8	32.9±32.6	0.000

Key:MPD_a- malaria parasite density before drug administration (parasites/μl of blood).MPD_b-malaria parasite density after drug administration (parasites/μl of blood).

Table III: Frequency of parasitaemia based on gravidity

Key:

Low: 20-250 Parasites/µl of blood

Moderate: >250-850 Parasites/µl of blood

Gravidity	Before drug administration			After drug administration			
	Prim	Secun	Mult	Gravidity	Prim	Secun	Mult
Parasitaemia frequency				Parasitaemia	frequency		
Moderate	28(75.7)	26(89.7)	18(94.7)	Nil	6(16.2)	4(13.8)	4(21.1)
High	9(24.3)	3(10.3)	1(5.3)	Low	31(83.8)	25(86.2)	15(78.9)
Total	37(100)	29(100)	19(100)	Total	37(100)	29(100)	19(100)

High: >850-1,250 Parasites/µl of blood

Prim: Primigravidae

Secun: Secundigravidae

Mult: Multigravidae

Table IV: Effects of sulfadoxine-pyrimethamine on parasitaemia based on dose received.

Gravidity	No assessed	Two doses		P value	One dose		P value	Compared*
		MPD (mean±SD)			MPD (mean±SD)			
		a	b		a	b		
Primigravidae	37(43.5)	694.2± 234.0	35.0± 24.9	0.000	889.3± 116.2	64.3± 16.8	0.000	0.114
Secundigravidae	29(34.1)	623.8± 206.9	35.0± 30.5	0.000	669.4± 160.5	63.9± 11.6	0.000	0.016
Multigravidae	19(22.4)	512.5± 216.3	10.9± 12.4	0.000	579.5± 121.4	48.9± 33.8	0.000	0.408

Key:

a: Parasitaemia before drug administration

b: Parasitaemia after drug administration.

Table V: Knowledge, utilization, adverse effects and compliance with Sulfadoxine-pyrimethamine among respondents

Variables	N=85	
	Frequency	Percentage
Know SP as a malaria prophylactic drug during pregnancy	83	97.7
Knew the timing when SP is safe	79	92.9
Knew the function of the drug	85	100
Knew the correct no of tablets to be taken per dose	82	96.5
Knew the recommended dose to be taken during pregnancy	70	82.4
Knew interval between first and second dose	70	82.4
Adverse effects of SP		
Nausea	17	20.0
Abdominal discomfort	13	15.3
Slight itching	4	4.7
Diarrhea	1	1.2
No symptomatic effects	50	58.8
Drug compliance with SP		
Number that took the two doses (recommended doses)	58	68.2
Number that took one dose	27	31.8
Number that took their drug home for taking	15	17.7
Number that took the drug as DOT	70	82.4

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