Original Article

Comparative study of proguanil and sulphadoxine–pyrimethamine in the prevention of malaria in pregnancy

Adewale Jamiu Lasisi, Rukiyat Abdus-salam[1], Olusegun Badejoko[2], Adebanjo Adeyemi[2], Olabisi Loto[2]

Department of Obstetrics and Gynaecology, Ring Road Specialist Hospital, Ring Road, [1]Department of Obstetrics and Gynaecology, Adeoyo Maternity Teaching Hospital, Ibadan, [2]Department of Obstetrics and Gynaecology, Obafemi Awolowo University Teaching Hospital Complex, Ile-Ife, Osun State, Nigeria

ABSTRACT

Background: Intermittent preventive treatment of malaria in pregnancy with sulphadoxine–pyrimethamine (SP) is recommended for prevention of malaria in pregnancy. However, chemoprophylaxis with proguanil (PG) is being used in pregnancy for preventing malaria in selected cases.

Objective: To compare the efficacy of daily PG and intermittent monthly SP in preventing malaria and its complications during pregnancy.

Patients and Methods: This was a prospective comparative study conducted among 270 consenting pregnant women with parity ≤2 at gestational age of 18–24 weeks. Participants were enrolled and randomized to PG or SP group following a baseline hemoglobin estimation and blood film negative for malaria parasite. At 36 weeks of gestation, maternal blood sample was checked for hemoglobin concentration and malaria parasitaemia, and the infant birth weight was assessed at delivery.

Statistical Analysis: Appropriate univariate, and bivariate analysis employed and level of significance set at $P < 0.05$.

Results: One hundred and thirty-five participants in each group (246) completed the study. Ten (8.5%) had malaria parasitaemia in the PG group at 36 weeks compared to 15 (11.7%) in the SP group ($P = 0.40$); 5 (4.3%) in the PG compared with 6 in SP group (4.7%) had anemia (Hb <10 g/dl) at 36 weeks ($P = 0.86$). In addition, 6 (5.1%) participants in the PG group developed clinical malaria compared to 3 (2.3%) in the SP group ($P = 0.25$). The mean infant birth weight in the PG and SP groups were 3.05 kg and 3.00 kg, respectively ($P = 0.24$).

Conclusion: PG and SP were comparable in efficacy and outcome for malaria prevention during pregnancy. IPT-SP is recommended for prevention of malaria in pregnancy. However, PG is beneficial in selected patients with known adverse reactions to sulphonamide.

Key words: Intermittent preventive treatment; malaria infection; malaria prevention; malaria in pregnancy; proguanil; sulphadoxine–pyrimethamine.

Introduction

Malaria in pregnancy, a major public health problem, has continued to result in high morbidity and mortality in Sub-Saharan Africa, South-east Asia, and Papua New Guinea.[1-3] It is associated with deleterious effects to the mother, fetus, and the newborn.[4,5]

There are at least 300 million acute cases of malaria each year globally resulting in more than a million deaths.

Address for correspondence: Dr. Adewale Jamiu Lasisi, Department of Obstetrics and Gynaecology, Ring Road Specialist Hospital, Ring Road, Ibadan, Oyo State, Nigeria.
E-mail: walelass@yahoo.com

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About 90% of these deaths occur in Africa, mostly in young children and pregnant women.[2-5] According to the World malaria report, Nigeria accounts for a quarter of all malaria cases in the 45 malaria endemic countries in Africa, highlighting the challenge of malaria in Nigeria.[6,7] Every year, at least 30 million pregnancies occur among women in malaria-endemic areas of Africa, most of who reside in areas of stable malaria transmission.[4,5] The Sub-Saharan Africa region represents areas of high and moderate (stable) malaria transmission.[3-5] Women who have lived in endemic areas without protection from malaria will have acquired partial immunity from recurrent parasitaemia by the time they are old enough to become pregnant, just like any other adult indigenous to endemic areas.[5,8-11]

Most malaria infections are caused by *Plasmodium spp.*; *P. falciparum falciparum*; causing the most severe and life-threatening form of the disease.[4] There are other identified species causing human malaria, namely, *P. vivax*, *P. ovale*, *P malariae*, and *P knowlesi*.[4,12] In Nigeria, 98% of all cases of malaria are caused by *P. falciparum*.[1,5,7]

Malaria in pregnancy is an obstetric, social, and medical problem; and pregnant women constitute the main adult high-risk group.[10] Malaria and pregnancy are mutually aggravating conditions.[4,10] The physiological changes during pregnancy and pathological changes due to malaria both have synergistic effects on the course of the pregnancy and disease.[10] The frequency and severity of malaria are greater in the pregnant than the nonpregnant state, and the complications of malaria are more likely to result in mortality in pregnant than that in nonpregnant women.[5,10] Nonimmune primigravidae are most affected compared to multigravidae who have developed immunity from previous episodes of malaria parasitaemia in pregnancy.[5,11,12]

The pathophysiology of malaria in pregnancy is due to the altered immunity and presence of the placenta in pregnancy. Multigravidae are able to develop strain-independent antibodies against chondroitin sulphate A (CSA)-specific parasite antigen. These are antiadhesive antibodies and prevent *P. falciparum* sequestration in the placenta; these antibodies are lacking in the primigravidae, resulting in susceptibility to malaria infestation.[10,12]

Most immune pregnant women are asymptomatic in the presence of parasitaemia. The complications of malaria include anaemia, hypoglycemia, cerebral malaria, and pulmonary edema; and maternal mortality can occur from severe malaria.[3,10] Others include miscarriage or preterm labor, delivery of low birth weight infants, prematurity, intrauterine growth restriction (IUGR), and intrauterine fetal death (IUFD).[1,9-12] All these account for relative increase in maternal and perinatal morbidity and mortality associated with malaria in pregnancy.[11]

Previous studies have shown that regular chemoprophylaxis prevents malaria attack and its associated complications. More recently, intermittent preventive treatment for malaria using sulphadoxine–pyrimethamine (SP) has been shown to be cost-effective and efficacious in reducing malaria infection and complications of malaria in pregnancy.[1,5,13-15] Some studies have shown that use of regular chemoprophylaxis against malaria in addition to the use of iron and folate supplementation as part of routine antenatal care remains a life-saving regimen through the prevention of acute malaria and its associated complications, especially anemia.[1,5,10]

Some studies, including randomized controlled trials and prospective studies conducted in Kenya, Malawi, and Mozambique,[5,16-18] have demonstrated the efficacy, safety, and cost-effectiveness of SP in preventing maternal anemia and low birth weight arising from malaria in pregnancy. However, SP is not recommended in the first trimester of pregnancy because of the risk of congenital malformations and neural tube defects. It is associated with adverse reactions, especially in individuals allergic to sulphonamide, and there is a rise in resistance to SP.[14,19-21]

Proguanil (PG) has been in use for prophylaxis against malaria; it is safe, well-tolerated, and effective in malaria prevention.[14,22] Studies in Nigeria have also shown its efficacy when used alone or in combination with chloroquine in reducing the prevalence of falciparum parasitaemia.[22,23] One of such studies comparing PG only to chloroquine–proguanil for malaria chemoprophylaxis found a reduction of malaria parasitaemia at recruitment from 32% and 35% in the respective groups to about 2% in both groups during follow-up at 28 weeks and 36 weeks. It also reduced severe anemia from 18% to 3% and increased mean birth weight by approximately 132 g.[22,23]

It is necessary to seek alternate regimens of proven efficacy for malaria prevention during pregnancy. The aim of this study is to compare the efficacy of PG in the prevention of malaria in pregnancy with SP as an alternative to SP for patients with allergy or adverse reactions to sulphonamides.

Patients and Methods

Ethics: Ethical approval was obtained by the State research ethics review committee.

Study design: This was a prospective study conducted at the obstetric unit of a secondary health care facility in Southwestern Nigeria. The study was conducted following ethical approval by the State research ethics review committee. The study was a comparative study conducted over a 7-month period among pregnant women in their first or second pregnancies receiving antenatal care in the hospital.

The sample size was calculated using a parasitologic failure rate of 6.6% among women using IPT-SP for prevention of malaria in pregnancy found by a previous study in Ile-Ife,[5] a power of 80%, confidence interval of 95%, and an attrition rate of 10%; a sample size of 270 was obtained. Two hundred and seventy (270) participants were enrolled into the study with 135 in each group.

The inclusion criteria were pregnant women with parity not more than Para 2, singleton pregnancy who have not had IPT-p, gestational age 18–24 weeks, no clinical or laboratory evidence of malaria, Hb A genotype, and no known adverse reaction to sulphadoxine, pyrimethamine or PG.

The exclusion criteria were evidence of malaria infection at recruitment, moderate-to-severe anemia, sickle cell disease, multiple pregnancies, adverse reactions to sulphadoxine, pyrimethamine, or PG, and HIV positive patients.

Eligible participants were enrolled after counselling and obtaining informed consent. Enrolment was done by the investigator and research assistant trained for the study. A data collection form was filled for each participant and subsequently randomized using a simple random technique.

Allocation into groups

Paper ballots were generated for the two groups – group A, the intervention group (PG) and group B, the control group (SP); paper ballots were generated by an assistant blinded to the groups and sealed ballots were placed in a concealed envelope. These were administered by the trained research assistant who was also blinded and participants were asked to pick a single ballot from the concealed envelope and allocated appropriately. Blinding was thus limited to group allocation as the drugs were of different dosing regimen; thus, participants were not blinded. Serial numbers were allocated and recorded as well as participants' hospital number. A structured questionnaire was administered to obtain sociodemographic and clinical information about the participant.

Participants in group A received oral PG 200 mg daily (Reludrine, Osaka pharmaceuticals India); they were counseled regarding the need for strict compliance. Compliance was ensured by double checking sachets of drugs used during subsequent antenatal clinic visits as described below. They were advised and encouraged to take the drug as part of routine antenatal hematinic to encourage compliance.

Participants in group B received two doses of oral SP (Malareich, Meidreich Ltd India) as direct observed therapy at clinic visits. Each dose comprised three tablets of SP each containing 500 mg of sulphadoxine and 25 mg of pyrimethamine. The first dose was administered at entry point (18–24 weeks gestation) and the second dose at least 4 weeks apart ensuring both doses are in the second and early third trimester (26–32 weeks). Routine hematinic (Ferrotone, Mega life pharmaceuticals Nigeria) were provided for all participants.

Maternal blood sample was taken for hemoglobin estimation at enrolment and at 36 weeks. Baseline thick and thin blood films for malaria parasite and species determination was carried out (using standard Giemsa staining) at enrolment to exclude asymptomatic malaria parasitaemia and repeated at 36 weeks. This was also done for participants with symptoms of malaria to confirm diagnosis prior to treatment. Participants with confirmed malaria parasitaemia were treated with arthemeter-lumefantrine combination therapy (Lonart, Bliss Gvspharmaceuticals India).

The participants continued routine antenatal care and patient's compliance ascertained verbally and cross checked with a pill count by the research assistant; the research assistant thereafter dispensed more drugs. Noncompliant participants were advised to opt out of the study.

At 36 weeks gestation, participants had repeat blood film for malaria parasitaemia and hemoglobin concentration. At delivery, the infant birth weight was measured within 30 min of delivery using an analogue infant weighing scale. Participants who did not deliver at the study site were considered lost to follow-up.

Data analysis

All data collected was collated, entered and analyzed using STATA version 11 statistical package. Frequency tables were drawn and proportions generated. Association was determined for categorical variables using Chi-square (χ^2) test and student's *t*-test for continuous variables. The level of statistical significance was set at $P < 0.05$.

Results

Two hundred and seventy (270) women participated in the study. A total of 246 participants completed the

study, with 118 participants (87.41%) in the PG group and 128 participants (94.81%) in the SP group. Twenty-four participants (8.9%) were lost to follow-up and poor compliance; 17 (12.59%) and 7 (5.19%) in the PG and SP groups, respectively.

The sociodemographic characteristics of participants are shown in Table 1. The mean age was significantly higher in the PG group, 27.6 ± 3.62 years compared to 26.3 ± 3.32 years in SP group ($P = 0.01$). There was no statistically significant difference in gestational age at enrolment, parity, educational status, and occupation of the participants.

All participants had negative blood film for malaria parasite at enrolment. The incidence of clinical malaria in both study groups is shown in Table 2. Six participants (5.1%) in the PG group and 3 participants (2.3%) in the SP group had malaria infection ($P = 0.25$). Only two participants (1.7%) in the PG group and none in the SP group had repeat malaria episode during the study period ($P = 0.23$). Ten participants (8.5%) in the PG group compared to 15 (11.7%) in the SP group had positive malaria parasitaemia at 36 weeks ($P = 0.40$).

The mean hemoglobin concentrations at recruitment and at 36 weeks gestation are shown in Table 3; these were 10.53 g/dl and 10.63 g/dl in the PG and SP groups, respectively, at recruitment ($P = 0.40$), while at 36 weeks it was 11.17 g/dl and 11.24 g/dl respectively ($P = 0.78$). Twenty eight participants (23.7%) had anaemia (Hb< 10 g/dl) at recruitment in the PG group compared to 22 participants (17.2%) in the SP group ($P = 0.20$). At 36 weeks, 5 participants (4.3%) in the PG group and 6 participants (4.7%) in the SP group had Hb <10 g/dl, $P = 0.86$ [Table 3].

The mean infant birth weight at delivery was 3.05 kg in the PG group and comparable to 3.00 kg in the SP group ($P = 0.24$).

Discussion

In this study, only 8.5% of participants in the PG group had peripheral malaria parasitaemia at 36 weeks of gestation in contrast to 11.7% of the participants in the SP group. This difference was not statistically significant or clinically significant.

The incidence of malaria parasitaemia in the PG group was higher than that reported by a previous study by Harrison *et al*. in Zaria,[24] which found an incidence of 2%. The participants in the study were recruited at about 24 weeks of gestation and were followed up till 36 weeks of gestation; peripheral malaria parasitaemia was checked at 28 weeks and at 36 weeks. This difference may be due to the variation in the study population and climatic variation between the southwest and Northern parts of Nigeria. The longer period of follow-up in this study may also be contributory to the observed difference. The incidence of malaria in this study is also lower than the incidence of 9.3% in the PG group in another study comparing PG with chloroquine among pregnant women.[25]

The incidence of peripheral malaria parasitaemia at 36 weeks gestation in the SP group of this study (11.7%) was higher compared to incidence of 6.6–10.4%, 5.3%, and 6% reported in similar studies in Nigeria, Kenya, and Mozambique, respectively;[5,15,16,18] however, lower than 36% reported fro Malawi.[26]

Table 1: Sociodemographic characteristics of participants

Variable	Proguanil (*n*=118)	SP (*n*=128)	Statistics *P*
Mean age (years)	27.6±3.62	26.3±3.32	0.01
GA at booking (mean)	21.8±2.0	21.7±2.02	0.66
Marital status			
Married	115 (97.5)	118 (92.2)	0.07
Not married	3 (2.5)	10 (7.8)	
Parity			
0	42 (35.6)	58 (45.3)	0.06
1	46 (39.0)	52 (40.6)	
2	30 (25.4)	18 (14.1)	
Educational status			
None/primary	10 (8.5)	4 (3.1)	0.11
Secondary	65 (55.1)	66 (51.6)	
Post-secondary	43 (36.4)	58 (45.3)	
Occupation			
Housewife/Unemployed/students	21 (17.8)	25 (19.5)	0.43
Business/trading	59 (50.0)	60 (46.9)	
Artisan	17 (14.4)	12 (9.4)	
Civil servant/salaried worker	21 (17.8)	31 (24.2)	
Tribe			
Yoruba	109 (9246)	122 (95.3)	0.34
Non-Yoruba	9 (7.6)	6 (4.7)	

Non-Yoruba - Igbo/Hausa/others

Table 2: Malaria infection and parasitaemia

Variable	Proguanil *n*=118 (%)	SP *n*=128 (%)	Statistics *P*
Malaria parasitaemia			0.40
Positive	10 (8.5)	15 (11.7)	
Negative	108 (91.5)	113 (88.3)	
Clinical malaria			
Yes	6 (5.1)	3 (2.3)	0.25*
No	112 (94.9)	125 (97.7)	
Repeat episode of malaria			
Yes	2 (1.7)	0 (0.0)	0.23*
No	116 (98.3)	128 (100.0)	

*Fischer's exact test

Table 3: Maternal anemia and infant birth weight

Variable	Proguanil (mean±SD)	SP (mean±SD)	*P*
Mean Hb concentration at enrolment	10.53 (±1.05)	10.63 (±1.08)	0.40
36 weeks	11.17 (±0.81)	11.24 (±0.75)	0.78
Variable	**Proguanil *N* (%)**	**SP *N* (%)**	**Statistic *P***
Hb.Concentration (booking)			
Hb <10	28 (23.7)	22 (17.2)	
Hb >10	90 (76.3)	106 (82.8)	0.20
Hb concentration at 36 weeks			
Hb <10	5 (4.3)	6 (4.7)	0.86
Hb >10	113 (95.7)	122 (95.3)	
Variable	**Proguanil (mean±SD)**	**SP (mean±SD)**	***P***
Birth weight (kg)	3.05 (±0.33)	3.00 (±0.29)	0.24

Hb - Hemoglobin

There was an increase in mean Hb concentration in the PG and SP groups at 36 weeks of gestation. In the PG group, about a quarter of the participants had Hb concentration <10 g/dl at recruitment which reduced to 4.3% at 36 weeks. This finding corroborates with results from previous studies on effectiveness of PG in reduction of maternal anemia in pregnancy, especially when used with hematinic.[14,22-24] The reduction in the incidence of maternal anemia is consistent with the findings of a previous study that also demonstrated a reduction in anemia from 18% at recruitment (24 weeks) to 3% at 36 weeks.[24]

In the SP group, a similar reduction was demonstrated. Less than one-fifth of the participants had Hb concentration less than 10 g/dl at recruitment which reduced to 4.7% at 36 weeks gestation. This compares to findings from previous studies[5,15,16-18] and further supports the efficacy of SP for IPT in prevention of maternal anemia due to malaria infestation during pregnancy. The relative increased reduction in anemia among participants in the PG group at 36 weeks compared to the SP group may be related to the fact that daily use of PG enhances compliance to routine antenatal hematinics.

Low birth weight is a known complication of malaria infestation during pregnancy. In this study, the mean birth weight was similar and comparable between both the study groups. The mean birth weight in the SP group was lower compared to results from an earlier quoted study,[15] which reported mean birth weight of 3.2 kg in a similar group of participants. The sample size difference may account for this. The finding of this study signifies that PG may have a positive effect on infant birth weight at delivery. However, several variables have been associated with increased birth weight. These include maternal age, maternal/paternal anthropometric characteristics, sex of the infant, tribe, socioeconomic status, and diet among others.[3] Malaria preventive strategies, including drugs and insecticide treated nets, have been proven to be beneficial for malaria prevention and associated complications in pregnant women. The findings from this study agree with earlier studies which suggest that PG and SP are effective in reducing the incidence of low birth weight following malaria prevention during pregnancy.

This study would have been better if the participants in the study groups were matched for gestational age, parity, environmental living conditions, and educational status. However, patient recruitment would have taken longer and resources for the research were limited. In monitoring compliance to PG, the use of customized charts to mark drug (PG) use was not strictly adhered to by most participants. The investigator had to rely on empty sachets of used drug (PG) and hematinic to assess participants' compliance in the PG group.

This study reiterates the effectiveness of IPT-SP at preventing or reducing malaria and associated complications in pregnancy with its comparatively low cost and observed compliance. PG chemoprophylaxis was also found to be effective in combating malaria during pregnancy and as such may be a suitable alternative to SP, and can be given in selected patients with allergic reactions to sulphonamides.

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Conflicts of interest
There are no conflicts of interest.

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