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Intermittent preventive treatment for malaria in pregnancy: Is directly observed therapy still necessary? A prospective cohort study in a tertiary hospital, Southern Nigeria

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ABSTRACT

Objective: Malaria is a major cause of indirect maternal death. In the last two decades several efforts have been made to combat the menace of this disease especially among pregnant women and children in developing countries. Directly observed therapy (DOT) was recommended to enhance the uptake of intermittent preventive treatment (IPT) of malaria with sulfadoxine – pyrimethamine among pregnant women. Due to challenges involved in the practice of DOT especially with regards to shortage of man power and clean water in rural areas, there is need to evaluate impact of DOT on the effectiveness of treatment.

Material and Methods: A cohort study was carried out among 320 healthy pregnant women receiving ante natal care with equal assignment of subjects. The study group (160) received two doses of IPT by DOT while 160 matched controls were given prescription for self- drug administration at home. Malaria tests were done using microscopy method and the hemoglobin values determined using centrifuge one month after the second dose of IPT. Umbilical cord blood samples were obtained for a repeat microscopy at delivery.

Results: The results showed that there were no statistical significant differences in the venous blood parasitemia, placental parasitemia and anaemia between the DOT group and the control group ($P = 0.215$; $P = 0.100$; $P = 0.966$) respectively. Lower social class was the main predictor of anaemia in pregnancy ($P = 0.032$).

Conclusion: The delivery of IPT through DOT may not influence uptake in some settings. Effort may need to be channeled into ante natal education and women empowerment.

Keywords: Malaria, Microscopy, Anemia in pregnancy, Sulfadoxine-pyrimethamine, Social Class of women

INTRODUCTION

Malaria has been recognized as a public health priority since the beginning of 1980s.[1] Most cases and deaths due to the disease occur in African region.[2] In Africa, about 30 million women living in malaria endemic areas become pregnant each year.[3] From the 2015 WHO Global Malaria report,[4] about 3.2 billion people were at risk of malaria. In 2015 alone 430,000 people died due to complications of malaria.[4] Most of these deaths occurred in pregnant women and children in sub-Saharan Africa. Specifically, 35% of these deaths occurred in two countries, namely,

Nigeria and Democratic Republic of Congo.[4] For women of reproductive age group in this region, malaria is a serious threat to their survival and their infants' health.

Pregnant women are particularly vulnerable to malaria as pregnancy reduces a woman's immunity to malaria infection and increases the risk of illness, severe anemia, and death.[5] The severity of clinical manifestations is determined by the level of immunity before pregnancy, which depends on the intensity and stability of malaria transmission.[1] In low and/or unstable transmission areas, the degree of acquired immunity of women before pregnancy is low, and both the mother and her fetus are at risk for the most severe consequences of infection.[5,6] In contrast, in areas of high malaria transmission, women have acquired a protective immunity before pregnancy.[5-7]

In areas of stable transmission, where adult women have considerable acquired immunity *Plasmodium falciparum* infection during pregnancy typically does not cause symptomatic malaria but may lead to maternal anemia and placental malaria due to sequestration of the parasite in the placenta,[4] especially among women having their first and second children.[4,5] This placenta malaria leads to the low-birth weight, the single greatest risk factor for neonatal death and a major contributor to infant death.[1-3]

Following a randomized trial in Tanzania in 1999 which proved that intermittent preventive treatment (IPT) of pregnant women and children with sulfadoxine/pyrimethamine (S/P) effectively reduced the incidence of clinical malaria, the WHO included IPT as a major strategy to combat malaria in pregnancy.[8] When IPT was first adopted by the WHO, the recommendation was that it should be dispensed using the directly observed therapy (DOT) to ensure effectiveness of treatment.[9] The Federal Ministry of Health in Nigeria and most other African countries then formulated a policy whereby IPT was include in antenatal care (ANC) package to ensure distribution of the drug to pregnant women during ANC in public health facilities,[3,10]

The Africa Summit on Roll Back Malaria in April 2000 adopted the Abuja declaration in which regional leaders committed to ensuring that 60% of pregnant women in malaria-endemic communities accessed effective prevention and treatment of malaria by 2005.[3]

However, almost two decades after the initial adoption of this treatment protocols, the coverage for IPT is still reported very low. Apart from unevenly distribution of public health facilities women who receive ANC in private health or faith based clinics are not gathered for. A recent study has shown that IPT by DOT is no more sustainable in many setting in view of the dwindling government resources. Sometimes the administration of the drug by a health worker, if available is met with other challenges related to women coming to clinic without food and nonavailability of clean drinking water in the facilities.[11]

These raise the fundamental questions: What is the level of awareness among the women? What is the rate of compliance or drug adherent among women who receive prescription from their service providers to purchase the drug out of their pockets for self-administration? And very importantly, is DOT still necessary for administration of IPT to pregnant women? Hence, the objective of this study was to determine whether DOT significantly reduces incidences of malaria in pregnancy and neonatal malaria.

MATERIAL AND METHODS

Study design and setting

This was a quasi-experimental cohort study conducted at the maternity unit of the University of Calabar Teaching Hospital for a period of 3 months. The University of Calabar Teaching Hospital was the only tertiary hospital in Calabar involved in maternal care at the time of the research. Calabar was the first Capital of Nigeria and is located in the South-south geo-political zone. It has an area of 406 km^2 and a population of 371,022 at the 2006 census.[12]

Recruitment of subjects, data collection, and research protocols

Three hundred and twenty pregnant women in their second trimester were recruited into the study. Information was collected using interviewer-administered questionnaire designed by the investigators and administered by trained interviewer with the investigators. Information on the socio-demographic profile, medical, and obstetrics history were recorded. The social class for each woman was calculated from her highest educational qualification, occupation of spouse, and estimated income.[13] The study group received two doses of sulfadoxine-pyrimethamine in the hospital during their ANC clinic visit by DOT. Matched controls were selected from other pregnant women who were given prescription to purchase the drug for home self-administration. Each participant received two doses of SP for IPT at interval of 1 month. One month after the second dose, blood sample was collected for malaria parasite test using microscopy and packed cell volume (PCV) was determined using the centrifuge and hematocrit reader. The laboratory analysis was performed by experienced laboratory scientists using standardized methods recommended by the WHO. Anemia was defined as PCV of 33% and below using the WHO classification. The participants were then followed up to delivery. Umbilical cord blood samples were collected for placental parasite check.

Exclusion criteria

The following criteria were excluded from the study:
1. Women with known allergy to SP
2. HIV positive women on Co-trimoxazole
3. Women with moderate to severe anemia.

Ethical issues

Approval was obtained from the hospital's ethical committee before commencement of the study. Participation was voluntary. A written informed consent was obtained from each participant. It is important to state here that those with positive malaria test were treated, as well as those with abnormal hemoglobin.

Data analysis

Data entry and analysis were performed using Statistical Package for the Social Sciences (SPSS) version 22 SPSS Inc. Chicago IL, USA. Data were summarized using frequency tables; bivariate analysis was performed with Chi-square proportions for categorical variables. The results were considered to be significant when $P < 0.05$.

Study limitations

The use of insecticide treated net (ITN) was considered a strong confounder in this study. However, use of ITN was not popular when the study was conducted. Hence, the majority of the patients were not using ITN at the time.

RESULTS

Socio-demographic of study participants, malaria parasite, and placental parasitemia among women treated by DOT and the control

Three hundred and twenty women were recruited into the study on 1:1 assignment into the two groups. Two hundred and ninety-five (92.2%) continued to delivery at the UCTH out of which 156 received IPT by DOT while 139 were given prescription to take IPT at home. Overall, more than half of the participants (54.9%) were in the 21–29 years age group. The difference in mean age between cases and control was not significant statistically ($P = 0.153$). Similarly, there was no significant difference in the parity mean ($P = 0.032$). The proportion of participants in the upper social class was equal between cases and control (46.6%), and there was no significant difference in the proportion of those in middle and lower classes ($P = 0.112$).

Malaria parasitemia and placental parasitemia

As shown in Table 1, the proportion of respondents with positive malaria parasitemia was higher among controls compared with the women treated with DOT (2.3% vs. 0.6%). However, the difference was not statistically significant ($P = 0.215$). The proportion of women with positive placental parasitemia was also slightly lower among women treated by DOT compared with the control (4.3% vs. 4.6%), but the difference was not statistically significant ($P = 1.000$). The prevalence of anemia was slightly lower among pregnant women treated by DOT compared with the control (8.4% vs. 8.5%), but the difference was not statistically significant ($P = 0.966$).

The influence of social class on malaria parasitemia and anemia

Table 2 shows the influence of social class on malaria parasitemia. The difference in malaria parasitemia across difference social classes did not show any statistical significance ($P = 1.000$). Table 3 shows that proportion of women with anemia was highest among those in the lower class (15.6%) compared with the proportion of those in the middle (5.3%) and upper (6.5%) social classes. The difference was statistically significant ($P = 0.032$).

DISCUSSION

This study aimed to assess the impact of DOT regarding malaria control in the delivery of IPT to pregnant women in a public health facility in southern Nigeria. One disease which treatment and control have largely been believed to be successful through DOT is tuberculosis. This is because of the longer duration of therapy needed for cure. In this case, apart from the health workers monitoring to ensure drug adherence, the side effect of the drugs is also often detected and modification in the treatment plan instituted during this period.[14] This may not necessary apply to IPT which involves single drug dose, taken twice or more, in all setting especially where women and families are empowered. Furthermore, although previous case series suggested that DOT increased treatment completion and decrease drug resistance for tuberculosis in communities, a meta-analysis of randomized clinical trials of DOT has shown no significant impact of DOT on treatment outcomes.[15,16]

This study failed to show any significant difference in the interval blood malaria parasite count and placental parasitemia between the IPT-DOT and the non-IPT-DOT treated (control) women ($P = 0.215$). The positive parasite test was used to indirectly assess drug adherence and treatment effectiveness which is the main reason for adopting DOT method for IPT as self-reporting adherence may not be as reliable in assessing drug compliance.[17] This is in contrast to findings in a study in Tanzania which reported that free drug availability significantly improved uptake of IPT (0.0001).[17] This was a multi-centered study in different rural

Table 1: Socio-demographic of study participants, malaria parasite, and placental parasitemia among women treated by DOT and the control.

Variable	IPT DOT			Fisher's exact	*P*-value
	No *n*=131	Yes *n*=164	Total *n*=295		
Age group/years					
20	8 (6.1)	15 (9.1)	23 (9.1)	2.975	0.226
21–29	79 (60.3)	83 (50.6)	162 (54.9)		
31–40	44 (33.6)	66 (40.2)	110 (37.3)		
Mean age/SD	28.4/4.5	29.2/5.2	28.9/4.9	*t*-test,1.436	0.153
Parity					
Low parity ≤2	125 (95.4)	145 (88.4)	270 (91.5)	4.608	0.032*
High parity (3 $ above)	6 (4.6)	19 (11.6)	25 (8.5)		
Social class					
Upper	61 (46.6)	62 (46.6)	123 (41.7)	4.370	0.112
Middle	34 (26.0)	61 (37.2)	95 (32.2)		
Lower	36 (27.5)	41 (25.0)	77 (26.1)		
Malaria parasitemia					
Negative	128 (97.7)	163 (99.4)	291 (98.6)	Fisher's exact, 1.537	0.215
Positive	3 (2.3)	1 (0.6)	4 (1.4)		
Placental parasitemia					
Negative	125 (95.4)	157 (95.7)	282 (95.6)	0.017	1.000
Positive	6 (4.6)	7 (4.3)	13 (4.4)		
Anemia					
Present	11 (8.4)	14 (8.5)	25 (8.5)	0.261	0.966
Absent	120 (91.6)	150 (91.5)	270 (91.5)		

IPT: Intermittent preventive treatment, DOT: Directly observed therapy

Table 2: The influence of social class on malaria parasitemia.

	Malaria parasite			Fisher's exact test	*P*-value
	Negative frequency (%)	Positive frequency (%)	Total frequency (%)		
Social class					
Upper	121 (98.4)	2 (1.6)	123 (100.0)	0.387	1.000
Middle	94 (98.9)	1 (1.1)	95 (100.0)		
Lower	76 (98.7)	1 (1.3)	77 (100.0)		
Total	291 (98.6)	4 (1.4)	295 (100.0)		

Table 3: The influence of social class on anemia.

	Anemia				
	Present *n*=8.5	Absent *n*=270	Total *n*=295	Chi-square	*P*-value
Social class					
Upper	8 (6.5)	115 (93.5)	123 (100.0)	6.897	0.032*
Middle	5 (5.3)	90 (94.7)	95 (100.0)		
Lower	12 (15.6)	65 (84.4)	77 (100.0)		
Total					

*Statistically significant

communities unlike our study which took place in a tertiary hospital in an urban area. Most of those rural women might not have educated on preventive medicine and also perhaps not financially empowered. Other studies also revealed that rural women were less likely to take two or more doses of IPT compared to their urban counterparts.[18,19]

One of the main risks in malaria infection in pregnancy is maternal anemia due to hemolysis. Infant low birth weight and intrauterine growth restriction are also due to maternal chronic anemia. The post-treatment hemoglobin values were determined during the time of checking for interval malaria parasite count. There was no significant difference

in incidence of anemia in the two groups (0.966). However, the social profile of the women negatively correlated with incidence of anemia in pregnancy across both groups. This is in keeping with the previous studies which show that the social profile of women such as level of education, age, and marital status is major determinants of anemia in pregnancy.[20,21]

Among the major factors affecting medication adherence are the level of education and the level of family income. Hence, the method used in calculating the social class of the women in this study incorporated highest level of educational qualification of the women and the occupation of their spouses since majority of them were married.[22] The study did not show that social factor affects uptake of IPT. One of the advantages of adopting S/P as a drug of choice for IPT is that of low cost of the drug. This makes it available in many dispensary outlets in communities and easily accessible and affordable by the low-income earners. Moreover, the medication is administered once a month unlike hematinic which requires daily administration throughout the period of pregnancy.

CONCLUSION

Administration of sulfadoxine-pyrimethamine for IPT of pregnant women is still an effective strategy for control of malaria in endemic areas. However, its delivery through DOT may not necessarily improve uptake especially in urban areas. Education, ante natal counseling, and improved status of women and families may promote healthy pregnancy.

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Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent.

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Conflicts of interest

There are no conflicts of interest.

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