Evaluation of the effectiveness and compliance of intermittent preventive treatment (IPT) in the control of malaria in pregnant women in south eastern Nigeria

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Controlling malaria in pregnancy has been an important component of the millennium development goal and intermittent preventive treatment (IPT) is considered an important tool in controlling malaria among pregnant women. In this study, we evaluated the level of compliance to IPT use as well as its effect on malaria infection among pregnant women attending antenatal clinic in south eastern Nigeria. Peripheral blood smears and placental histology were used as diagnostic tools to determine infection rate. Our data show that compliance to IPT use was poor (33%) when compared with non-compliance (67%). Infection rate was significantly lower among IPT users (39%) than in non-users (71%) ($X^2=39.95$; $P<0.05$). Maternal anaemia was also lower in IPT users (4%) than in non-users (18%). Taken together, IPT use appears to be important in reducing infection rate and maternal anaemia. Therefore, its adoption is highly recommended and this could be improved through public enlightenment campaign and adequate funding.

INTRODUCTION

In Africa, *Plasmodium falciparum* infection among pregnant women is responsible for diverse pregnancy outcomes. About 24 million women that become pregnant in the endemic areas of the region yearly are at increased risk of contracting malaria and suffering the associated complications (Steketee *et al.*, 1996; Okoko *et al.*, 2003). On the maternal side, the consequences range from anaemia to severe complications such as renal failure, cerebral malaria, pulmonary odema and maternal death

(Brabin *et al.*, 2001; Kakkilaya, 2009). Poor foetal outcomes such as abortion, stillbirth, low birth weight, intrauterine growth retardation and preterm delivery have been reported (Menendez *et al.*, 2000; Worrall *et al.*, 2004; Mayenque *et al.*, 2004). Dolan *et al.* (1993) observed an association between maternal anaemia and the probability of the infant dying within 1 year of age. In addition, infants delivered from *P. falciparum* parasitized placenta have been reported to show higher susceptibility to the infection than those delivered from unparasitized placenta (Le-Hesran *et al.*, 1997).

P. falciparum infection poses its severest threat on pregnant women and children under the age of 5 years (Granja *et al.*, 2001; UNICEF, 2006). The placenta has been associated with severe parasitization by the parasites, which prefers and replicates

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grossly in it. The parasite during its erythrocytic stage of development remodels the infected red blood cells by transporting parasite-encoded proteins called *Plasmodium falciparum* erythrocyte membrane protein 1 to the erythrocyte surface (Oguariri *et al.*, 2001; Oguariri *et al.*, 2003), which enhance adhesion and binding of the infected erythrocyte to host receptors, for instance chondroitin sulphate A (Fried and Duffy, 1996). Consequently, parasites sequester on the surface of the placenta membrane especially on the trophoblastic villi, extravillous trophoblast and syncytial bridges. The intervillous spaces become filled with parasites and macrophages and thus interfering with oxygen and nutrient supply to the developing foetus with other placental pathology developing leading to diverse maternal and foetal consequences (Kakkilaya, 2009).

Malaria prevention and control have been global issues that have attracted both government and non-governmental organizations. Nigeria was a signatory to the Abuja Declaration of the African Union, which stated as one of the targets, that 60% of pregnant women should receive intermittent preventive treatment (IPT) by the end of 2005. In order to achieve this goal, Nigeria adopted IPT for malaria in pregnancy using sulphadoxine-pyrimethamine (SP) as one of the intervention packages [Federal Ministry of Health (FMH), 2005]. IPT refers to the use of an effective anti-malarial drug given in treatment doses at predefined intervals after quickening to clear presumed burden of parasite. It consists of two doses of SP to be taken at least 1 month apart in the second and third trimesters of pregnancy. This is taken as directly observed treatment in antenatal clinics (FMH, 2009). The current Federal Government target is to have 80% of pregnant women taking the two doses of SP for IPT. IPT during pregnancy confers certain advantages which include: (1) reduction in malaria cases among pregnant women; (2) protection against maternal anaemia and low birth weight; and (3)

reduced risks of stillbirth, abortion, preterm deliveries and maternal death.

The Nigerian government has taken giant strides since the nation's Roll Back Malaria inception in the year 2000 in developing the policy environment and infrastructure capacity required to accelerate malaria control activities at national level. Progress has been made in areas of partnership and policy, funding and communication. This work, therefore, was designed to identify the level of compliance to IPT use by pregnant women in selected settlements in south eastern Nigeria, identify the effect of IPT use on infection rates and maternal anaemia among pregnant women and determine the performance of peripheral blood smear and placental histology in the diagnosis of malaria in pregnancy.

MATERIALS AND METHODS

Study Area

The study was carried out in the southeast geographical zone of Nigeria. The zone is situated on the coastal hinterland of Nigeria east of the Niger and occupied by the Igbo speaking tribe. The zone is made up of five states which include Abia, Anambra, Ebonyi, Enugu and Imo states. Three of these states (Abia, Ebonyi and Imo) were randomly selected for the study. One location was selected from each of the three states and consequently Umuahia (Abia), Afikpo (Ebonyi) and Okigwe (Imo) were selected. In these locations, both private and public clinics were selected and used.

Study Population and Ethical Approval

A total population of 844 randomly selected pregnant women who were in the second stage of their labour was enlisted. This is made up of 256 from Umuahia, 287 from Afikpo and 301 from Okigwe. Of the 844, a total of 276 were IPT women and 568 were non-IPT women. Ethical clearance was obtained prior to the commencement of

the study. Local Government Health Authorities in these locations were written a letter for express permission to use their health facilities, followed by a letter of approval to the Chief Medical Directors of the public clinics and managers of the private clinics to enable us to use their facilities. Personal consultations were made with the chief nursing officers in charge of the maternity sections and their co-operations were solicited. Only qualified nurses and midwives who received training were recruited for sample collections.

Questionnaire Administration

Prepared questionnaires containing obstetrics and demographic questions relating to age, parity, types of control, number of anti-malaria treatments received during pregnancy, type of drug received, number of fever episode, etc. were given to each pregnant woman during the second stage of their labour.

Blood Sample Collection

Peripheral blood samples were collected by venipuncture of the second fingers using lancet. Thick smears were made and allowed to dry at room temperature. Heparinized tubes were used to collect about 2 ml of blood for haemoglobin concentration count.

Placental Tissue Collection

The placenta from each selected pregnant woman was collected after delivery, placed maternal side up and cleaned with sterile normal saline, and a paracentric area was incised. A lump of biopsy specimen of about 2.5 cm³ was cut and placed in a specimen bottle containing fixatives (10% neutral buffered formaline) and corked.

Laboratory Examination of Samples

Sildes of thick peripheral blood smears were transported to the microbiology laboratory of Federal College of Agriculture Ishiagu for

examination. The slides were fixed and stained with Field Stain according to Ochei and Kolhatkar (2008). Slides were then mounted on a high power light microscope and viewed under oil immersion.

The placenta biopsy specimens were transported in batches to Abia State University Teaching Hospital Aba for processing with the help of a histopathologist. Staining was done using Harris haematoxyline. The tissues after sectioning were fixed on slides, stained and counterstained with eosin. Dehydration in graded alcohol was done for 10 minutes. This was then cleared in xylol for 15 seconds and mounted under cover slip using Canada balsam. Microscopic examination of the slides was carried out to detect the parasites as black dots.

Data collected were analysed using X^2 statistics. The true positives, true negatives, false positives and false negatives of the two diagnostic methods employed were calculated and used in determining the sensitivities of the two diagnostic procedures.

RESULTS

As shown in Table 1, of the 844 pregnant women, 134 (16%) were tested positive by peripheral blood smear method. This was made up of 31/276 (11%) of IPT pregnant women and 103/568 (18%) of non-IPT pregnant women. In contrast, placental histology showed 512 (60.7%) positive cases out of the 844 pregnant women examined. Of this number, 108/276 (39%) and 404/568 (71%) were from IPT and non-IPT pregnant women, respectively. Because placental histology showed higher sensitivity than the peripheral blood smear, the placental histology was used as an index of active infection in this study.

In Okigwe town, 301 pregnant women were examined for placental malaria. As shown in Table 2, 103 (34%) were compliant for IPT use while 198 (66%) were non-compliant. Of the 103 IPT users, 28 (27%)

TABLE 1. Comparison of peripheral and placental screening method among IPT and non-IPT women

Screening method	IPT women			Non-IPT women			Total		
	No. of tested	No. of positive	%	No. of tested	No. of positive	%	No. of tested	No. of positive	%
Peripheral	276	31	11.2	568	103	18	844	134	16
Placenta	276	108	39	568	404	71	844	512	61

were positive for placental malaria, while 172 (87%) of the 198 non-IPT users were infected. In Afikpo location, 108 (38%) of the 287 pregnant women examined were compliant for IPT while 179 (63%) did not use IPT. IPT users had 32% infection while non-IPT users recorded 74% infection. In Umuahia, 65 (25%) of the 256 women examined used IPT while 191 (75%) were non-compliant. IPT users had 25% infection as against 52% in non-IPT users. Statistical analysis showed that the difference in compliance and infection levels in the various locations and between IPT compliant and non-compliant groups were significant ($P < 0.05$).

The prevalence of infection and maternal anaemia among pregnant women who used or never used IPT (non-IPT users) from the three study locations are shown in Table 2. Overall, maternal anaemia (haemoglobin < 11 g/dl) was found in 10 (~4%) of pregnant women who used IPT while 100 (18%) of non-IPT women had anaemia. Among the non-IPT women, maternal anaemia was similar and slightly higher in Afikpo and Okigwe (19%) than in Umuahia

(15%). In the IPT women, however, anaemia was slightly highest in Umuahia (5%), followed by Okigwe (4%) and least in Afikpo (3%). Infection rates varied according to the towns. In Okigwe, 27% of the IPT users were infected, while Afikpo and Umuahia had 32 and 71% infected, respectively. The non-IPT users had 87, 74 and 52% infection in Okigwe, Afikpo and Umuahia, respectively. Statistical analysis of the difference in infection rates among IPT and non-IPT users in the three locations yielded a significant result ($X^2 = 39.95$; $P < 0.05$).

Analysis of the data collected from the questionnaire revealed that of the 844 pregnant women in this study, 300, 286 and 258 were primiparous, secundiparous and multiparous, respectively (Table 3). One hundred and fifty-six (52%) of the primiparous, 80 (28%) of secundiparous and 40 (16%) of the multiparous women were IPT-compliant (Table 3). The difference in compliance by parity was statistically significant ($P < 0.05$). Next, we determined the relationship between parity and infection rate among IPT users and non-IPT

TABLE 2. Prevalence of infection and maternal anaemia among IPT and non-IPT pregnant women in the four study locations

Location	IPT women			Non-IPT women		
	No. of pregnant women tested	No. of infected (%)	Maternal haemoglobin < 11 g/dl (%)	No. of pregnant women tested	No. of infected (%)	Maternal haemoglobin < 11 g/dl (%)
Okigwe	103	28 (27)	4 (4)	198	172 (87)	37 (19)
Afikpo	108	34 (32)	3 (3)	179	133 (74)	34 (19)
Umuahia	65	46 (71)	3 (5)	191	99 (52)	29 (15)
Total	276	108 (39)	10 (4)	568	404 (71)	100 (18)

users. Primiparous IPT users had 40% infection compared with 41 and 33% for secundiparous and multiparous IPT users, respectively. In contrast, the rate of infection among non-IPT primiparous, secundiparous and multiparous women were 72, 78 and 65%, respectively. Overall, no significant difference was found between parity and infection rate among IPT or non-IPT users ($P>0.05$). Most of the women reported multiple episodes of fever with SP or 'fansidar' and chloroquine as the most common anti-malarial drugs taken.

DISCUSSION

FMH (2005) revealed that Nigeria was a signatory to the Abuja declaration by the African Heads of states, which set as one of its targets that, as part of measures to control malaria during pregnancy, 60% of pregnant women should receive IPT drugs during pregnancy by the end of 2005. In pursuance of this target, SP drugs were packaged into IPT. However, it is doubtful if this target was achieved within this period. We carried out this investigation in selected towns in the southeast of Nigeria to determine infection levels among pregnant women who used IPT and those who did not use IPT using peripheral blood microscopy and placental histology. Haemoglobin concentration was also determined for both the IPT and non-IPT women.

The result showed that ~33% of pregnant women in the study area used IPT. Compliance to IPT use in the three study sites was more in Afikpo (38%), than in Okigwe (34%) and Umuahia (25%), respectively. Primiparous women showed the highest level of compliance (52%) compared with secundiparous (28%) and multiparous (16%). The higher compliance to IPT use in the primiparous women may be due to their early registration at antenatal care (ANC) and willingness to adhere to instructions. The result is higher than the country overall rate of 17% (FMH, 2009). Even though the result is an improvement in the country's overall IPT adoption, both however have demonstrated the failure of the country's health delivery system to meet the 2005 target of having 60% IPT adoption among pregnant women attending antenatal clinics. It also points to the impending failure of the 2009–2013 scale-up target of 80% IPT adoption among pregnant women attending antenatal clinics. It is true that the Federal Government has made progress in developing the policy thrust, partnership and funding necessary for effective control of malaria in pregnancy, and the much expected results are yet to be achieved. The fact remains that most of the policies and program translation end up in Government Health Facilities. Private clinics and maternity homes located mostly in rural communities are left in the shadow of Government activities. In the southeast, most pregnant women prefer

TABLE 3. *Relationship between IPT use, positive pregnant women and parity*

Parity	IPT women			Non-IPT women		
	No. of pregnant women tested	No. of infected (%)	No. of uninfected (%)	No. of pregnant women tested	No. of infected (%)	No. of uninfected (%)
Primiparous (<i>n</i> =300)	156 (52)	62 (40)	94 (60)	144 (48)	103 (72)	41 (28)
Secundiparous (<i>n</i> =286)	80 (28)	33 (41)	47 (59)	206 (72)	160 (78)	46 (22)
Multiparous (<i>n</i> =258)	40 (16)	13 (33)	27 (67)	218 (84)	141 (65)	29 (15)
Total	276	108 (39)	168 (61)	568	404 (71)	100 (18)

private clinics and maternity homes for ANC than those owned by the Government which they claim are highly regimented and do not offer personalized attention. Since these private clinics and maternity homes are nearest to the people, they have the capability to influence the people more and could serve as great leverage for the translation of government policies and programs to the grass root.

We also discovered that many pregnant women register for ANC very late and often towards the end of second trimester and some comply poorly with directives. This is especially so among multigravid women who appear relatively strong and think they have no need to register for ANC early. Late registration for ANC hampers effort in the adoption of IPT as an intervention package for malaria in pregnancy and can be checked through aggressive enlightenment at community and religious levels.

Women who used IPT showed lower rate of infection (Table 1) than those who did not use it and this is in support of previous reports (Schultz *et al.*, 1994; FMH, 2005). However, in Umuahia (Table 2), higher infection was seen among the IPT. We do not know the reason for this result but whether it is due to technical issues has to be determined. The differences in infection rates among IPT users and non-IPT users in the three study locations were statistically significant. Maternal anaemia was lower among IPT users than non-IPT users. This is an indication that IPT use not only helps in reducing the rate of malaria infection during pregnancy but also helps in reducing maternal anaemia and its related adverse outcomes. This calls for increased action by the government in making available SP in our health facilities at a cheaper rate, strengthening efforts through the National Agency for Food, Drug Administration and Control in ensuring that only effective anti-malarials are allowed into the country. Community mobilization through information networks, community leaders and religious bodies for proper education

and enlightenment of our remote communities on Government health delivery programs is essential. Seminars and workshops usually meant for staff of public health facilities should be extended to the operators of private clinics and maternities since they have good patronage among the people. In Nigeria today, IPT is given to pregnant women free of charge. This is a welcome development and needs to be strengthened.

Of the two diagnostic methods used in this work, placental histology proved more sensitive being able to determine 61% of the infections compared with the peripheral blood smear which detected only 16% of the infected women. With a sensitivity of 100%, the placental histology appears more useful in the detection of malaria in pregnancy. Similar higher diagnostic performance of placental histology has also been observed by Rogerson *et al.* (2003) and Mockenhaupt *et al.* (2002). Taking the placental histology result as an index of active infection, the implication is that about 74% of those infected by *P. Falciparum* which were not detected by peripheral blood smear constitutes a significantly large group that may often be neglected in any malaria control program though they suffer malaria-related morbidity and pathologies.

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