

ORIGINAL ARTICLE

Effects of Maternal *Plasmodium falciparum* Malaria and HIV infection on Birth Weight in Southeastern Nigeria

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ABSTRACT: The effects of malaria and HIV infection on birth weight were assessed among 300 women in childbirth in Southeastern Nigeria using standard techniques. Prevalence of maternal *Plasmodium falciparum* malaria infection was 16.0%. Individuals of younger age, primigravidae, anemic (with Hgb <11.0g/dl) and those who had never attended antenatal clinic (ANC) were more likely to have malaria infection. Prevalence of HIV infection was 3.6% and malaria prevalence was significantly higher among HIV-positive than HIV-negative women (37.5%, 95% CI, 4.0-71.0% versus 14.3%, 95% CI, 9.6-19.0%), ($\chi^2 = 13.3$, $P < 0.05$). Malaria-infected women had a significantly higher proportion of LBW babies than the uninfected (F-ratio=15.05, $P < 0.05$). A higher proportion of low birth weight (LBW) was recorded among anemic women, primigravidae and those who never attended ANC. LBW babies were significantly higher among HIV-positive than HIV-negative women (25.0% vs 16.6%), (F-ratio=130.8, $P < 0.05$). Malaria and HIV interventions via ANC are crucial for reduction of their adverse effects on pregnancy outcome.

KEYWORDS: Maternal malaria, *Plasmodium falciparum*, HIV infection, birth weight

INTRODUCTION

Malaria, caused by the human Plasmodium parasites infection, and Acquired Immunodeficiency Syndrome (AIDS) constitute severe health problems in many parts of the world. The combination of malaria and HIV infection result in more than 4 million deaths per year, with the greatest impact in Africa, India, Southeast Asia, and South America (1,2). Malaria, which has been described as the disease of poverty and underdevelopment, is considered the most complex and overwhelming health challenge facing humanity in the vast majority of developing tropical and sub-tropical countries, with 300 to 500 million cases and 2 to 3 million deaths per year (3). Sub-Saharan Africa remains the most malaria-affected region with about 90% of all

malaria deaths in the world today, largely due to Plasmodium falciparum. The most dangerous of the four human malaria parasites, it causes the majority of infections and accounts for an estimated 1.4 and 2.6 million deaths per year in this region (4,5). In addition, the most effective malaria vector, the mosquito Anopheles gambiae, is widespread in the region and difficult to control (5).

Sub-Saharan Africa remains by far the most-affected region of the global HIV/AIDS epidemic, with 25.4 million people living with HIV, 64% of the world's affected population (6). In this region, females are the more severely affected with women of reproductive age making up almost 57% of adults living with HIV, and accounting for up to 80% of the world's HIV-infected women (7,8). In sub-Saharan Africa the HIV and malaria epidemics do overlap with severe public health consequences particularly among women of child bearing age. Each year in the sub-region, approximately 25 million women become pregnant and are at increased risk of infection by *Plasmodium falciparum* (9). Also the HIV prevalence rate has sometimes been

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reported as exceeding 40% among pregnant women in the sub-region (10). It is therefore estimated that approximately one million pregnancies per year are complicated by co-infection with malaria and HIV in sub-Saharan Africa (11). This is because the two diseases are known to critically intersect in pregnancy and have serious consequences in pregnant women, fetuses, and infants (12,13). Both malaria and HIV infection have potentially severe effects on pregnant women and on the outcome of pregnancy, with each infection contributing adverse outcomes of low birth weight (LBW) through prematurity or intrauterine growth retardation (IUGR), known to be the single greatest risk factor for neonatal and infant mortality (14).

Studies from sub-Saharan Africa have showed that infant mortality is three times higher for LBW babies than for those of normal weight (15). The effects on neonatal mortality are even more marked; a LBW baby being nine times more likely to die in the first month of life than a normal-weight baby (16). The mechanisms by which either malaria or HIV infection lead to LBW remain unclear (17-21). However, malaria is thought to reduce birth weight through a combination of systemic and local effects. Malaria may affect birth weight through malaria-induced anemia. It may also reduce birth weight through placental infection (18). Advanced-stage HIV disease, previous history of preterm birth, a CD4 cell count <200 cells/mm, primiparity, maternal literacy, and infant HIV infection at birth were also significantly associated with low birth weight (21).

In Nigeria and other parts of West Africa with similar settings, there is a scarcity of population-based data on the association of maternal malaria, anemia, HIV infection and birth weight. This dearth of information has made the formulation of policies that would transform into effective and sustainable malaria and HIV intervention/control programs for pregnant women an enormous challenge. The major objectives of this present study were two fold: 1) To provide scientific data on the contributory role of maternal malaria, anemia and HIV infection at full pregnancy term on neonatal birthweight. 2) To provide information that would have public health significance and relevance to policy development and program implementation, as it relates to the overall maternal, fetal and infant wellbeing in Nigeria and other developing nations threatened by both malaria and HIV infection.

MATERIALS AND METHODS

Study Area

This study was conducted in Abakaliki, the capital of Ebonyi State in South Eastern Nigeria, from June 2006 to December 2006. The study area is defined by

longitude 8°06'16.11"E and latitude 6°22'12.811"N, elevated at 380ft above sea level. The characteristic vegetation is that of the tropical rain forest with an average annual rainfall of 1,600mm and an average atmospheric temperature of 30°C. There are two distinct seasons: the wet and the dry seasons; the former takes place between April and October, while the latter occurs from November to March. Malaria transmission in the area is perennial but usually at the peak towards the end of the rainy season. The study was conducted at the Ebonyi State University Teaching Hospital (EBSUTH) in Abakaliki. Apart from being the largest health facility in the area, EBSUTH serves as a referral centre for gynecological services and runs the biggest antenatal clinic and maternity ward in Ebonyi State.

Ethical Considerations

The study protocol was approved by the Infectious Diseases Research Division of the Department of Medical Microbiology/Parasitology at Ebonyi State University. Ethical approval was obtained from the Ethical Committee of the EBSUTH. The approval was on the agreement that patient anonymity must be maintained, good laboratory practice/quality control be ensured, and that every finding would be treated with utmost confidentiality and for the purpose of this research only. All work was performed according to the international guidelines for human experimentation in clinical research (22).

Study Population/Sampling Technique

The study population comprised of 300 women at full pregnancy term. A pregnant woman was eligible for participation in the study if she attended the antenatal clinic at EBSUTH and met the following study inclusion criteria: (i) had an uncomplicated singleton birth pregnancy > 32 weeks gestation (based on the fundal height estimation), (ii) resided in Abakaliki or neighboring local government areas, and (iii) had no known underlying chronic illness. Women who did not attend ANC at EBSUTH or any other antenatal clinic but met the other study inclusion criteria were also enrolled in the study.

Following informed consent, at delivery, 5ml of the maternal peripheral blood was obtained from each participant by venepuncture technique into a sterile EDTA container. Information was obtained on the delivery outcome including baby's sex, mode of delivery and birth weight (kg). The birth weight was determined using an electronic weighing machine immediately after child birth. Information on the participants' age, parity, use of insecticide-treated bed nets (ITNs) and frequency of antenatal clinic visits were obtained from the case files of each individual and by interview.

Laboratory Analysis

Giemsa-stained thick and thin blood films were performed to determine malaria infection and the Plus System was used for the determination of parasite density as previously outlined (23). All the films were double-checked blindly by experienced parasitologists and if there was disagreement, an additional assessment was made by another observer and the average of the two agreeing counts using the Plus System was recorded. Parasitaemia was graded as 1-10 parasites per 100 thick film fields ('+' or 4-40 parasites per mm³), 11-100 parasites per 100 thick film fields ('++' or 41-400 parasites per mm³), 1-10 parasites per single thick film fields ('+++)' or 400-4000 parasites per mm³).

The hemoglobin concentration was determined to assess maternal anaemia using the cyanmethaemoglobin method described previously (24); reading was done using a spectrophotometer (Bayer RA 50). The HIV Tri Line Test kits, commercially available (Biosystem INC, Austria) were first used to screen each subject's serum sample which was separated from the blood to detect antibodies to HIV-1 and HIV-2. Thereafter the HIV-seropositive samples were confirmed by immunoblot analysis using the BIORAD New Lav Blot kits, which are commercially available (Bio-Rad Novapath Diagnostic Group US.). Manufacturer's instructions were strictly followed to determine the sero-status of the samples. All the analysis was done at the Research Laboratory of Department of Medical Microbiology, Ebonyi State University, Abakaliki.

Statistical Analysis

Percentage prevalence rates were calculated with their respective 95% confidence intervals. Difference between proportions were evaluated using chi-square tests while differences in means were evaluated using one-way analysis of variance ANOVA. Statistical significance were achieved at $P < 0.05$.

RESULTS

A total of 300 women at full pregnancy term were studied during childbirth in this research, and of these, 278(92.7%) had spontaneous vaginal delivery (SVD), 19(6.3%) had caesarean section (CS), and 3(1.0%) had vacuum extractor (ventouse). Information was available on the babies born to 226 of the mothers. Of the 231 babies, of which 119 (51.5%) were males and 112 (48.5%) were females, 219 (116 males and 103 females) were single births, 12 were twins (3 sets of females; 3 sets of male and female), and 3 were triplets (2 males and 1 female). Information on the babies of the

remaining 74 mothers could not be obtained due to logistic problems encountered at the labor ward during the study. The non-availability of the information was because maternal blood sample was collected at the inception of labour after which it usually took between 30 minutes to 10 hours for actual delivery. Thus, the nurses who were on duty at the labour ward during such times failed to record the birth weight of some the babies after childbirth in the project data collection forms provided due to the following reasons; (a) they were unaware of the research, (b) out of inadvertence, and (c) reluctant to do "extra work".

According to investigation criterion, malaria parasites were found in the peripheral blood of 48 (16.0%) women. Of the 48 women infected by malaria parasite, 1-10 parasites per 100 thick film fields were recorded in 11 women (22.9) while 11-100 parasites per 100 thick film fields were recorded in the remaining 37 (77.1%). The prevalence of malaria infection in relation to maternal age, parity, ANC attendance, and HIV infection among the women at childbirth is summarized in Table 1. Individuals of age group 20-24 years had the highest prevalence of maternal malaria (20.8%,

Parameter	Number Examined	Number (%) with Malaria Infection	95% Confidence Interval
Age			
≤ 19	11	2(18.2)	4.6-41.0
20-24	72	15(20.8)	11.4-30.2
25-29	106	16(15.1)	8.3-21.9
30-34	78	11(14.5)	6.6-28.7
35-39	26	8(11.5)	0.8-23.8
≥ 40	9	1 (11.1)	9.4-31.6
Total	300	48(16.0)	11.9-20.1
Parity			
Primigravidae	89	16(18.0)	10.0-26.0
Multigravidae	211	32(15.2)	10.4-20.0
Total	300	48(16.0)	11.9-20.1
Antenatal Visits			
None	35	6(17.1)	4.6-29.6
≤ 4	71	15(21.1)	11.6-30.6
5-9	86	11(12.8)	5.7-19.9
≥ 10	45	4(8.9)	0.6-17.2
Total	237	36(15.2)	10.4-19.9
HIV Status			
Positive	8	3(37.5)	4.0-71.0
Negative	217	32(14.3)	9.64-19.0
Total	225	35(15.6)	10.9-20.3
HbC (g/dl)			
<7.0	2	2(100)	-
7.0-8.9	7	3(42.9)	6.2-79.6
9.0-10.9	22	7(31.8)	12.3-51.3
≥ 11	149	28(18.8)	12.5-25.1
Total	180	40(22.2)	16.1-28.3
ITNs Possession			
Yes	17	2(11.8)	3.5-27.1
No	283	46(16.3)	12.0-20.6
Total	300	48(16.0)	11.9-20.1

Table 1: Prevalence of malaria infection in relation to demographic/obstetrics data, HIV infection and haemoglobin concentration among women at childbirth in Abakaliki, Nigeria.

95%CI., 11.4-30.2%) while the least was recorded among those older than 39 years (11.1%, 95% CI, 9.4-31.6%), but there was no significant difference in the trend ($\chi^2=2.02$, $df=4$, $P>0.05$). Malaria infection was more frequent among the primigravidae (18.0%, 95% CI, 10.0-26.0%) than the multigravidae (15.2%, 95%CI., 10.4-20.0%) but there was no significant difference in the trend ($\chi^2=0.17$, $df=1$, $P>0.05$). Women who did not attend antenatal clinic (ANC) during pregnancy and those who attended ANC less than 5 times were more likely to have malaria infection, although the difference was not statistically significant ($\chi^2=3.79$, $df=3$, $P>0.05$). The prevalence of malaria infection was higher (16.3%, 95% CI., 12.0-20.6%), among individuals who did not have insecticide treated bednets (ITNs) than among those who had (11.8%, 95% CI, 3.5-27.1%) but the difference was not statistically significant ($\chi^2=1.33$, $df=1$, $P>0.05$). Result showed that the prevalence of HIV infection was 3.6% and HIV-positive women had higher prevalence of malaria infection than the HIV-negative women (37.5%, 95% CI, 4.0-71.0% versus 14.3%, 95% CI, 9.6-19.0%), the difference was statistically significant ($\chi^2 =13.3$, $df=1$, $P<0.05$). The prevalence of malaria infection decreased with increase in Hgb and the difference was statistically significant ($\chi^2=23.8$, $df=3$, $P<0.05$) (Table 1).

The results of the association of neonatal birth weight with maternal malaria infection, HIV infection, parity, and ANC attendance are summarized in Table 2. A higher proportion of malaria infected women (21.6%) had babies with low birth weight compared to women without malaria infection (18.8%). Statistical analysis using the one-way analysis of variance ANOVA showed a significant difference in the trend (F-ratio=15.05,

$df1/df2=2/3$, $P<0.05$). Anemic women (with Hgb $<11.0g/dl$) had a higher proportion of low birth weight babies (20.0%) than the non-anemic women (16.4%) but the difference was not statistically significant (F-ratio=7.34, $df1/df2=2/3$, $P>0.05$). The frequency of low birth weight was higher among the primigravidae (30.8%) than among the multigravidae (13.1%), there was no statistically significant difference in the trend using ANOVA (F-ratio=0.29, $df1/df2=2/3$, $P>0.05$) (Table 2). Similarly the HIV positive women had higher proportion of LBW babies (25.0%) compared to the HIV negative women (16.5%) and there was a statistically significant difference in the trend using ANOVA (F-ratio=130.8, $df1/df2=2/3$, $P<0.05$). The highest proportion of LBW occurred among women who never attended the ANC during pregnancy (25.0%) and the least among those who attended up to ten times (8.3%). Statistically, there was no significant difference in the trend using ANOVA (F-ratio =1.05, $df1/df2=2/9$, $P>0.05$).

DISCUSSION

In this study, a peripheral blood malaria infection prevalence of 16.0% was obtained from the subjects at full pregnancy term during delivery. This is comparable to the malaria prevalence figures obtained among women at delivery in various parts of the sub-Saharan Africa. In southern Ghana a malaria infection prevalence of 19.0% was obtained (25), 8.6% in Kampala, Uganda (17), 17.6% in Zanzibar, Tanzania (26), and 17.3% in Maputo, Mozambique (27). As with malaria in children, the prevalence and manifestation of malaria in pregnancy varies with transmission intensity, access to treatment, coverage and quality of antenatal

Maternal Parameters	Neonatal Birthweight(Kg)(%)			Overall Total	Mean Birthweight (Kg)
	< 2.5	2.5-3.5	≥ 3.6		
Malaria Infection					
Infected	8(21.6)	26(70.3)	3(8.1)	37	2.37
Uninfected	34(18.8)	115(63.5)	32(17.7)	181	2.94
Total	42	141	35	218	
Haemoglobin concentration					
<11.0g/dl	5(20.0)	16(64.3)	4(16.0)	25	3.04
$\geq 11.0g/dl$	19(16.4)	83(71.6)	14(12.1)	116	2.97
Total	24	99	18	147	
HIV Status					
Positive	1(25.0)	3(75.0)	0(0.0)	4	2.58
Negative	30(16.5)	122(67.0)	30(16.5)	182	2.98
Total	31	125	30	186	
Parity					
Primigravidae	20(30.8)	40(61.5)	5(7.7)	65	2.71
Multigravidae	20(13.1)	113(73.9)	20(13.1)	153	3.05
Total	40	153	25	218	
Antenatal Visits					
None	4(25.0)	9(56.3)	3(18.8)	16	2.80
1- 4	12(21.4)	39(69.6)	5(8.9)	56	2.85
5-9	7(9.2)	58(76.3)	11(14.5)	76	3.04
≥ 10	2(8.3)	19(79.2)	3(12.5)	24	3.22
Total	24	126	22	180	

Table 2: Association of neonatal birthweight with maternal malaria infection, demographic/obstetrics data, HIV infection and haemoglobin concentration among women at childbirth in Abakaliki, Nigeria.

services, and drug resistance, among others. Variations in these factors account for the differences in the prevalence figures obtained from various sites of the sub-Saharan Africa.

Individuals of the ≤ 19 years and 20-24 years age categories were more likely to be infected with malaria than other age groups categories, although the difference in the trend was not statistically significant. This observation supported previous findings from eastern Sudan (28) and in Kigali, Rwanda (29) which indicated that age was not significantly associated with malaria during pregnancy. In contrast however, a number of earlier studies reported a significant association between maternal age and malaria infection during pregnancy (30,31). In a study conducted in Blantyre, Malawi, after stratifying by gravidity, associations between age and parasite prevalence were reportedly stronger than those between gravidity and prevalence after stratifying by age (31). The reason for the occurrence of these age-related differences in malaria prevalence may probably be related to host or environmental factors.

The prevalence of malaria infection was higher among the primigravidae than the multigravidae, although the difference in the trend was not statistically significant. This finding is consistent with reports from other parts of the sub-Saharan Africa which have consistently indicated that primigravidae are more susceptible to malaria infection than the multigravidae. This is probably because immune suppression is more marked in primigravidae and the protective immunity acquired through malaria infection during the first pregnancy, appears to reduce susceptibility in subsequent pregnancies (32).

The women with HIV infection had a higher prevalence of malaria infection than those without HIV infection. Similar findings were reported in a number of sub-Saharan African countries including Malawi (33), Zimbabwe (13), Kenya (34), and Rwanda (29). The reason for the higher prevalence of malaria infection among the HIV positive individuals may be due to the impairment of the ability of pregnant women to control *P. falciparum* infection, which was earlier demonstrated (12), and the interference with the maintenance of immune recognition of malaria by HIV infection in pregnancy (34).

In this study, anemic women were more likely to have malaria infection than non-anaemic women. This was consistent with reports from a number of sub-Saharan African countries which indicated that the prevalence of anemia was consistently higher among pregnant women infected with malaria parasites than those uninfected (28,32). Individuals with no insecticide-treated bed nets and those who never visited the ANC or attended ANC

less than 5 times during pregnancy were more likely to have malaria infection. In Kenya (35) and Burkina Faso (36), similar results were reported. These findings underscore the importance of ANC attendance during pregnancy. It has been demonstrated that substantial reductions in maternal malaria, anemia, and LBW have been achieved by intervention programs, including the use of ITNs, preventive intermittent treatment and chemoprophylaxis administered at the ANC (16,35,36). Interventions also exist for maternal anemia (e.g., good nutrition, iron and folate supplementation, and hookworm treatment) and these have been provided through antenatal care programs. In fact, studies from sub-Saharan Africa have suggested that between 25% and 90% of these adverse events might be prevented by full implementation of existing interventions at the ANC (37).

Low birth weight (LBW) was associated with maternal malaria infection and babies born by infected mothers had a lower mean birth weight compared to the uninfected mothers. The prevalence of LBW was higher among babies born by primigravidae than the multigravidae. This is consistent with the findings from similar studies conducted in south-western Cameroon (25), Zanzibar, Tanzania (26) and rural Malawi (39). *Falciparum* malaria during pregnancy has long been recognized as an important determinant of low birth weight (40). A number of randomized controlled trials of preventive antimalarial measures during pregnancy have confirmed this causal effect by showing that preventing malaria increases birth weight (41,42). Therefore, the prevention of malaria in pregnancy, and thus, of malaria-attributable low birth weight should increase the survival of young babies.

It is already well established that the major adverse effect of malaria in pregnancy on the mother is anemia. In malarious areas, malaria and anemia are likely to act together to reduce birth weight but their independent effects are difficult to distinguish (43). In this study however, the prevalence of LBW was considerably higher among women who were anaemic than the non-anaemic women. In a similar study conducted in Papua New Guinea to examine the separate contribution of anaemia or malaria to low birthweight (44), it was observed that there was a trend towards increased low birthweight with decreasing hemoglobin levels. Furthermore, in another related study (45), it was showed that there was a positive correlation ($r = 0.76$; $P = 0.01$) between haemoglobin concentration and weight of the infants at birth and the mean birth weight of the infants born to anaemic subjects was significantly lower compared to that of infants born to non-anaemic subjects. These previous observations, in addition to those of this present study, suggest that anaemia had a

significant influence on the birth weight of the infant. Therefore, the treatment of anaemia in pregnancy is most likely to improve birthweight. However in an attempt to quantify the separate effects of anemia- and malaria-attributable low birth weight, Brabin and Piper (44) concluded that, in malarious areas, malaria was a more important risk factor for low birth weight than was anemia.

Interestingly, the prevalence of LBW was considerably higher among the HIV positive women than the HIV-negative women in this present study. This is similar to the findings in northern Zimbabwe (13), where HIV infection was independently associated with increased risk of low birth weight (OR = 3.16, 95% CI: 1.80-5.54) and very low birth weight (OR = 10.74, 95% CI: 2.12-54.41). Furthermore, in Kigali, Rwanda, it was observed that the frequencies of low birthweight, prematurity, and intrauterine growth retardation were higher in infants born to HIV-positive women than to HIV negative women (19). In yet another study conducted in Kigali, Rwanda, low birth weight was significantly more frequent in full-term infants born to HIV-positive mothers than to HIV-negative mothers (20). These results underscore the need for nutritional surveillance and dietary counseling, hoping to improve the prognosis of pregnancy in HIV-positive women, regardless of other therapeutic interventions.

It was noted in this study that a very high proportion of LBW occurred among babies born by women who did not attend the antenatal clinic and the prevalence of LBW reduced with increase in the number of antenatal clinic visits. This finding clearly demonstrates the efficacy of antimalaria chemoprophylaxis and haematenics which are usually administered during ANC in the prevention of malaria and anaemia and improvement of neonatal birth weight. This finding supported earlier reports from The Gambia where the birth weight of children born to women who received chemoprophylaxis was increased by an average of 153 g (41). In another related study the administration of chemoprophylaxis led to a reduction in the prevalence of low birth weight babies and to an increase in the median birth weight and the perinatal mortality rate was lower, although not significantly so, among the babies of women who had received chemoprophylaxis (46). Furthermore, in a study in rural Malawi (39), it was noted that the use of an effective antimalarial was protective against LBW through its effect on reducing placental and umbilical cord blood malaria infection. The study concluded that effective prevention of malaria in pregnant women in malaria-endemic settings may reduce the likelihood of LBW by 5-14%, and may reduce the amount of preventable LBW by more than 30%. Therefore, when evaluating antenatal care

programs, health policy makers must consider providing an effective preventive drug as a means to prevent low birth weight and its consequences.

Our inability to assess other possible factors such as nutritional deficiency, hookworm, urinary schistosomiasis, tuberculosis, etc which may contribute to anaemia during pregnancy in the present study population, was a major drawback to this investigation. The lack of any iron indicator, i.e. ferritin or serum transferrin receptor, is a major limitation of this study. Another limitation of this study was the failure to obtain the information on the birth weight of all the babies born by the 300 mothers from whom blood samples were obtained. Furthermore, lack of information on the disease stage of HIV-infected women is yet another limitation to this study. These limitations may have affected the adequate assessment of the contributory role of malaria, HIV infection and anaemia on the birth weight of the babies assessed. Future research incorporating these aspects is advocated.

In conclusion, in most part of the developing world, maternal and child health services are the most accessible health services in many communities. In these settings ANC clinics serve as the main entry point for prevention and care services for pregnant women and their children. But they also serve as a good link to other health services for families and communities. In sub-Saharan Africa, antenatal care utilization is relatively high as more pregnant women are encouraged to avail themselves with the antenatal care services offered. Delivery of malaria and HIV interventions within existing health services may permit effective utilization of human resources and address serious resource constraints. The challenge is to ensure coherence at each level of the health system, and to maximize the use of available resources for integrated service delivery.

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