HIV AND MALARIA CO-INFECTION IN PREGNANCY IN A TEACHING HOSPITAL IN SUB-SAHARAN AFRICA

***Omole-Ohonsi A. FWACS **Nwokedi EE. FMCPath**
*Department of Obstetrics and Gynaecology, Bayero University/Aminu Kano Teaching Hospital, Kano, Nigeria.
**Department of Microbiology, Benue State University, Makurdi, Benue State, Nigeria.

ABSTRACT

Background: The high prevalence of Human immunodeficiency virus (HIV) and malaria infection in sub Saharan Africa, makes co-infection a burden in this region, as together, they are responsible for 4 million deaths annually. A study of the health implications of this interaction in our pregnant women is important.

Objective: To determine the incidence and recurrence, incidence of febrile malaria infection in different stages of HIV infection among pregnant women, at Aminu Kano Teaching Hospital, Kano, Nigeria.

Method: A retrospective analysis of 95 HIV-infected and 95 HIV-uninfected pregnant women, who met the recruitment criteria between January 2005 and December 2007. The study variables of interest were age and parity; occurrence and recurrence of febrile malaria infection in both groups; the incidence of febrile malaria infection in different stages of HIV-infection. The data was prospectively obtained and retrospectively analysed using Z and Chi-square tests. Odds ratio (OR) and confidence interval (CI) were determined where appropriate.

Results: The incidence of febrile malaria co-infection among HIV-infected women was 22.1%. The occurrence of febrile malaria infection was three times higher (OR = 3.09, CI=1.21 – 8.11, P < 0.05), and recurrence was nine times higher (OR = 9.33, CI=0.83 – 241.31, P < 0.05) among HIV-infected pregnant women. Febrile malaria co-infection was significantly higher among those in the symptomatic stages compared to asymptomatic stage.

Conclusion: There is ***increased frequency of febrile malaria parasitaemia*** among HIV-infected pregnant women. Effective Highly Active Antiretroviral Therapy (HAART) and antimalarial interventions through structured antenatal programs are needed

Keywords: HIV/AIDS, malaria fever, incidence, clinical course.

INTRODUCTION

The HIV-infection pandemic is currently a global public health problem, especially in countries in sub-Saharan Africa[1-4]. Sub-Saharan Africa is more heavily affected by HIV and Autoimmune Deficiency Syndrome (AIDS) than any other region of the world[5-9], and about 22.4 million people are living with HIV in the region[10]. In sub-Saharan Africa, 55% of the HIV-infected adults are women in their reproductive age, accounting for 80% of the world's HIV-infected women[11]. Nigeria has a HIV prevalence of 3-5%, with an estimate of 2.6 million people living with HIV[1,3,10]. Malaria and HIV infection which are truly diseases of the poor[11], have similar global distribution, with the majority of those affected living in sub-Saharan Africa, where HIV and malaria are among the leading causes of morbidity and mortality during pregnancy[10,11]. In 2008, 1.4 million people died from AIDS in sub-Saharan Africa[7]. In addition, 500 million are infested by malaria annually, while 1 million of these die from malaria[3,10]. It is estimated that each year 75,000 to 200,000 infant deaths are associated with malaria infestation in pregnancy, and majority of the cases occur in sub Saharan Africa. Failure to apply known effective antimalarial interventions through antenatal programs continues to contribute substantially to infant deaths globally[12].

Correspondence: Omole-Ohonsi A,
P.O.Box 14578, General Post Office, Kano.
Tel No.- +234 80-37870540
Email: aomohonsi@yahoo.com

The effect of either infection on the course of the other significantly impacts on public health, considering the number of people at risk for coinfection[10,12-15]. Malaria and HIV co-infection in pregnant women has been associated with maternal morbidity and mortality from conditions like pyrexia, anaemia and gastrointestinal problems. In addition, perinatal mortality from increased risk of vertical transmission, low birth weight babies from prematurity, and intrauterine growth retardation as a result of high placental placental parasitisation have been documented[7,13-15]. Studies to determine if high placental (malaria) parasite burden increased mother-to-child HIV transmission showed conflicting results, possibly reflecting a complex balance between malarial immune responses and stimulation of HIV viral replication[11]. Some of the studies showed that increased placental parasitization alter the uteroplacental barrier, creating a situation like a hole in a sieve, which makes the HIV to pass through easily, thereby increasing the risk of mother to child transfer of the virus[2-4,8,9]. There is a clear need to strengthen the deployment of existing malaria and HIV prevention and intervention measures for pregnant women[11,16,17].

While early population-based studies showed no difference in outcomes between HIV-positive and HIV-negative individuals with malaria[12], more recent work suggests that those with HIV infection have more frequent episodes of febrile malaria[18-21]. Further investigation of these interactions is needed to better define effects of coinfection[10]. This informed why our study was designed to determine the incidence, recurrence and clinical course in the different stages of HIV infection at Aminu Kano Teaching Hospital, Kano, Nigeria, and to make recommendations which will reduce its incidence and improve fetomaternal outcome.

PATIENTS AND METHODS.

This is a retrospective study, which was conducted in Aminu Kano Teaching Hospital, Kano, Nigeria, between January 2005 and December 2007, to determine the incidence, recurrence, and incidence of febrile malaria in the different stages HIV infection, among pregnant women with malaria and HIV co-infection who attended our antenatal clinic. Ninety five HIV infected and 95 HIV uninfected age and socio-economic status matched pregnant women (because they are variables which could affect the immune status of the women[6]), who met the recruitment criteria.

For the purpose of this study, febrile malaria infection refers to a temperature rise of 37.5^0c or more, due to malaria infection in the absence of symptoms/signs of other infections. Malaria infection was said to be present if there was at least one asexual parasite per 200 white blood cells in a thick film, while a negative slide was one in which no asexual form was found after counting 1000 white blood cells.

Regarding the stages of HIV infection, a woman who had no opportunistic infection and whose CD4 cell count was more than 500cells/ul was said to be in the "Asymptomatic stage". "Early stage" referred to those who had opportunistic infections which were not life threatening and a CD4 cell count between 200 and 500cells/ul. Those with life threatening opportunistic infections and a CD4 cell count less than 200cells/ul were said to be in the "Late stage" (i.e. Acquired Immune Deficiency Syndrome)[10].

In our centre, Voluntary Counselling and Testing (VCT) are done at booking, followed by post-test counselling and further management. Highly Active Anti-retroviral drugs (ARVs) were given to all HIV infected pregnant women, or continued in those whose status was known and were on ARVs before they got pregnant. Those who were HIV negative were counselled on how to remain negative. Those who were sero-positive were counselled on safe sex to avoid infection with new strains of HIV.

HIV antibody testing was conducted on the serum of women who gave consent using HIV 1 and 2 pack assay, and Rapid enzyme immunoassay Gene II for HIV 1 and 2 antibodies. Where further confirmation was required, immuno-confirm for HIV 1 and 2 antigen detection was used, which test for p^{24} (core antigen), p^{31} (endonucleus polymerase antigen) and gp^{41} (envelope antigen). HIV-antibody testing was repeated 3 months later

in those who were HIVantibody negative at the time of recruitment, in order to exclude the window period, and in the postnatal clinic to confirm that they remained negative.

Following VCT, 95 HIV infected pregnant women (cases) and 95 HIV uninfected pregnant women (control) who met the recruitment criteria were recruited into this study after obtaining informed consent. The recruitment criteria were women who: (a) were Para 1-3 at booking, in order to avoid primigravidae and grandmultiparae who may have lower immunity; (b) were married, in order to exclude those that may engage in unsafe sex; and (d) carried their pregnancy to term, delivered in our hospital and attended the postnatal clinic.

Intermittent Preventive Therapy in Pregnancy (IPT_p) was given at 4 weeks interval from 16 weeks gestation, 2 doses were given to HIV uninfected women, and 3 doses to HIV infected women. The women in either group with pyrexia had the diagnosis confirmed by examining peripheral blood films for malaria parasites, after excluding other causes of pyrexia. Patients with positive smears were treated with Artesunate Combination Therapy (ACT).

The study variables of interest were age and parity, occurrence and recurrence of febrile malaria infection among the women in both groups, and the incidence of febrile malaria infection in the various stages of HIV infection.

The data were prospectively obtained from the women using pre-designed proforma and retrospectively analyzed. Statistical analysis was done with chi-square test and Z-test using a commercial statistical package (SPSS/PC version 11.0, SPSS Inc., Chicago IL. USA.). The Odds Ratio (OR) and 95% confidence intervals (CI) were determined where appropriate. A P-value of less than 0.05 was considered significant.

RESULTS

The age range of the pregnant women with HIV infection was 15 – 34 years, with a mean age of 23.7 $\pm$ 6.7 years, while for the HIV uninfected pregnant women it was 16 – 34 years, with a mean age of 24.6 $\pm$ 7.1 years. There was no significant difference in the mean age between the HIV infected and HIV uninfected women ($Z = 0.139$, $P > 0.05$).

The mean parity among the pregnant women with HIV infection was 2.2 $\pm$ 1.0, while among the HIV uninfected women, it was 2.1 $\pm$ 0.7. There was no significant difference in the mean parity between the HIV infected and HIV uninfected women ($Z = 0.84$, $P > 0.05$). (see Table 1).

Among the pregnant women with HIV infection, 21 women had febrile malaria infection, while 8 women had among the control group. The incidence of febrile malaria infection among HIV infected pregnant women was 22.1%, while it was 8.4% among HIV uninfected pregnant women. The odds of occurrence of febrile malaria infection among HIV infected pregnant women was three times higher than among HIV uninfected pregnant women (OR=3.09, CI=1.21-8.11, P>0.05). (see Table 2).

The odds of recurrence of febrile malaria infection among HIV infected pregnant women was nine times higher than among HIV uninfected pregnant women (OR = 9.33, CI = 0.83 – 241.3, $P < 0.05$). (see Table 3).

The incidence of febrile malaria infection in pregnancy among the HIV infected women in the various stages of the infection, was not statistically significant among the women in the asymptomatic stage, (OR= 0.09, CI= 0.03-0.33, $P < 0.05$), but was statistically significant among the women in the symptomatic stages, with the frequency being 4 times higher among the women in the late symptomatic stage (OR=18.0, CI=2.93-141.89, $P <0.05$), compared to early symptomatic stage (OR=3.51, CI=1.13-11.05, $P <0.05$). (see Table 4).

DISCUSSION

The incidence and recurrence of febrile malaria infection was significantly higher among HIV infected pregnant women in this study, compared to the uninfected. This is similar to the findings in studies from malaria endemic areas[3-6]. This has been attributed to immuno-suppression[13-15]. In our

environment where malaria is endemic, our women have partial immunity against malaria infestation, and the depression in immunology in the HIV infected women compared with the uninfected, will play an important role in determining the incidence and recurrence of febrile malaria infection in pregnancy[3-5,12].
However, it did not agree with studies from malaria non-endemic areas, where there was no difference in the incidence or recurrence of febrile malaria infection among HIV infected and HIV uninfected pregnant women[9]. This may be because the prevalence of malaria in pregnancy is low, and the women are not immune in non-endemic areas[3].

In this study, the incidence of febrile malaria infection in pregnancy was not significant among the women in the asymptomatic stage of HIV infection, but was significantly higher with increasing stage of the HIV infection, which may be because there is decreasing immune status with increasing stage of the HIV infection[13,16], and the association with febrile malaria parasitaemia strengthens with decreasing immune competence[22]. Studies from malaria endemic areas found that febrile malaria infection rates was inversely related to CD4 counts, and parasite density increased with decreasing CD4 counts[18].

Studies have found that HIV positive individuals have increased treatment failure, with a high incidence of new uncomplicated infections, and p***atients with severe immunosuppression were at increased risk of treatment failure with anti-malarial therapies[20]***. Molecular genotyping revealed that clinical treatment failures seen in HIV infected adults were due to new infections rather than to recrudescence of existing infections[18], because in 2000 patients who presented with fever and positive thick blood smears, more than 6 fold increased risk for new falciparum infections were found in HIV positive patients compared to HIV negative patients[18]. Treatment failure and increased risk of new infections with decreasing immune competence, may explain the increased incidence and recurrence of malaria parasitaemia among HIV infected pregnant women in this study, and why it increased with increasing stage of HIV infection.

This emphasizes the importance of HAARTS in the management of malaria in pregnancy, by preventing ***severe immunosuppression, and ensuring the efficacy of anti-malarial therapies,*** as defined by disappearance or decreased parasitemia by 90% after initial standard treatment[18,20].

IPT_p which is the most practical public health approach for preventing malaria-related complications in pregnancy[2,3], should be given to all HIV infected pregnant women as prophylaxis[20]. Clinical malaria should be treated with artemisinin combination therapy, and artemether-lumefantrine[18-20]. Because of the increased susceptibility of HIV positive pregnant women to new infections and febrile malaria parasitaemia, the authors suggest that IPTp should be given as *Direct Observation Therapy (DOT)* in the antenatal clinic to ensure compliance.

Maternity patients, especially those who are HIV infected should be adequately counselled to avoid mosquito bites, which are best achieved by sleeping under insecticide-impregnated bed nets (ITNs)[18]. Alternatives include using mosquito repellents on skin or clothing or sleeping in a room with burning mosquito-repellent coils or tablets[18,20]. They should also be advised to rid their environments of breeding places for mosquitoes, and where possible fumigate their surroundings[18].

A recent study found that the use of HAART, IPTp and insect treated bed nets was associated with 95% reduction of febrile parasitemia in HIV positive pregnant women[18], which call for community mobilization, to ensure that HIV infected pregnant women are provided with HAART, IPTp and ITNs free of charge by governmental and non-governmental organizations.

Efforts must be made to establish a diagnosis of malaria parasitaemia in all cases of pyrexia in pregnant women with HIV infection[20], as was done in this study, as this will forestall empirical treatments and the undesirable effects of drugs[17,18], especially because the pharmacokinetic interactions between antimalarials and antiretrovirals are still inconclusive[18,21].

CONCLUSION AND RECOMMENDATIONS

The incidence and recurrence of febrile malaria infection is significantly higher among HIV infected pregnant women, and the frequency increases with increasing stage of HIV infection. Use of HAART to prevent immune compromise, and effective and evidence based antimalarial programs like the "*Role Back Malaria" (RBM) and "Malaria No More" programmes,* should be integrated into the antenatal clinic protocol, especially in malaria endemic areas, in order to reduce fetal and maternal morbidity and mortality from malaria parasitaemia, and reduce the risk of mother to child transmission of HIV.

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Table 1:
Distribution of HIV infected and HIV uninfected women according to age and parity.

Variable	HIVinfected women n = 95	HIVuninfected women n = 95	Test	P-value
Mean age	23.7 ± 6.7	24.6 ± 7.1	Z = 0.139	> 0.05 (N/S)
Mean parity	2.2 ± 1.0	2.1 ± 0.9	Z = 0.84	> 0.05 (N/S)

N/S = Not statistically significant

Table 2:
Occurrence of malaria fever in HIV infected women compared to HIV uninfected women.

Patients	Frequency of occurrence n(%)	OR	CI	P-value
HIV infected n = 95	21 (22.11)	3.09	1.21 – 8.11	< 0.05 (S)
HIV uninfected n = 95	8 (8.42)			

S = statistically significant

Table 3:
Distribution of HIV infected and HIV uninfected pregnant women according to recurrence of malaria fever.

Variable	Frequency of recurrence n(%)	OR	CI	P-value
HIV infected n = 21	12 (57.14)	9.33	0.83-241.31	< 0.05 (S)
HIV uninfected n = 8	1 (12.5)			

S = statistically significant

Table 4:
Distribution of HIV infected women with malarial fever according to stage of infection.

Stage of HIV infection	Frequency n (%)	OR	CI	P - Value
Asymptomatic n = 62	5 (8.07)	0.09	0.03-0.33	<0.05(N/S)
Early symptomatic n = 24	10 (37.50)	3.51	1.13-11.05	<0.05(S)
Late symptomatic n = 9	7 (77.78)	18.0	2.93-141.89	<0.05(S)

S = statistically significant

N/S = Not statistically significant.