An assessment of the impact of placental Plasmodium falciparum malaria on perinatal outcome in Nigeria

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Citation

C Uneke, F Iyare, I Sunday-Adeoye, J Ajayi. *An assessment of the impact of placental Plasmodium falciparum malaria on perinatal outcome in Nigeria*. The Internet Journal of Parasitic Diseases. 2007 Volume 3 Number 2.

Abstract

Apparently healthy women at full pregnancy term were enrolled. At child birth, maternal and placental malaria parasite microscopy, fetal length and head circumference and birth weight were determined using standard techniques. P. falciparum was found in the peripheral blood of 48(16.0%) of the 300 women studied. Women with peripheral malaria infection had significantly higher proportion (54.2%) of placental infection than those without peripheral malaria (3.5%) (χ^2=94.4, P<0.05). Of the 278 placental blood samples analyzed, 34(12.2%) had malaria parasites. A significantly higher proportion (33.3%) of malaria infected placentas had the lowest placental weight (0.4kg) (χ^2=6.99, P<0.05) and a higher proportion of babies born by mothers with malaria infected placenta had low birth weight (<2.5kg). A higher proportion of infected placenta was associated with lower fetal length and head circumference, although no significant difference was observed (P>0.05). Effective linkages between malaria control and antenatal care programs are advocated to improve perinatal outcome.

INTRODUCTION

Malaria during pregnancy is a serious problem in sub-Saharan Africa, affecting an estimated 24 million pregnant women [1]. Each year between 75,000 and 200,000 infant deaths are attributed to malaria infection in pregnancy globally [1,2]. The sub-Saharan Africa records the greatest severity of malaria because about 90% of all deaths attributable to malaria in the world today occur in the sub-region and this is because majority of infections are caused by Plasmodium falciparum, the most dangerous of the four human malaria parasites [3]. Although P. falciparum infection in pregnancy in sub-Saharan Africa, is usually asymptomatic it largely contributes to maternal deaths and congenital malaria with risk for infant death particularly in areas of lower malaria endemicity [1].

One of the major features of P. falciparum malaria during pregnancy is the sequestration of the parasite in the placenta which is most common among the primigravidae [4]. P. falciparum–infected erythrocytes frequently sequester in the intervillous space of the placenta and cause pathologic alterations [5,6,7], which is associated with a variety of adverse perinatal outcome including a significant decrease in infant birth weight [8,9,10]. Thus placental P. falciparum malaria has been identified as a risk factor for low birth weight (LBW) mainly mediated by intrauterine growth retardation (IUGR) and pre-term deliveries (PTDs), although the exact mechanisms by which malaria leads to LBW remain unclear [11,12]. The distribution of placental P. falciparum malaria in infected gravid women has been described to vary with the endemicity of malaria and acquired immunity [12]. Histological abnormalities described in parasitized placenta show pathological changes that could reduce the area of syncytium exposed to maternal blood and, thus, impair materno-foetal exchanges [5,6]. Likewise, considerable abnormality in intervillous spaces may jeopardize the nutritional function of the placenta, resulting in poor foetal outcome [12,13,14]. Because placental infection may be detected in the absence of peripheral blood parasitemia and may persist after initiation of antimalarial treatment [15], the diagnosis of placental malaria in pregnancy is therefore very important for both operational and research purposes.

Despite the availability of considerable number of literature on malaria in pregnancy in sub-Saharan Africa, the impact of placental malaria on perinatal outcome is poorly documented in many parts of the sub-region including Nigeria. This paucity of scientific data continues to limit the understanding of events at the maternal-fetal interface which encompass immunological and pathological processes which relate to the epidemiological pattern of malaria in pregnancy and on perinatal outcome in areas of both high and low

malaria transmission. The objective of this present study therefore, was to evaluate the possible effects of placental P. falciparum malaria on pregnancy outcome particularly its impacts on the neonatal health. This is with a view to providing scientific information that would lead to an enhanced understanding of the mechanisms involved in this process which is of key importance in the design of protective interventions that are effective and acceptable during the gestation period in malarious areas of the world.

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 at the Ebonyi State University Teaching Hospital (EBSUTH), Abakaliki, which is the largest health facility in this region. The climatic condition of the area is characterized by 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.

ETHICAL CONSIDERATIONS

The study protocol was approved by Department of Medical Microbiology/Parasitology, Faculty of Clinical Medicine, Ebonyi State University, Abakaliki, Nigeria. Ethical approval was obtained from the Ethical Committee of the EBSUTH, Abakaliki. All work was performed according to the international guidelines for human experimentation in clinical research [16].

STUDY POPULATION/SAMPLING TECHNIQUE

Pregnant women who fulfilled the following study inclusion criteria were enrolled into the study: (i) attended the antenatal clinic at EBSUTH, (ii) had an uncomplicated singleton pregnancy 32 weeks' gestation (based on the fundal height estimation), (iii) reside in Abakaliki or neighbouring local government areas, (iv) had no obvious clinical evidence of malaria (asymptomatic), and (v) had no known underlying chronic illness. Shortly before child birth informed consent was obtained from each participant and about 5ml of the maternal peripheral blood, was obtained from each participant by venepuncture technique into sterile EDTA container for laboratory analysis. Immediately after child birth, the placenta of each subject was collected as soon as it was voided into a transparent sterile plastic container. Placental blood was collected into EDTA by incising the cleaned maternal surface of the placenta and aspirating blood welling from the incision. Information was obtained on the delivery outcome including; baby's sex and mode of delivery. The placental weight and the birthweight were determined in kilogram (Kg) using an electronic weighing machine immediately after child birth, while the fetal length and fetal head circumference were determined in centimeters (cm) using a measuring tape.

LABORATORY ANALYSIS

Each pair of maternal and placental blood sample was analyzed for malaria parasite infection by performing the microscopy of Giemsa-stained thick and thin blood films. The Plus System was used for the determination of parasite density as previously outlined [17]. All the films were double-checked blindly by experienced parasitologists and if there were differences 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 41-400 parasites per mm3).17

STATISTICAL ANALYSIS

Percentage prevalence rates were calculated with their respective 95% confidence intervals.

Difference between proportions were evaluated using the chi-square tests. Statistical significance was achieved at $P<0.05$.

RESULTS

According to the criteria of this investigation malaria parasites were found in the peripheral blood of 48(16.0%) out of the total of 300 women at full pregnancy term who were recruited in this study. P. falciparum was the only species identified. Of the 48 women infected by malaria parasite, 1-10 parasites per 100 thick film fields were recorded in 11(22.9) while 11-100 parasites per 100 thick film fields were recorded in the remaining 37(77.1%). A total of 278 placental blood samples were available for study and of these, 34(12.2%, 95% CI., 8.4-16.0%) had malaria parasites of between 1-10 parasites per 100 thick film fields. Placental weight was determined for 214 placental samples. Neonatal birthweight was determined for 231 babies while the fetal length and fetal head circumference were determined for 195 and 190 babies respectively (Table 1).

The association of placental malaria infection with placental

weight, neonatal birthweight, maternal malaria infection, fetal length and fetal head circumference is summarized Table 1.

Table 1: Association of placental malaria with maternal malaria, placental weight and fetal parameters in Abakaliki, south-eastern Nigeria.

Figure 1

Parameter	Number Examined	Number (%) with Infected placenta	95% Confidence Interval
Maternal Malaria Infection			
Infected	48	26(54.2)	53.9-54.5
Uninfected	230	28(3.5)	1.1- 5.9
Total	278	34(12.2)	8.4-16.0
Placental Weight (Kg)			
≤ 0.4	30	10 (33.3)	16.4-50.2
0.5-0.7	164	21(12.8)	7.7-17.9
≥ 0.8	20	3(15.0)	0.7-30.7
Total	214	34(15.9)	11.0-20.8
Birthweight (Kg)			
≤ 2.5	52	8(15.4)	5.6-25.2
2.6- 3.5	139	20(14.4)	8.6-20.2
≥ 3.6	36	5(13.9)	2.6-25.2
Total	231	33(14.3)	9.8-18.8
Fetal length (cm)			
≤ 45	29	4(13.8)	1.2-26.4
46-50	131	15(11.5)	6.0-17.0
≥51	35	2(5.7)	2.0-13.4
Total	195	21(10.8)	6.4-15.2
Fetal head circumference (cm)			
<35	51	6(11.8)	2.9-20.7
≥ 35	139	15(10.8)	5.6-16.0
Total	190	21(11.1)	6.6-15.6

Results showed that of the total of 214 placental sample of which the weight was determined, 34(15.9%, 95% CI., 11.0-20.8%) had malaria parasite infection with a higher proportion (33.3%, 95% CI., 16.4-50.2%) of malaria infected placentas having placental weight equal or less than 0.4kg. There was a statistical significant difference in the trend (?2=6.99, df=2, P<0.05). A higher proportion of babies born by mothers with malaria infected placenta had LBW (15.4%, 95% CI., 5.6-25.2%), but statistical analysis showed no significant difference in the trend (?2=0.031, df=3, P>0.05) (Table 1).

Women with peripheral malaria infection had significantly higher proportion (54.2%, 95% CI.,53.9-54.5%) of placental malaria infection than those without peripheral malaria infection (3.5%, 95% CI., 1.1-5.9%) (?2=94.4, df=1, P<0.05). When placental malaria was related to fetal length and fetal head circumference, a higher proportion of infected placenta was associated with lower fetal length and lower fetal head circumference although no significant difference was observed in the fetal length (?2=1.313, df=2, P>0.05) and fetal head circumference (?2=0.036, df=1, P>0.05) (Table 1).

DISCUSSION

Placental infection measured by placental smear at delivery has been described as a standard indicator, which is widely used to characterize malaria infection in pregnant women [18]. Using this technique, a placental P. falciparum malaria prevalence of 12.2% was obtained in this study. Placental malaria prevalence results from various parts of sub-Saharan Africa have been discordant, and one of the major factors in the discordance is that different techniques of diagnosis of employed based on the differences in the definition of placental malaria [19].Using the placental blood smear microscopy, placental malaria prevalence rates of 9.5%,18.5%,19.9%, and 37.1% were obtained in Senegal [20], Sierra Leone [21], Cameroon [22], and Gambia [12] respectively. By placental histological examination, placental malaria prevalence rates of 35% was obtained in Gabon [23], 35.2% in Tanzania [24], 51.1% in Gambia [12], and as high as 75.5% in south-eastern Tanzania [25]. Two West African studies evaluated the prevalence of placental malaria using histidine-rich-protein-2 (HRP2) capture test and polymerase chain reaction (PCR). The first study conducted in Ouagadougou, Burkina Faso recorded placental malaria prevalence rates of 43.1%, and 51% by HRP2 capture test and PCR respectively [26], while in the second study conducted in southern Ghana the corresponding prevalence rates were respectively 41% and 59% [27].

These results indicate that placental malaria is still unacceptably high in the sub-Saharan Africa and calls for the intensified efforts in malaria control in pregnancy. The importance of effective control measures cannot be overstated because apart from the adverse perinatal outcomes associated with placental malaria, some studies also suggest that children born to mothers with placental malaria are at a high risk of acquiring larger numbers of P. falciparum infections in the first 2 years of life compared to infants born to women without placental malaria [28]. Furthermore, it was reported that placental malaria infection diminished the development of antibody responses to malarial epitopes in the first year of life, the age at which most of the severe malaria-associated morbidity occurs in areas of holoendemicity [29].

In this study maternal peripheral malaria infection was significantly associated with placental malaria (P<0.05). This is consistent with a report from Burkina Faso, where a

strong correlation was found between placental infection and peripheral infection at the end of pregnancy [18]. The authors suggested that peripheral parasitemia at the end of pregnancy is a very strong risk factor for placental infection (a five fold increase), thus confirming the importance of late maternal malaria infection which was noted in another study [30]. Interestingly, up to 3.5% of the mothers without detectable peripheral parasitemia had placental infection in this present study. In Ghana, roughly half of the women with microscopically proven placental parasitemia had a negative peripheral blood film; it was thus suggested that a negative peripheral blood film in pregnant women in endemic areas is hardly informative [25]. This finding underscores the importance of assessment of placental malaria, because placental infection may be detected in the absence of peripheral blood parasitemia and may persist after initiation of antimalarial treatment [31].

The least placental weight was found to be significantly associated with the highest proportion of placental malaria infection ($P<0.05$) in this present study. Two earlier studies that evaluated the relationship between placental malaria and placental weight in Haut-Ogooue and Franceville, both in Gabon indicated that the mean weight of term placentas with malarial changes was significantly less than that of placentas without such changes [5,32]. Similarly, LBW, lower fetal length and lower fetal head circumference were also associated with higher proportion of malaria infected placenta in this study, although the differences were not statistically significant. It was noted that despite the prevalence of placental infections for women of all gravidities, ranging from 5% to 52% in sub-Saharan Africa, the risk of LBW associated with infection was relatively consistent, with babies born to mothers with an infected placenta being twice as likely to be of LBW than those born to mothers with an uninfected placenta [33]. In southeastern Tanzania, chronic malaria infection of the placenta was associated with significant reductions in mean head circumference, neonatal length, and body index (weight/length2), whereas past infections were associated with reduced mean length at birth only [22], but in the Ubangi district of Zaire, malarious placentas had no consistent relationship with neonatal length or head circumference [34]. The reduction in the length and head circumference of the newborns associated with chronic infections probably indicate a prolonged effect on fetal nutrition, caused by P. falciparum placental parasitization suggested in other studies [35,36].These findings were not surprising because, maternal P. falciparum malaria was already found to be strongly associated with placental malaria which adversely affects birth weight and fetal anthropometric parameters, thought to be mediated through placental insufficiency, leading to preterm delivery (PTD) and intrauterine growth retardation (IUGR) [37].

The processes by which placental malaria leads to LBW and lower fetal anthropometric parameters remain unclear, though it has been suggested that IUGR and PTD associated with maternal malaria could play contributory roles [11,12]. Many hypotheses, based on a systemic or local failure of the immunological response to malaria, have been proposed to explain the 'preference' of the parasites for replication in the placenta but the exact mechanisms leading to placental changes and determining the observed impairment of materno-foetal exchange are incompletely understood [13].However it has been suggested that parasites are unlikely to be directly responsible for the placental pathology, but leucocytes, through the production of non-chemotactic cytokines, might be associated with the thickening of the trophoblastic basement membrane, and might cause a mechanical blockage of oxygen and nutrient transport across the placenta [13]. Thus, the high frequency of adverse perinatal outcomes including prematures, hypotrophic neonates and still-births in the malarial population associated with P. falciparum placental infection is explained by the intervillous macrophages, which decrease the maternal blood output and the perivillous excess of fibrin which reduces the materno-fetal exchanges [14]. These may explain why placental malaria was associated with the reduced placental weight, LBW and lower fetal anthropometric parameters observed in this study.

Epidemiological evidence has shown that the assessment of the impact of malaria on the outcome of pregnancy is complicated because the greatest incidence of infection occurs during the second trimester, and placental and peripheral blood parasitaemia may have resolved by the time of delivery [38]. This may have accounted for the absence of a significant effect of placental malaria on the birthweight observed in this study even though the LBW babies recorded slightly higher proportion of infected placenta. Nevertheless the importance of the assessment of placental malaria cannot be overstated. This is to enable adequate care and monitoring of infants born by mothers with placental malaria, since these infants may be at an increased risk of anemia, increased malaria prevalence rates, and mortality, during their first year of life [11,38,39].

In conclusion, it is important to state that a major limitation of this study was the use of placental smear as the technique to diagnose placental malaria. Although the use of placental smear is reasonably diagnostic, the possibility of under-estimation may not be ruled out completely. This is because it has been demonstrated that placental blood film is less sensitive than placental histology [25,26]. Placental histology is thus the "gold standard" for the diagnosis of malaria at delivery, but it is relatively costly and labor-intensive and, hence, is frequently not available in most settings of malaria endemic developing countries. However, the use of histological diagnosis of placental malaria in epidemiological studies will allow more detailed characterization of the burden of morbidity attributable to malaria in pregnancy. This is advocated in future studies. As part of public health measures, there is the need for effective linkages between malaria control and antenatal care programmes in order to improve the success of efforts to control malaria during pregnancy. To reduce the burden of malaria infection in pregnancy a three-pronged approach has been recommended by the World Health Organization [2,3] these include; use of intermittent preventive treatment (IPT), insecticide-treated nets (ITN), and case management of malaria illness.

ACKNOWLEDGEMENT

The authors are grateful to the management of Ebonyi State University Teaching Hospital, Abakaliki-Nigeria, for logistic support.

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