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REVIEW

Impact of Placental *Plasmodium falciparum* Malaria on Pregnancy and Perinatal Outcome in Sub-Saharan Africa

II: Effects of Placental Malaria on Perinatal Outcome; Malaria and HIV

Chigozie J. Uneke

Faculty of Clinical Medicine, Ebonyi State University, Nigeria

Placental malaria is recognized as a common complication of malaria in pregnancy in areas of stable transmission, and, as a consequence, serious health problems arise for the mother and especially her baby [1]. Although malaria in pregnancy is a major factor associated with adverse perinatal outcome, the link between malaria and perinatal morbidity/mortality is less clear in areas with stable endemic malaria where pregnant women have acquired immunity [2]. Histological examination of the placenta is a predictor of fetal morbidity, as well as being the most sensitive detector of maternal infection [3].

Adverse perinatal outcome has been described as an important indicator of poor quality of obstetric care and social development [4]. A variety of adverse perinatal outcomes associated with placental malaria have been described, including low birth weight, preterm delivery, intrauterine growth retardation, fetal anemia, congenital malaria, and fetal mortality. The most common clinical features in 80 percent of perinatal cases are fever, anemia, and splenomegaly [5]. Other signs and symptoms include hepatomegaly, jaundice, regurgitation, loose stools, poor feeding, and, occasionally, drowsiness, restlessness, and cyanosis also can be seen [5,6].

A review of studies that investigated these poor fetal outcomes associated with placental malaria in sub-Saharan Africa is presented here.

ADVERSE OUTCOMES OF PLACENTAL MALARIA

Congenital malaria

Malaria during pregnancy may result in fetal exposure to malaria if parasites are transmitted across the placenta and could result in congenital malaria. Transplacental transmission of *P. falciparum* has been well described, and the reported frequency of this event in babies born in malaria-exposed pregnancies has ranged from 0 percent to more than 25 percent [7-11]. Thus, placental malaria is known to be a major determinant

To whom all correspondence should be addressed: Chigozie J. Uneke, Department of Medical Microbiology/Parasitology, Faculty of Clinical Medicine, Ebonyi State University, PMB 053 Abakaliki, Nigeria. Tele: 234-08038928597; Fax: 234-043221093; E-mail: unekecj@yahoo.com.

†Abbreviations: LBW, low birth weight; PTD, preterm delivery; IUGR, intrauterine growth retardation; MTCT, mother-to-child transmission.

of congenital malaria. Although previously thought to be a rarity in sub-Saharan Africa, a recent review has indicated that congenital malaria is more common than previously thought [12]. While still debatable, congenital malaria may be defined as the presence of asexual stages of *P. falciparum* in cord blood smear at delivery or in peripheral blood smear of the infant in the first seven days of life, irrespective of clinical symptoms [12]. Normally, symptoms occur 10 to 30 days postpartum; however, the disease may be seen in a day-old infant or appear after weeks to months [6]. Interestingly, earlier reports from sub-Saharan Africa rarely identified clinical disease as a consequence of congenitally acquired malaria, and only a few reports before the 1970s documented detectable parasitemia in infants younger than one month [7,13]. These studies were interpreted as showing either that transplacental transmission of malaria occurs infrequently or that after transplacental transmission some elements of immunity acquired from the mother protects infants [8]. It has been demonstrated that in hyperendemic areas, newborns more rarely become ill with malaria because of passive maternal antibody and high levels of fetal hemoglobin [14,15].

Postulated mechanisms for congenital transmission include maternal transfusion into the fetal circulation either at the time of delivery or during pregnancy, direct penetration through the chorionic villi, or penetration through premature separation of the placenta [16]. However, the effectiveness of the placenta to restrain malaria parasite passage to the fetus and the remarkable capacity of the fetus to resist infection has been demonstrated [17]. This resistance may reflect, among other things, the physical barrier of the placenta to infected red cells, the passive transfer of maternal antibodies, and the poor environment afforded by fetal erythrocytes for plasmodial replication due to their fetal hemoglobin composition and low free-oxygen tension [16-18]. It has been implied that transplacental transmission of malaria parasite and, consequently, congenital malaria seemed to occur rarely. However, increasing reports from many parts of sub-Saharan Africa consistently have indicated high prevalence of umbilical cord parasitemia ranging from 1.5 percent to 54.2 percent, and in some of these studies, there was a strong association between placental malaria and umbilical cord parasitemia [12].

Until recently, it was unclear whether the presence of *P. falciparum* malaria parasites in umbilical cord blood is an indication of antenatally acquired infection or contamination with infected maternal blood at delivery. In a study in Kenya, it was unequivocally shown that malaria parasites identified in cord blood are acquired antenatally by transplacental transmission of infected erythrocytes and primigravid and secundigravid women with placental malaria are at increased risk for congenital infection [19]. The high rate of transplacental transmission of malaria appears to suggest the placental barrier is not very effective when infected with malaria parasites [8].

Perinatal mortality

Placental malaria and its effects on perinatal mortality (fetal or infant deaths from 28th week of pregnancy up to the seventh day after birth) have been investigated in various parts of sub-Saharan Africa. The impact of placental malaria on perinatal death (stillbirth and early neonatal death) is still under debate, and conflicting results have been obtained from various studies that investigated the relationship between them. Newman et al. reported a seven-fold increased risk of stillbirth in association with placental parasitemia in areas with unstable malaria transmission in Ethiopia [20]. McGregor et al. [21] observed some seasonal differences in stillbirth rates, with the lowest rate occurring during the three months of the late dry season when placental malaria prevalence was low. Conversely, in a more recent study, Okoko et al. [22], in The Gambia, observed a two-fold increased risk of stillbirth among mothers with malaria-infected placenta and noted that placental malaria infection was independently associated with a higher risk of delivering stillbirths in the population studied. The same conclusion was reached based on a meta-

analysis of 17 cross-sectional studies from sub-Saharan Africa [23]. However, in some studies in individual countries [21,24], this association was not always found to be statistically significant. Interestingly, placental malaria infection has been identified as possibly protective against perinatal mortality among low birth weight (LBW†) infants [25]. The explanations for this, however, remain a mystery and therefore require further exploration.

Low birth weight

In sub-Saharan Africa, the rate of LBW (i.e., < 2.5kg) newborns ranges from 3.9 percent to 24 percent [22,26-29], and malaria is thought to be an important contributor to the 3.5 million LBW babies born annually in sub-Saharan Africa [30]. Malaria is thought to reduce birth weight through a combination of systemic and local effects [26]. Although malaria may affect birth weight through malaria-induced anemia, it also may reduce birth weight via the effects of placental infection [22,31,32]. In this case, parasites either directly cause a mechanical compromise of placental circulation via widespread trophoblast basement thickening and increased fibrinoid necrosis and cytrophoblast prominence or indirectly interfere with placental functions and/or induce pathological lesions [33,34]. Despite the prevalence of placental infections for women of all gravidities, ranging from 5 percent to 52 percent, infection-associated LBW risk is elevated two to four times in various studies [28,29,35]. A contradictory study in The Gambia showed increased birth weight in infected placentas, but widespread trophoblast basement membrane thickening was associated with decreased birth weight. A non-significant correlation was found between LBW and increased fibrinoid necrosis and cytotrophoblast prominence [36]. Similarly, in Ubangi district, Zaire, malarious placentas had no consistent relationship to birth weight, and although infants born to infected mothers with malarious placentas averaged 100 g less, there was, however, no significant difference in the trend [24]. There is still no agreement as to the main mechanisms mediating reductions in birth weight in placental malaria [26]. When birth weight is stratified and related to the types of placental infections (chronic or active) in different studies, there were conflicting findings [22].

Since LBW is the single greatest risk factor for neonatal and infant mortality, its prevention through effective control of placental malaria cannot be overstated [37]. In some studies in sub-Saharan Africa, infant mortality is three times higher for LBW babies than for those of normal weight; effects on neonatal mortality are even more marked, with a LBW baby being nine times more likely to die in the first month of life [38-39].

Preterm delivery and intrauterine growth retardation

The relationship between placental malaria and preterm delivery (PTD)/intrauterine growth retardation (IUGR) has been evaluated in various studies. Two earlier studies among semi-immune women failed to show a difference in the proportion of PTD among infected and non-infected mothers, but other reports across sub-Saharan Africa have shown that placental malaria was significantly associated with PTD and IUGR [40-43]. This is in contrast with reports from Yaoundé, Cameroon, Malawi, and The Gambia, where, after adjusting for potentially confounding variables, the association of placental malaria with PTD was not found to be significant [21,44,45].

Although the precise effect of malaria-parasitized placentas on PTD is uncertain, malaria-infected placentas frequently carry antibodies, cytokines, and macrophages, which are indicative of an active immune response, and this immune response may stimulate early labor [35,46]. The biological processes that mediate IUGR as a result of placental malaria remain uncertain, given that they can be studied only after the placenta has been delivered. However, the IUGR effect appears to relate to nutrient transport to the fetus [35]. A high density of parasites and chronic parasite infection in the placental blood and the associated cellular immune response may result in consumption

of glucose and oxygen that would have gone to the fetus. Histopathological studies of infected placentas have found thickening of the cytotrophoblastic membranes, which may interfere with nutrient transport [35,46].

Although IUGR is more common than PTD with chronic placental infection, chronic infection of the placenta (with pigment and parasites) may be associated with LBW, through both prematurity and IUGR [26,47]. Active placental infections were associated with a statistically significant lower risk of LBW as a result of IUGR and with a non-significant increase in the risk of LBW as a result of prematurity [26]. This finding suggests that acute infections toward the end of pregnancy may play an important role in the induction of PTD, consistent with higher rates of abortions and preterm deliveries that have been observed during malaria transmission seasons [48]. Because premature infants are more likely to die than IUGR babies, the prevention of placental malaria particularly toward the end of gestation in malarious areas becomes absolutely imperative [49].

Effects on Neonatal Anthropometric Parameters

Neonatal anthropometric parameters such as neonatal length, head circumference, and placental weight have been related to placental malaria. In southeastern Tanzania, chronic ongoing malaria infection of the placenta was associated with significant reductions in mean head circumference, neonatal length, and body index (weight/length), whereas past infections were associated only with reduced mean length at birth [26]. In southeastern Nigeria, a slightly higher proportion of infected placenta was not significantly associated with lower neonatal length and lower head circumference; in the Ubangi district of Zaire, malarious placentas had no consistent relationship with neonatal length or head circumference (Uneke et al., unpublished data) [24]. Reduction in newborn length and head circumference associated with chronic infections probably indicates a prolonged effect on fetal nutrition, which previously has been suggested [49,50]. Similarly, it has been suggested that the reduction in the body mass index may reflect the severity and duration of fetal malnutrition [26].

Two earlier studies evaluated the relationship between placental malaria and placental weight in Gabon. The mean weight of term placentas with malarial changes was significantly less than that of placentas without such changes [51,52]. In southeastern Nigeria, placental malaria was significantly associated with lower placental weight (Uneke et al., unpublished data). The reason for this reduction is not fully known, but it may be associated with changes in the placenta, including the presence of parasitized erythrocytes and malarial pigment particles in the intervillous space, chronic basal villitis, malarial pigment deposits in the trophoblasts, trophoblastic damage with focal necrosis, partial loss of microvilli, and thickening of the trophoblastic basement membrane [53]. As a result of these changes, a high density of parasites and chronic parasite infection in the placental blood and the associated cellular immune response may result in consumption of glucose and oxygen that would have gone to the fetus [35]. Placental insufficiency also could be attributable to physical blockage by parasitized red blood cells and the massive monocyte infiltration of the intervillous spaces. Such infiltrate is likely to be a source of cytokines, including interferon-g, interleukin-2, interleukin-6, and tumor necrosis factor–a, which are considered detrimental to pregnancy because they are associated with growth retardation [54].

Fetal anemia

The prevalence of fetal anemia, defined as cord hemoglobin level < 12.5g/dl, is reportedly very high in sub-Saharan Africa. In two separate studies conducted in southern Malawi, fetal anemia prevalences of 23.4 percent [55] and 23.3 percent [56] were recorded, while in Maputo Mozambique, up to 93 percent of newborns were found to have fetal anemia [57]. Interestingly, a statistically significant link was established between fetal anemia and maternal malaria infection in all of these studies. The contrib-

utory role of placental malaria to fetal anemia has been evaluated in a number of studies with varying results.

In southern Malawi, a higher prevalence of fetal anemia occurred with increasing peripheral *P. falciparum* parasite density, and geometric mean placental parasite densities were higher in babies with fetal anemia than in those without it [55]. Other studies have found no statistically significant connection between evidence of malaria infection and fetal anemia [58].

This lack of consistency in the findings from various studies may be explained by the fact that malaria in pregnancy varies with transmission intensity, access to treatment, coverage and quality of antenatal services, and drug resistance, among other factors [56,59,60]. The etiology of fetal anemia is complex and multifactorial; placental malaria could play either a major or minor role, depending on the local epidemiological situation [61]. It has been suggested that exposure of the fetus to malaria antigens due to damage of the placental barrier may make the newborn more susceptible to immunologically mediated hemolysis or to dyserythropoiesis [61].

MOTHER-TO-CHILD TRANSMISSION OF HIV

Maternal HIV infection

Approximately 1 million pregnancies per year are thought to be complicated by co-infection with malaria and HIV in sub-Saharan Africa, because the two diseases are known to critically intersect in pregnancy [62,63]. HIV infection has been associated with an increased prevalence and density of malaria in pregnancy in a number of studies in sub-Saharan Africa [62,64-66]. In most studies, the prevalence of placental malaria infection was significantly more prevalent in HIV-positive compared with HIV-negative mothers [66-70]. In one study in Malawi, however, HIV infection was not significantly related to the likelihood of malaria as detected by placental histology [71]. Nevertheless, the increased susceptibility to both peripheral malaria and placental malaria by HIV infected pregnant women is likely due to immunodeficiency, as it has been shown that HIV may impair the immune response to malaria in pregnancy [65].

Although *in vitro* experiments showed that higher placental virus load was seen when malaria antigen was present [72,73], it was suggested it might be that this local increase in virus concentration is not reflected in the systemic maternal virus load [69]. Furthermore, in Malawi, a similar twofold increase in placental HIV-1 RNA concentrations was found, with the greatest increase in women with the highest placental parasite densities [74]. It was noted that these observations were independent of the degree of immunosuppression as assessed by CD4 cell counts and thus cannot be explained by an increased risk of malaria in subjects with more advanced immunosuppression and potentially greater HIV-1 viral load [74].

Whether dual infection with placental malaria and HIV increases the risk of mother-to-child transmission of HIV (MTCT) is yet to be unequivocally established, as studies examining these relationships have inconsistent findings and a wide range of unanswered questions. Reported prevalence of MTCT ranges from 19.4 percent to 19.9 percent [64,68-69]. In some studies, no correlation was found between placental malaria and perinatal HIV transmission; in others, a higher prevalence of MTCT was observed among HIV-positive mothers with placental malaria, although other factors were not controlled for [68-69]. One report notes a lower prevalence of MTCT among HIV-positive mothers with placental malaria, and indicates that placental malaria, especially at lower density parasitemia (< 10,000 parasites/μL), is significantly associated with reduced risk for perinatal MTCT [64].

These conflicting results on the relationship between placental malaria and the risk of MTCT, ranging from an increased risk to no effect to a significant protective effect suggests there exists a complex interaction between placental malaria and HIV infection.

During pregnancy, the presence of malaria parasites is associated with a higher HIV-1 load [75], and placental HIV-1 viral load is increased in women with placental malaria, especially those with high parasite densities [74]. It can be hypothesized that increased placental HIV-1 load, due to the presence of malaria parasites, might be associated with increased excretion of HIV-1 in the genital tract, thus increasing the risk of MTCT. Maternal immune responses to malaria on the one hand may stimulate HIV viral replication in the placenta, thereby increasing the local viral load. Alternatively, maternal immune responses may control the severity of malarial infection and HIV replication and may either have a protective effect or increase the risk of MTCT [62,76]. It has been suggested that the direction of the effect may depend on the degree of HIV-related immunosuppression and, thus, the degree of placental monocyte infiltrates and proinflammatory cytokine and chemokine responses [62] and on the severity of the malaria. More studies are urgently needed to evaluate the immunological bases for the increased susceptibility of HIV-infected mothers to both peripheral and placental malaria and for the effect of co-infection on mother-to-child transmission of HIV.

CONCLUSIONS

In sub-Saharan Africa, with high birth rates, a high endemicity of malaria, and alarming rates of new cases of HIV, prophylaxis against both diseases with combination agents during pregnancy has been described as a great challenge [77]. Low adherence, poor-quality drugs, and drug resistance decrease the effectiveness of both antiretroviral and anti-malarial drugs and may further hamper treatment outcome and overall improvement of maternal and infant health. This calls for more research on malaria and HIV infection treatment and prevention intervention strategies because only with sufficient evidence can appropriate public health policy be devised on integrating the prevention, care, treatment, and support activities for malaria and HIV among pregnant women in the sub-region.

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