Impact of placental *Plasmodium falciparum* malaria on pregnancy and perinatal outcome in sub-Saharan Africa

Part III: Placental Malaria, Maternal Health, and Public Health

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*Plasmodium falciparum* infections of the placenta remain a major medical challenge among pregnant women in sub-Saharan Africa. A number of factors influence the prevalence of placental malaria in pregnant women, including maternal age, gravidity, use of prophylaxis, nutrition, host genetics, and level of anti-parasite immunity, as well as parasite genetics and transmission rates [1]. Maternal anemia has been shown to be one of the major complications of placental malaria in sub-Saharan Africa. The mechanisms by which malaria causes anemia are fairly well understood. The pathophysiology of malaria-associated anemia is multifactorial. The most likely mechanisms include (i) hemolysis or the direct destruction of parasitized red blood cells that occurs both intravascularly and by sequestration in the microcirculation, mainly in the spleen; (ii) specific/nonspecific immune responses, whereby red cell survival is shortened; (iii) nonspecific, defective, red cell production, which depresses erythropoiesis, inhibits reticulocyte release, and prematurely destructs red cells during maturation in the bone marrow; and (iv) hypersplenism associated with a reduction in all three blood cell series, that is, causing not only anemia but also thrombocytopenia and leucopenia [2,3].

The relationship between maternal anemia with obstetric factors, however, is not fully understood, and, thus, evaluating the link between malaria, obstetric disorders, and maternal death has been recommended [4]. There have been efforts to quantify the contribution of malaria to maternal morbidity and mortality with the expectation that this would provide the evidence necessary to improve the effectiveness of advocacy to incorporate malaria prevention strategies in Safe Motherhood Programs [5,6]. The effects of placental malaria on maternal health can better be understood when considered in relation with various maternal parameters, including maternal age, parity, peripheral malaria infection, anemia, and HIV infection.

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†Abbreviations: sVEGFR1, soluble vascular endothelial growth factor receptor 1; VEGF, vascular endothelial growth factor; CSA, chondroitin sulfate A; WHO, World Health Organization; IPT, intermittent preventive treatment.
MATERNAL HEALTH AND MALARIA

Increased Morbidity and Mortality

Although pregnant women in malaria-endemic areas have higher rates of parasitemia and parasite density compared with non-pregnant women, infection is largely asymptomatic because some degree of pre-existing immunity is retained during pregnancy [7]. However, even malaria-immune women (i.e., those who have evolved some level of immunity against severe infection as a result of long residence in areas of stable malaria transmission) are susceptible to placental malaria [1,8,9]. Because so many parasites become sequestered within the placenta, peripheral blood smears often fail to detect evidence of infection. The resulting lack of appropriate or timely treatment may lead to adverse pregnancy outcome, including severe anemia, which is the main maternal consequence of malaria and can be deadly [7]. Apart from anemia, malaria may contribute to maternal mortality by increasing the risk and severity of obstetric conditions such as pre-eclampsia/eclampsia and postpartum hemorrhage by as much as 50 percent [10,11].

Maternal anemia

Anemia is the most common consequence of *P. falciparum* malaria infection. In sub-Saharan Africa, it is estimated that between 200,000 and 500,000 pregnant women develop severe anemia as a result of malaria [12], and *P. falciparum* malaria in pregnancy is the primary cause of up to 10,000 maternal anemia-related deaths in sub-Saharan Africa annually [6,13]. However, there have been conflicting reports from parts of sub-Saharan Africa on the relationship between placental malaria and maternal anemia. An earlier report from the Ubangi district of Zaire noted that malarious placentas had no consistent relationship to maternal anemia [14]. In other studies, maternal anemia and placental malaria were associated in all gravidity and age groups, with maternal anemia higher among women with placental malaria than those without placental malaria (by gravidity, prevalence ranged from 28.8 percent to 31.6 percent for positive cases and 15.3 percent to 16.7 percent for negative cases; by age, prevalence ranged from 26.5 percent to 31.8 percent for positive cases and 15.3 percent to 17.7 percent for negative cases) [1]. The reason for this variation is not clear, but it may be connected to the complex and multifactorial etiology of anemia in pregnancy in sub-Saharan Africa [2].

In most areas of malaria endemicity, many other causes of anemia have been identified, including both nutritional (iron, folate, and protein deficiency) and non-nutritional (hookworm or HIV infection, hemoglobinopathy) factors [3,15]. Since many of these causes of anemia occur concurrently in pregnancy and no unique hallmarks of malaria-driven anemia have been identified, it is difficult to evaluate the contribution made to anemia in pregnancy by placental malaria infection [16]. Apart from its significant contribution to maternal mortality and to both maternal and fetal morbidity, anemia in pregnancy is a risk factor for infant iron deficiency anemia [17] that, if left uncorrected, can be associated with adverse behavioral and cognitive development [18]. Severe anemia in pregnancy is an important direct and indirect cause of maternal death. During pregnancy, severe anemia may result in circulatory changes associated with an increased risk of heart failure and acute onset of anemia due to rapid cardiac decompensation and decreases in hemoglobin (Hb) concentration to < 80 g/L. Such changes can result in the failure of compensatory mechanisms, accumulation of lactic acid, and breathlessness at rest [19]. Furthermore, during labor, women with severe anemia are less able to endure even moderate blood loss and, as a consequence, are at a higher risk of requiring a blood transfusion during delivery [3]. For the fetus, severe maternal anemia may result in intrauterine growth retardation, still birth, and low birth weight [20-23]. The mechanism of malaria-driven anemia can be described in association with iron status in pregnancy. The iron status in pregnancy is affected by malaria parasites, which influences the anemia observed in preg-
nancy. *P. falciparum* may affect iron status through (i) reducing intestinal iron absorption; (ii) sequestrating iron within the malarial pigment hemozoin; (iii) consuming iron for its own metabolism; (iv) promoting/stimulating the mobilization of iron to body stores; and (v) releasing iron into the circulation during intravascular hemolysis [2,3].

**Maternal Age and Malaria Infection**

A number of studies conducted in sub-Saharan Africa have reported a significant association between maternal age and malaria infection during pregnancy [24-27]. In a study conducted in Blantyre, Malawi, after stratifying by gravidity, associations between age and parasite prevalence were stronger than those between gravidity and prevalence after stratifying by age [25]. Under conditions of low-to-moderate transmission, pregnancy-specific immunity is slow to develop, and age-related immunity may influence malaria prevalence in childbearing years [25].

Studies have shown that young women of child-bearing age may be more susceptible than older women to malaria because they are still in the process of acquiring natural immunity [28-30]. In Cameroon, age was a major risk factor for placental malaria, with younger, first-time mothers more likely to have placental malaria [1]. Similarly in Zaire, mothers with malarious placentas were younger (mean age 24 years old) than mothers with non-malarious placentas (mean age 29 years old) [14]. It was suggested that development of pregnancy-associated immunity, i.e., production of antibodies that inhibit the adherence of placental parasites to chondroitin sulfate A (CSA), may be very important in women younger than 25 who have lower levels of acquired immunity (through less frequency of exposure to the bites of *P. falciparum*-infected mosquitoes) than in older women who may have obtained adequate immunity following repeated exposures and thus are less dependent on anti-cytoadherent antibodies [1]. However, it is important to state that in malarious areas, pregnancy-associated and age-dependent immunity to placental malaria may be influenced by host or environmental factors.

**PARITY AND HEALTH**

The relationship between placental malaria and parity is well established. Many recent studies have found the prevalence to be higher in primigravidae than multigravidae, and in these studies, results are controlled for age [1,31,32]. These observations are consistent with the findings of earlier studies in malaria-endemic regions, where, among several factors, parity independently influenced the placental malaria prevalence rate, with primigravidae having a two- to four-fold increased risk of placental malaria compared to multigravidae [33,34]. In the Gambia, it was observed that the severest form of placental parasitization occurred in a higher proportion of the primigravidae than in the multigravidae [31].

In the Tanga region of Tanzania, placental malaria was associated with hypertension in young first-time mothers with histologic features of chronic disease but was not related to hypertension in older or multigravid women. Similarly, placental malaria was associated with elevated levels of placentally derived soluble vascular endothelial growth factor receptor 1 (sVEGFR1) in first-time mothers but not in multigravid mothers with age being controlled [35]. sVEGFR1 may cause systemic endothelial dysfunction by binding to and sequestering free serum vascular endothelial growth factor (VEGF) and placental growth factor [36,37], which is associated with higher risk adverse perinatal outcome among primigravidae with as much risk as up to 25 percent [36]. The exact reason why primigravidae are more susceptible to placental malaria and suffer from its consequences more than multigravidae is yet to be fully elucidated. However, a common explanation is that pregnancy is associated with a decrease in immunity, which is more pronounced in primigravidae than in multigravidae and may be associated with age [38]. Immunological studies have shown that this increase in susceptibility could be
related to the property of parasitized erythrocytes to adhere to chondroitin sulfate A (CSA) expressed by the syncytiotrophoblast of the placenta [39,40]. Thus, the placenta may select for the CSA-binding \textit{P. falciparum} phenotype, putting primigravidae with no previous exposure to this parasite form at increased risk for developing placental malaria. The decreasing susceptibility to pregnancy-associated malaria with increasing parity is reflected in the acquisition of antibodies specific to parasites’ variant antigens expressed on the surface of infected erythrocytes [41]. Another possible explanation for this parity-related susceptibility is given by the findings of Duffy and Fried [42], who showed that multigravid mothers develop malaria antibodies that block adhesion of parasites to CSA receptors in the placenta in subsequent pregnancies. More studies using both immunological and molecular biological tools are urgently needed to properly elucidate this parity-related susceptibility to placental malaria. However, since pregnant women in malarious areas produce antibodies that specifically recognize CSA-binding \textit{P. falciparum}, this could form a basis for the development of a vaccine to protect pregnant women against placental malaria.

**PERIPHERAL MALARIA INFECTION**

The relationship between maternal peripheral parasitemia and placental malaria has been evaluated in some parts of sub-Saharan Africa. There are no rigorous studies on whether placental infection reflects the existence of peripheral infection over a short period preceding the delivery or whether it is related to infection during pregnancy. Two studies have shown some relation between a late infection (i.e., infection acquired late in pregnancy) and positivity of placental smears or presence of pigment [43,44], but it has been argued that a single measure can hardly reflect the entire history of infection during pregnancy. In one study, the occurrence of peripheral parasitemia at the beginning and at the end of pregnancy was significantly related to placental infection, whereas peripheral parasitemia in the middle of pregnancy was not [38]. This suggests that a peripheral parasitemia at the beginning of pregnancy may persist within the placenta throughout gestation, with possibly more severe consequences for the placenta and the newborn, than an infection acquired later in pregnancy. Other studies have shown that peripheral infection confers a five-fold increased risk for placental malaria, thus confirming the importance of late maternal infections [38]. Although maternal peripheral infection toward the end of pregnancy (post seven months) predisposes the woman to placental malaria, risk of placental infection is greater if peripheral infection occurs at the beginning of pregnancy [45]. In Malawi, placental infection was more frequent in women who were infected at enrollment in the study (i.e., during the first trimester of pregnancy) than those who were not infected at enrollment [46]. Early peripheral infection during pregnancy may be a particularly important risk factor for placental infection, due to lower immune protection at the beginning of pregnancy. Nevertheless, susceptibility may be correlated to high exposure to malaria, and repeated episodes of parasitemia, as well as the interplay between several other factors, should form the basis for further investigations.

**CONCLUSIONS: PUBLIC HEALTH CONSIDERATIONS**

Despite considerable improvement in health care delivery services in the African continent, the control of malaria in pregnant African women, one of several child survival strategies applied through antenatal care, continues to be particularly challenging. Prevention and control recommendations for typical areas of high \textit{P. falciparum} transmission have promoted the use of antimalarial chemoprophylaxis to prevent placental infection and its associated adverse perinatal outcome. This confirms prior findings [47]. Other randomized trials show a protective effect of prophylaxis on placental infection or peripheral parasitemia [46,48,49]. However, persistently low program
coverage coupled with diminishing intervention effectiveness has forced a re-evaluation of the relative importance of malaria in pregnancy [50]. The prophylactic medicines include sulfadoxine pyrethamine, proguanil and pyrethromethamine, while the curative ones include artesunate, chloroquine and amodiaquine. These drugs are relatively safe in pregnancy and are widely used in malarious areas of sub-Saharan Africa [51].

In the face of the mounting evidence of the relative failure of many traditional antimalarial drugs, particularly chloroquine, the World Health Organization (WHO) has put forward new guidelines for combating and preventing malaria during pregnancy [24,51]. The guidelines recommend that women living in high transmission areas of Africa receive intermittent preventive treatment (IPT) with an effective antimalarial agent such as sulfadoxine-pyrimethamine (SP) at scheduled antenatal visits and that all pregnant women in targeted areas should undergo at least two sessions of IPT after first fetal movements (i.e., between 20 and 35 weeks) [51]. Unfortunately, the implementation of the WHO guidelines has been burdened by the notorious problems complicating health service delivery in the developing world, particularly in the African continent, namely, the logistical challenges of reaching remote regions, resource scarcity, lack of infrastructure, inadequate treatment, continuing poverty, and armed conflict.

It is well established that women in Africa use prenatal care extensively when it is available and accessible. This opportunity must be used to implement evidence-based actions with appropriate and realistic goals. There is an urgent need to improve access of rural women to antenatal clinic services in sub-Saharan Africa, either through increasing the number of rural health centers or by establishing functioning outreach services. The distribution of insecticide-treated bed nets needs to become implemented on a large scale.

Since pregnant women have increased specific risks of complications from both malaria and HIV infection, the financial and human resource constraints of health systems in countries most affected by malaria and HIV and the shared determinants of vulnerability for both diseases indicate the need for integration of preventive and curative services for malaria and HIV. The health systems that deliver these services must be strengthened [22]. Reproductive health services offer a critical opportunity for routine provider-initiated HIV testing and counseling. They can provide follow-up care with prevention of MTCT interventions according to national policy for those who test positive, coupled with entry to antiretroviral therapy programs for those sick and in need of immediate therapy. These services need to be strengthened to ensure the delivery of the WHO-recommended antenatal care schedule of four visits (focused antenatal care), which includes a minimum package of interventions for the prevention of both malaria and HIV [52].

Studies in malarious regions have demonstrated that substantial reductions in maternal malaria, anemia, and low birth weight have been achieved by intervention programs, including the use of preventive intermittent treatment, chemoprophylaxis, and the use of insecticide-treated nets. In fact, studies suggest that between 25 percent and 90 percent of these adverse events might be prevented by full implementation of existing interventions [12]. Interventions therefore should also exist for maternal anemia (e.g., good nutrition, iron and folate supplementation, and hookworm treatment) and for reduction of mother-to-infant HIV transmission (e.g., short-course zidovudine or nevirapine), and such can be provided through antenatal care programs [22,53-56]. Better application of these malaria, anemia, and HIV interventions could markedly reduce the infant mortality burden of these diseases.

Finally, collaboration between scientists, policy makers and control programs should be strengthened and community-level research encouraged in order to guide programs and monitor and evaluate markers of success.

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