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Publications 2023

OPEN ACCESS
ISSN: 2992-5460

NEWPORT INTERNATIONAL JOURNAL OF RESEARCH IN MEDICAL SCIENCES (NIJRMS)

Volume 3 Issue 2 2023

Placental Malarial Infection:A Review

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ABSTRACT

Placental malaria is the primary mechanism through which malaria in pregnancy causes adverse perinatal outcomes. Malaria in pregnancy poses a great health risk to mother and her fetus and results into complications, such as abortion, still birth, intra uterine growth retardation, and low birth weight. The heavy infiltration of Plasmodium falciparum-infected RBCs in the intervillous spaces of placenta seems to be responsible for all the complications observed. Infected RBCs in the placenta cause an inflammatory environment with increase in inflammatory cells and cytokines which is deleterious to the placenta. Increased inflammatory responses in the infected placenta result into oxidative stress that in turn causes oxidative stress-induced placental cell death. Moreover, heat shock proteins that are produced in high concentration in stressed cells to combat the stress have been reported in fewer concentrations in malaria-infected placenta. Pathologies associated with placental malaria seems to be the effect of a change in immune status from antibody-mediated immune response to cell-mediated immune response resulting into excess inflammation, oxidative stress, apoptosis, and decreased heat shock protein expression. However, we also need to study other aspects of pathologies so that better drugs can be designed with new molecular targets. The main strategy to combat placenta malaria is intermittent preventative treatment in pregnancy; however, increasing drug resistance threatens the efficacy of this approach. There are studies dissecting the inflammatory response to placental malaria, alternative preventative treatments, and in developing a vaccine for placental malaria.

Keywords: malaria, placenta, placental malaria, pregnancy

INTRODUCTION

Malaria according to world health organization (WHO) is a life-threatening disease caused by parasites that are transmitted to people through the bites of infected female Anopheles mosquitoes [1]. In 2016, there were an estimated 216 million cases of malaria in 91 countries, an increase of 5 million cases over 2015 [2]. The same report shows that, WHO African Region carries a disproportionately high share of the global malaria burden. For instance, in 2016, the region was home to 90% of malaria cases and 91% of malaria deaths [2]. Malaria infection during pregnancy is a significant public health problem with substantial risks for the pregnant woman, her fetus, and the newborn child. Malaria-associated maternal illness and low birth weight is mostly the result of *Plasmodium falciparum* infection and occurs predominantly in Africa [3]. Most cases of malaria in pregnancy in areas of stable malaria transmission are asymptomatic [4]. Depending on the endemicity of malaria in an area, it can be expected that 1–50% of pregnant women may carry malaria parasitaemia, especially in the placenta, without noticing it [5]. This is attributed to immunity acquired during previous exposure that protects against clinical malaria [6]. According to the latest World Malaria, released in November 2017, there were 216 million cases of malaria in 2016,

up from 211 million cases in 2015. The estimated number of malaria deaths stood at 446 000 in 2016 [7]. Pregnant women are three times more likely to suffer from severe diseases as a result of malarial infection compared with their non-pregnant counterparts, and have a mortality rate that approaches 50% [8]. The principal impact of malaria infection is due to the presence of parasites in the placenta, which causes maternal anaemia and low birth weight [9]. Beyond the post-partum period, the long- term consequences of malaria during pregnancy on the infant include poor development, behavioral problems, short stature and neurological deficits [10].

Malaria in pregnancy

Malaria in pregnancy is an important global health issue. The World Health Organization (WHO) reports that 11 million pregnancies in sub-Saharan Africa were at risk of malaria in 2018 alone [11]. Although malaria in pregnancy is mostly asymptomatic and severe disease is rare, malaria infection during pregnancy has remarkable negative consequences which not only affect maternal health but also birth outcomes. Most significant maternal outcome is anaemia. Of all severe anaemia among pregnant women in Africa, it is estimated that 25 % is caused by malaria [12]. Moreover, a study by Braun et al. found that submicroscopic infection was associated with increased risk of maternal anaemia [13]. Thus, asymptomatic and submicroscopic malaria also cause anaemia. The maternal mortality is also one of the negative outcomes caused by malaria and it remains to be poorly estimated. The mortality rates caused directly or indirectly by malaria range from 0.5 % to 23 % in hospital studies and from 2.9 % to 17.6 % in community-based studies [14]. For birth outcome, the most commonly reported adverse effect is an increased risk of low birth weight (LBW, defined as birth weight < 2500 g). LBW is highly associated with increase in infant mortality. The cause for LBW is thought to be intrauterine growth retardation (IUGR) or preterm birth which are partly caused by malaria in pregnancy. Also, association between placental malaria and stillbirth has been shown [12]. In South western Uganda (Rakai), by Kiggundu and colleagues found low prevalence of malaria (0.07 %) among pregnant women and no association to anaemia or LBW [15]. The diagnosis was made by rapid diagnostic tests (RDT). There was great loss in study population during the study period, and less than half of the enrolled was in follow up at the time of delivery. Malaria tests were planned to be taken at least three times during the study period until delivery, but there is no information on how this was fulfilled. Authors recognize, that the numbers are too low to show evidence of association.

Placental malaria

After the pre-erythrocytic liver stage, plasmodium parasites invade red blood cells (RBCs) and start to circulate in the bloodstream. Differing from the other species, P. falciparum parasites express the P. falciparum erythrocyte membrane protein 1 (PfEMP1) receptor on infected RBC membranes. During pregnancy, infected RBCs express a variant PfEMP1 receptor called VAR2CSA receptor that has an active Duffy- binding-like γ domain, which enables adherence and sequestration of infected RBCs in the intervillous spaces of the placenta [11]. Placental malaria is thought to occur via Plasmodium avoidance of spleen clearance through expression of the VAR2CSA protein that binds to the chondroitin sulfate A (CSA) in the placental intervillous space [11]. Plasmodium falciparum infections during pregnancy result in pregnancy-associated malaria (PAM) and placental malaria (PM). In PM, the parasite ligand VAR2CSA mediates adhesion of infected erythrocytes (IEs) to chondroitin sulphate A CSA in the placental syncytiotrophoblast [16]. Accumulation of IES in the placenta induces pathological changes that alter the materno-fetal exchange system and can lead to maternal morbidity and severe fetal and neonatal complications [17]. It is also known that P. falciparum IEs induce inflamemation by monocytic infiltration of the malaria infected placenta, which is associated with maternal anaemia and low birth weight (LBW). This inflammation may influence cellular functions by altering the balance of cytokines and chemokines in the peripheral and placental blood of the women, and some cytokines can help resolve infections while others may also contribute to pathology [17].

Malarial infection in placenta is characterized by sequestration of Plasmodium falciparum-infected erythrocytes and infiltration of immune cells within the intervillous spaces of the placenta. The placenta turns black due to deposition of the malarial pigment. The parasite densities are much higher in the placenta compared to peripheral blood. The thickening of placental basement membrane, perivillous fibrinoid deposits, and syncytial knotting results into altered exchange system between mother and fetus. The placental insufficiency to provide nutrients to the fetus causes IUGR [18].

Risk factors and prevention of malaria in pregnancy

The known risk factors for microscopic malaria in pregnancy on high transmission areas are primigravity, younger maternal age and second trimester [12]. On low transmission and seasonal malaria areas the gravidity hasn't been so strongly associated to risk of malaria. These suggest that in high and stable transmission areas immunity acquired is associated to both age and parity [19]. Maternal characteristics as risk factors are quite commonly investigated

but environmental factors affecting malaria prevalence hasn't been much studied, with the exception of bed net availability and usage [20-26]. In many countries, Malaria Indicator Survey (MIS) has been conducted regularly to determine the availability and usage of malaria control measures including insecticide treated bed nets (ITN) and determining the prevalence of malaria in risk groups and/or general population. In Eritrea at MIS 2015 the coverage of bed nets was high, at least one bed net was owned by 90 % of households and 87 % had at least one ITN. Of pregnant women, 60 % had slept under an ITN the previous night. The malaria prevalence in general population was 1.1 % [27]. For environmental factors affecting malaria prevalence among pregnant women, not many studies were available. In six studies the association between malaria prevalence in pregnancy and ITN coverage or usage was analyzed. The effect of season in the prevalence of malaria among pregnant women was analyzed in three studies with inconsistent findings [27]. High-risk season was associated with higher malaria prevalence in one study [28], but two studies found no association between dry or rainy season and prevalence of malaria. The effect of housing conditions and materials of walls, roofs, floors and windows on the prevalence of malaria was investigated in general population. The poor wall materials were found to be associated with prevalence of malaria. Another study found association between household size and malaria prevalence in pregnant women. Only two of the studies above included submicroscopic infections to the analysis. The need for malaria control strategies specifically targeted to pregnant women was evaluated in two studies. In the South African study of the prevalence of malaria was low (0.07 %) [29]. They suggest that malaria control measures for entire population benefit also during pregnancy, and there is no need for measures specifically aimed for pregnant women [30-33]. Another study investigated if a universal bed net campaign would reduce the burden of malaria among pregnant women in Malawi [34]. Following the bed net campaign, the use of bed nets increased from 50.3 % to 66.2 %. At the same time the prevalence of malaria decreased from 28.4 % to 15.0 %. However, there was no association between malaria infection and bed net use in individual level. Contradictory to the study by Lowe *et al.* [35], this study suggests that besides universal anti-malarial measures, specific strategies targeting pregnant women are still needed. All women had their first or second pregnancy, being in higher risk of malaria, which may explain the high prevalence [36-41]. And in the end, the bed net coverage in Malawi is still quite low, and as a universal method it cannot be compared with the yearly IRS of every household.

CONCLUSION

The evidence of the association between submicroscopic malaria infections and LBW is somewhat contradictory. On the other hand, microscopic malaria, either peripheral of placental, increases the risk of LBW unequivocally.

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ISSN: 2992-5460

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Emmanuel Ifeanyi Obeagu, Carine Byukusenge, Gertrude Namulondo and Ugwu Okechukwu Paul-Chima (2023). Placental Malarial Infection: A Review. *NEWPORT INTERNATIONAL JOURNAL OF RESEARCH IN MEDICAL SCIENCES (NIJRMS)* 3 (2): 1-5.