Unveiling the Intricacies of Maternal Malaria: Navigating Pathways to Adverse Birth Outcomes and Innovations in Prevention and Management

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ABSTRACT

Expectant mothers in regions where malaria is prevalent face increased susceptibility to malaria during pregnancy, leading to adverse effects on childbirth outcomes, such as delivering small-for-gestational-age and preterm infants. These infants are at a higher risk of having low birthweights, which in turn contributes to infant mortality and long-term health issues. During pregnancy-related malaria, infected red blood cells express a distinct surface antigen called VAR2CSA, facilitating their sequestration in the placenta. This process can trigger various host responses, fostering placental inflammation and disrupting placental development, impacting vasculogenesis, angiogenesis, and nutrient transport. Consequently, these disruptions impair placental functions, influencing fetal development negatively. This review provides an overview of malaria during pregnancy, outlining different pathological pathways leading to low birthweight associated with malaria during pregnancy. Current prevention and management strategies, along with potential therapeutic interventions for malaria during pregnancy, are discussed. The review concludes by highlighting research priorities aimed at alleviating this health burden.

KEYWORDS: Malaria, Pragnancy, VAR2CSA

INTRODUCTION

Despite global endeavors to combat malaria leading to reduced transmission in numerous regions over the past decade, certain populations, particularly young children and expectant mothers, remain susceptible, especially in areas with sustained transmission. Malaria, caused by the Plasmodium spp. parasite, poses a significant threat, resulting in severe morbidity and mortality. Plasmodium falciparum infection, globally responsible for the highest burden, takes center stage in this review (1). While childhood exposure typically builds immunity against malaria, first-time pregnant mothers or primigravidas face renewed susceptibility due to a combination of host and parasitic factors (2, 3). Malaria in pregnancy (MiP) leads to placental infection, known as placental malaria (PM), which heightens the risk of placental injury and insufficiency. Placental insufficiency, characterized by compromised placental function, is a common occurrence in PM and is hypothesized as a primary cause of low birthweight (LBW). LBW, defined as a live birth weighing <2,500 g irrespective of gestational age (4), can result from either preterm birth (live birth before 37 gestational weeks) or being small for gestational age (SGA) (birthweight < 10th percentile for gestational age). The mechanisms underlying MiP-associated preterm birth and SGA, however, remain elusive. P. falciparum infection may induce inflammation, potentially disrupting the delicate immunological balance required for maintaining pregnancy to term (5–7). Conversely, SGA is frequently linked to placental insufficiency, with substantial evidence suggesting dysregulated placental development in mothers with MiP (8). Notably, preterm birth and SGA rarely co-occur, underscoring the intricate nature of MiP-associated birth outcomes (1). LBW serves as a crucial indicator of infant mortality, with MiP estimated to cause around 900,000 LBW deliveries annually,

resulting in approximately 100,000 MiP-related infant deaths (1). Beyond the heightened risk of mortality, surviving LBW infants face increased morbidity, predisposing them to cognitive and social developmental challenges (2). LBW, attributed to fetal growth restriction, the underlying cause of SGA, is associated with a higher incidence of adult diseases like type 2 diabetes and cardiovascular conditions (3). Therefore, preventing MiP-associated LBW remains a paramount focus in research.

This review delves into recent discoveries regarding the causes of LBW in P. falciparum MiP, exploring diverse pathological pathways such as SGA and preterm birth contributing to MiP-associated LBW. Existing gaps in our understanding of the pathogenesis of LBW in MiP are identified, and current interventions are reviewed, concluding with suggestions for future research to enhance our comprehension and management of MiP.

MALARIA IN PREGNANCY: UNRAVELING PATHOGENESIS AND IMMUNE RESPONSES

The impact of malaria during pregnancy extends beyond the well-being of the mother, posing a threat to the developing fetus. An infected mother serves as a significant reservoir of Plasmodium infection. A notable characteristic of P. falciparum-infected erythrocytes (IEs) is their capacity to adhere to endothelial and placental receptors. This adhesive capability allows them to sequester in the placenta, resulting in placental infection and subsequent inflammation. Examination of histological sections from P. falciparum-infected placentas reveals the presence of IEs, particularly on the surface of the syncytio trophoblast—a key site for nutrient, waste, and metabolite exchange between maternal and fetal circulations. Within the placental intervillous spaces, occupied by maternal blood, there is an increased presence of phagocytic cells containing substantial amounts of ingested parasites, a phenomenon termed intervillositis (4,5). The binding phenotype of IEs during pregnancy is mediated by their expression of variant surface antigens (VSA). Placental-binding parasites express VAR2CSA, a major VSA predominantly expressed during pregnancy, binding specifically to the placental receptor chondroitin sulfate A (CSA) (6). Consequently, antibodies against placental-binding IEs are uncommon prior to pregnancy, making primigravidas susceptible to the adverse effects of placental malaria (PM) (2,3). In subsequent pregnancies, protective anti-VAR2CSA antibodies are naturally acquired in a gravidity-dependent manner, demonstrating efficacy against malaria in pregnancy (MiP) and its consequences, thereby preventing low birthweight (LBW) (2). However, the specific antigenic targets and protective mechanisms of these antibodies remain unclear. A recent systematic review indicated that antibodies against various placental-binding antigens, including VAR2CSA, were associated with an increased risk of PM and its consequences, hinting that they might serve as markers of infection rather than correlates of protection (2). Nonetheless, it is plausible that protective antibodies can hinder the binding of IEs to the placenta and/or aid in clearance through opsonizing phagocytosis, thus averting placental inflammation and subsequent adverse effects on fetal growth. Defining the characteristics of potentially protective antibodies remains a research priority.

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