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Role of Host Iron Metabolism in Malaria Severity among Pregnant Women in Sub-Saharan Africa: A Narrative Review

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ABSTRACT

Malaria continues to pose a serious threat to maternal health in Sub-Saharan Africa, with pregnant women facing heightened vulnerability due to physiological changes that affect immune and metabolic functions. A key factor influencing malaria severity in this group is host iron metabolism (a dynamic system essential for both maternal well-being and *Plasmodium falciparum* proliferation). This narrative review examined the complex relationship between iron status and malaria outcomes among pregnant women in malaria-endemic regions. The review drew upon peer-reviewed literature, government reports, and global health guidelines published between 2000 and 2023. We employed a structured narrative review methodology, using purposive selection of current, relevant literature across biomedical databases to synthesize physiological, clinical, and public health dimensions of iron–malaria interactions. The article explored how pregnancy alters iron absorption, the mechanisms by which *P. falciparum* utilizes host iron, and the paradoxical role of iron deficiency in potentially reducing parasite burden. It also reviewed the adverse effects of iron overload and critically assessed iron supplementation practices in antenatal care. Special attention is given to placental malaria and biomarker-guided supplementation strategies. Findings emphasized the need for individualized, context-specific iron interventions to ensure optimal maternal and fetal outcomes while minimizing malaria risk in vulnerable populations.

Keywords: Iron metabolism, Malaria severity, Pregnant women, Sub-Saharan Africa, Plasmodium falciparum.

INTRODUCTION

Malaria remains a major public health challenge in Sub-Saharan Africa, disproportionately affecting vulnerable populations, particularly pregnant women [1, 2]. The physiological and immunological changes that occur during pregnancy render women more susceptible to malaria infection and its complications. One factor that has drawn considerable scientific attention in recent years is the role of host iron metabolism in modulating the severity and clinical outcomes of malaria, especially in the context of pregnancy [3].

Iron is essential for both host and pathogen survival. For the human host, it plays a vital role in hemoglobin synthesis, cellular respiration, and immune function [4]. However, *Plasmodium falciparum*, the most virulent malaria parasite, also depends on host iron for its proliferation [5, 6]. This shared reliance creates a complex biological battleground during malaria infection, where iron availability becomes a double-edged sword: it is essential for maintaining maternal health and fetal development but may also facilitate parasite replication and pathogenesis.

In Sub-Saharan Africa, where both malaria and iron deficiency anemia are highly prevalent, the interplay between iron status and malaria severity poses a significant clinical dilemma [7, 8]. Pregnant women often present with anemia due to nutritional deficiencies, chronic infections, or genetic conditions such as hemoglobinopathies. Iron supplementation is routinely recommended in antenatal care to combat anemia, yet growing evidence suggests that excess iron may exacerbate malaria risk and severity. This narrative review aims to explore the multifaceted relationship between host iron metabolism and malaria severity among pregnant women in Sub-Saharan Africa. It discusses the physiological adaptations of iron metabolism in pregnancy, the mechanisms through which *Plasmodium* exploits host iron, the impact of iron deficiency and overload on malaria outcomes, and the contentious role of iron

supplementation. By synthesizing current evidence, this review seeks to provide insights that can inform safer and more effective public health strategies in malaria-endemic regions.

Iron Metabolism and Pregnancy: Physiological Considerations

Iron metabolism undergoes significant changes during pregnancy to meet the demands of increased maternal blood volume, fetal growth, and placental development [9]. Total iron requirements rise substantially to 1,000 mg throughout gestation. To accommodate this, maternal iron absorption increases, primarily regulated by the hepatic hormone hepcidin.

Hepcidin is the master regulator of iron homeostasis. During pregnancy, hepcidin levels are physiologically suppressed to allow greater intestinal iron absorption and mobilization from stores [10]. However, this regulatory shift may render pregnant women more vulnerable to infections that rely on iron, such as malaria. Lower hepcidin levels create an environment in which iron is more freely available in the plasma, potentially aiding the proliferation of *P. falciparum* [11]. Additionally, iron is actively transported across the placenta via specific transporters, such as ferroportin and transferrin receptors, to support fetal development. This maternal-fetal iron flux further depletes maternal reserves, predisposing women to iron deficiency anemia, a condition that has been historically linked to poor birth outcomes, including low birth weight and preterm delivery.

In Sub-Saharan Africa, where dietary iron intake is often inadequate and infection-related inflammation is common, disruptions in iron regulation are further compounded [12]. Understanding how these physiological changes interact with malaria pathogenesis is critical for developing tailored interventions.

Plasmodium falciparum and Host Iron Utilization

Plasmodium falciparum has evolved sophisticated mechanisms to exploit host iron during its intraerythrocytic lifecycle [13, 14]. Once inside red blood cells (RBCs), the parasite digests hemoglobin to access amino acids and releases toxic heme as a byproduct. To neutralize heme toxicity, the parasite converts it into an insoluble pigment known as hemozoin. However, in this process, iron is liberated and may be utilized by the parasite for essential enzymatic and metabolic functions.

Beyond hemoglobin digestion, *P. falciparum* can access non-transferrin bound iron (NTBI) and labile plasma iron pools, especially when host iron regulation is disrupted [15]. Conditions such as iron overload, often a result of high-dose supplementation or genetic disorders, can increase NTBI levels, facilitating parasite growth.

Experimental models have shown that malaria parasites proliferate more rapidly in iron-replete environments. Conversely, iron-deficient conditions can restrict parasite growth. This has prompted debate over the safety of universal iron supplementation policies in malaria-endemic regions, particularly for pregnant women. Moreover, malaria itself can disrupt host iron metabolism. Infection-induced inflammation triggers a rise in pro-inflammatory cytokines like IL-6, which upregulates hepcidin production, thereby trapping iron in storage sites and exacerbating functional iron deficiency. This feedback loop complicates clinical decisions on iron therapy during active or recurrent malaria infection.

Iron Deficiency and Malaria Severity

Iron deficiency is highly prevalent among pregnant women in Sub-Saharan Africa, with estimates ranging from 30% to 60%, depending on region and socioeconomic context [16]. While traditionally viewed as a detrimental condition, iron deficiency may confer partial protection against severe malaria.

Several observational studies have reported inverse relationships between baseline iron levels and malaria parasitemia. For example, iron-deficient pregnant women have been found to have lower parasite densities and reduced risk of severe malaria complications such as placental malaria and anemia [17]. The proposed mechanisms include limited iron availability for parasite growth and altered immune responses that are less favorable to parasite survival. However, this protective effect must be interpreted with caution. Iron deficiency itself contributes to maternal and fetal morbidity, including fatigue, impaired cognitive function, increased susceptibility to infections, and higher risk of maternal death. It also negatively impacts fetal development, leading to intrauterine growth restriction and low birth weight. Thus, while iron deficiency may reduce malaria severity in the short term, it poses significant long-term health risks. This paradox presents a clinical conundrum: Should iron deficiency be corrected aggressively in malaria-endemic areas, or should iron therapy be moderated to balance benefits and risks?

Iron Overload and Malaria Risk

Iron overload is less prevalent than deficiency but can occur due to repeated supplementation, parenteral iron therapy, or inherited disorders such as hemochromatosis [18]. In the context of malaria, iron overload may exacerbate disease severity.

Increased serum iron enhances the growth of *P. falciparum*, leading to higher parasitemia and increased risk of complications such as severe anemia, cerebral malaria, and placental sequestration [19]. Iron overload also promotes oxidative stress, which can damage red blood cells and vascular endothelium, compounding the pathological effects of malaria infection.

In pregnancy, excessive iron may cross the placenta, potentially affecting fetal iron regulation and immunity. Studies suggest that maternal iron overload is associated with increased risk of neonatal malaria and susceptibility to other infections.

Given these risks, the blanket use of high-dose iron supplementation in malaria-endemic regions is being reevaluated. Tailoring iron therapy based on individual iron status and infection risk may offer a safer alternative.

Iron Supplementation During Pregnancy: Controversies and Guidelines

Iron supplementation is a standard component of antenatal care, endorsed by the WHO to prevent and treat anemia [20, 21]. However, its use in malaria-endemic regions has been fraught with controversy.

A pivotal randomized controlled trial in Zanzibar (2006) found that iron and folic acid supplementation increased the risk of hospitalization and death in children living in high malaria transmission areas. Though pregnant women were not the focus, the findings raised alarms about iron's role in enhancing malaria morbidity.

Subsequent studies have offered mixed results. Some reports show no significant increase in malaria incidence with iron supplementation, especially when combined with effective malaria control strategies such as intermittent preventive treatment in pregnancy (IPTp) and insecticide-treated bed nets (ITNs). Others suggest that iron therapy during malaria infection may exacerbate disease progression.

Current WHO guidelines recommend iron supplementation for all pregnant women in malaria-endemic areas, alongside effective malaria prevention and treatment measures. However, implementation remains inconsistent, and many programs lack the capacity to monitor iron status or malaria exposure comprehensively.

Emerging approaches advocate for targeted supplementation based on biomarkers such as ferritin and transferrin saturation, allowing for more precise and safe iron therapy. This strategy requires a robust diagnostic infrastructure, which is often lacking in resource-constrained settings.

Placental Malaria and Iron Dynamics

Placental malaria is a distinct and severe manifestation of *P. falciparum* infection during pregnancy [22]. It is characterized by the sequestration of parasitized erythrocytes in placental intervillous spaces, leading to inflammation, impaired nutrient transport, and adverse pregnancy outcomes.

Iron metabolism plays a role in modulating placental malaria risk and severity [23]. Elevated maternal iron levels may enhance parasite accumulation in the placenta by increasing adhesion molecule expression and local oxidative stress. Conversely, iron deficiency may limit placental parasitemia but at the cost of impaired fetal growth and placental function.

Studies in Sub-Saharan Africa have shown conflicting associations between maternal iron status and placental malaria. Some indicate higher rates of placental malaria in iron-replete women, while others find no significant correlation. These discrepancies underscore the complexity of iron–malaria interactions and the influence of confounding factors such as parity, HIV status, and nutritional background. Understanding the role of iron in placental immunity and *P. falciparum* sequestration is crucial for optimizing antenatal care strategies. Further research is needed to clarify these mechanisms and develop integrated interventions that protect both maternal and fetal health.

Future Directions and Research Gaps

Despite substantial progress, many questions remain unanswered. First, there is a need for high-quality longitudinal studies that simultaneously assess iron status, malaria exposure, and clinical outcomes among pregnant women in diverse settings. These studies should account for genetic, environmental, and socioeconomic factors that influence both iron metabolism and malaria risk.

Second, biomarker-guided iron supplementation represents a promising but underutilized strategy. The development of affordable, point-of-care tests for ferritin and hepcidin could enable more precise diagnosis and treatment.

Third, greater attention should be paid to the timing and dosage of iron therapy, especially in regions with seasonal malaria transmission [24]. Intermittent or delayed supplementation may offer a compromise between correcting anemia and minimizing malaria risk.

Finally, the interplay between iron metabolism and the immune response deserves deeper investigation. Iron influences innate and adaptive immunity, and its modulation may affect susceptibility not only to malaria but also to co-infections such as HIV and helminths.

CONCLUSION

Iron metabolism plays a critical and complex role in determining malaria severity among pregnant women in Sub-Saharan Africa. While iron is indispensable for maternal and fetal health, its availability also facilitates the growth and virulence of *Plasmodium falciparum*. This duality presents significant challenges in managing iron deficiency and preventing malaria complications during pregnancy. Evidence suggests that iron deficiency may confer temporary protection against malaria, while iron overload may exacerbate disease severity and placental complications. However, the risks of untreated iron deficiency both for maternal well-being and fetal development remain substantial. Universal iron supplementation, though widely practiced, must be reconsidered in the context of malaria risk, especially where malaria control measures are suboptimal. This review highlights the need for personalized and context-sensitive approaches to iron supplementation in malaria-endemic regions. Integration of malaria prevention, nutritional support, and iron status monitoring into antenatal care protocols is essential. Future research should focus on elucidating the immunological and molecular mechanisms linking iron metabolism to malaria pathogenesis and developing evidence-based strategies that optimize both maternal and fetal outcomes. Balancing the benefits and risks of iron in pregnancy remains a delicate endeavor. With targeted interventions and continued scientific inquiry, progress toward safer maternal health in malaria-endemic settings is both necessary and achievable.

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