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Malaria and Pregnancy: Understanding The Concepts.

[*1] Olowe, R.A. and [2]Aluko, E.F.

[1]Research Ethics Unit, UNIOSUN Teaching Hospital UTH, Osogbo, Osun State, Nigeria; [2]Department of Global Public Health, School of Medicine and Dentistry, Griffith Universitv. Australia

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Abstract

Malaria remains a significant global health challenge particularly affecting vulnerable populations especially the pregnant women. The intricate relationship between malaria and pregnancy, elucidating the complexities, risks, and implications for maternal and fetal health. Pregnant women are uniquely susceptible to malaria infection due to changes in their immune system and physiological adaptations during gestation. Malaria infection during pregnancy poses grave risks to both the mother and the unborn child, leading to severe complications such as maternal anemia, organ failure, miscarriage, stillbirth, premature delivery, and low birth weight. The World Health Organization (WHO) recommends a multifaceted approach to malaria prevention and control in pregnant women, (IPTp), and prompt diagnosis and treatment of malaria infections. Understanding the concept of malaria and pregnancy is crucial for devising targeted interventions and improving maternal and neonatal health outcomes. By implementing comprehensive strategies that address both preventive and therapeutic aspects, we can mitigate the devastating impact of malaria on pregnant women and their unborn children, advancing towards the goal of malaria elimination and promoting maternal and child health worldwide

***Corresponding Author:** Olowe,R.A..; olowerita@gmail.com

Introduction

What is Malaria and Pregnancy? Pregnancy-associated malaria (PAM) or placental malaria presents a variant of the common illness, posing significant threats to both the mother and the developing fetus. PAM primarily stems from infection with *Plasmodium falciparum*, the most perilous among the four species of malaria-causing parasites affecting humans. Pregnancy substantially heightens the risk of malaria contraction and associated complications for women. Hence, prevention and treatment of malaria form integral aspects of prenatal care, especially in regions where the parasite is endemic, such as tropical and subtropical areas. Notably, placental malaria has also been observed in animal models, including rodents and non-human primates. (Perlmann and Blomberg, 2000; WHO 2003. Dufy and Fried 2005; WHO 2006; CDC, 2019)

While the average adult residing in an endemic region may possess some level of immunity against the parasite, pregnancy introduces complications that render both the woman and the fetus highly vulnerable. The parasite disrupts the transmission of essential substances across the fetal placenta, frequently leading to outcomes like stillbirth, spontaneous abortion, or dangerously low birth weight. Despite the considerable attention malaria receives in developing nations, particularly in sub-Saharan Africa, the unique complexities of PAM and its associated complications have only recently garnered adequate recognition within the international health community. (Doritchamou et al., 2019, Doolan *et al.*, 2009, White, 2004, CDC, 2011)

Malaria in Pregnancy

It has been reported that up to 30 million women become pregnant in malaria-endemic areas in Africa where 90% of the global malaria burden occurs yearly and this makes malaria to be a potential risk to them and their babies. Also, up to 200,000 newborn deaths can be attributed to malaria during pregnancy (Bouyou-Akotet *et al.*, 2003). Immunity against *Plasmodium falciparum* can be achieved during the first 10-15 years of life in malaria-endemic countries (Bouyou-Akotet *et al.*, 2003). The susceptibility of women to malaria during their first and second pregnancy is higher and immunity is usually acquired after several pregnancies. Women in non-endemic areas have lower levels of immunity and are more likely to exhibit symptoms during illness and also their likelihood of developing severe disease or death is higher (Lagerberg, 2008).

Burden of Malaria in Pregnancy

Malaria can double the risk of severe anaemia, triple the risk of preterm birth and quadruple the risk of fetal

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growth restriction in the uterus (Chua *et al*., 2021). In pregnancy, malaria has been reported to occur in 16% to 63% of pregnant women and only 12% to 33% in women who have had previous pregnancies (Goldenberg *et al*., 2003). Spontaneous abortion, stillbirth, premature delivery, and low birth weight in the unborn child can also be caused by malaria (Bouyou-Akotet *et al*., 2003). Reports have also shown that severe anaemia causes up to 10,000 deaths in pregnant women every year in Africa, with malaria causing 3-15% of anaemia, 8-14% of low birth weight, and 3-8% of infant mortality (Guyatt *et al*., 2001; Steketee *et al*., 2001). The immunity of pregnant women can be further reduced by other conditions such as HIV and this could lead to more symptomatic infections and increased risk of adverse outcomes and complications. The major cause of morbidity and mortality most importantly among the vulnerable groups is *P. falciparum* infection and pregnant women constitute the major adult risk group (Schantz-Dunn*et al*., 2009).

The presence of malaria parasites in the red blood cells of newborns aged less than 7 days is termed congenital malaria. This is a condition that was considered rare in endemic areas until studies started reporting high prevalence rates (Rai *et al*., 2015). Though has been documented for many years, it was previously thought to be uncommon, especially in indigenous populations; more recent studies, however, suggest that incidence has increased, and values between 0.30 to 33.00% have been observed from both endemic and non-endemic areas (Rai *et al*., 2015; Stassijns *et al*., 2016).

Low birth weight (LBW) which is defined a birth weight of less than 2.5 kg is usually more prevalent in primigravidae (Brabin, 2003) but an extend to second and third gravidae in areas of low malaria transmission (Nosten *et al*., 1991). In most studies designed to investigate the relationship between malaria during pregnancy and birth weight, potential confounding factors, such as socioeconomic status, maternal nutrition, and smoking, have not been taken into account (Menendez *et al*., 2007). However, several controlled trials of preventive antimalarial measures at random during pregnancy have confirmed this causal effect by showing that birth weight has been increased as a result of preventing malaria (Aribodor *et al*., 2009; Menendez *et al*., 2007).

Anaemia is a global problem, especially during pregnancy, and in malaria-endemic areas it is usually most severe in the second trimester of gestation, following a period of acute malaria infection in the first trimester Severe anaemia in pregnancy has been reported to be an important contributor to maternal and pre-natal morbidity and mortality (Dicko *et al*., 2003), low-birth weight, iron and foliate deficiency, especially in first pregnancies (Mockenhaupt*et al*., 2000).

P. falciparum resistance to antimalarial drugs

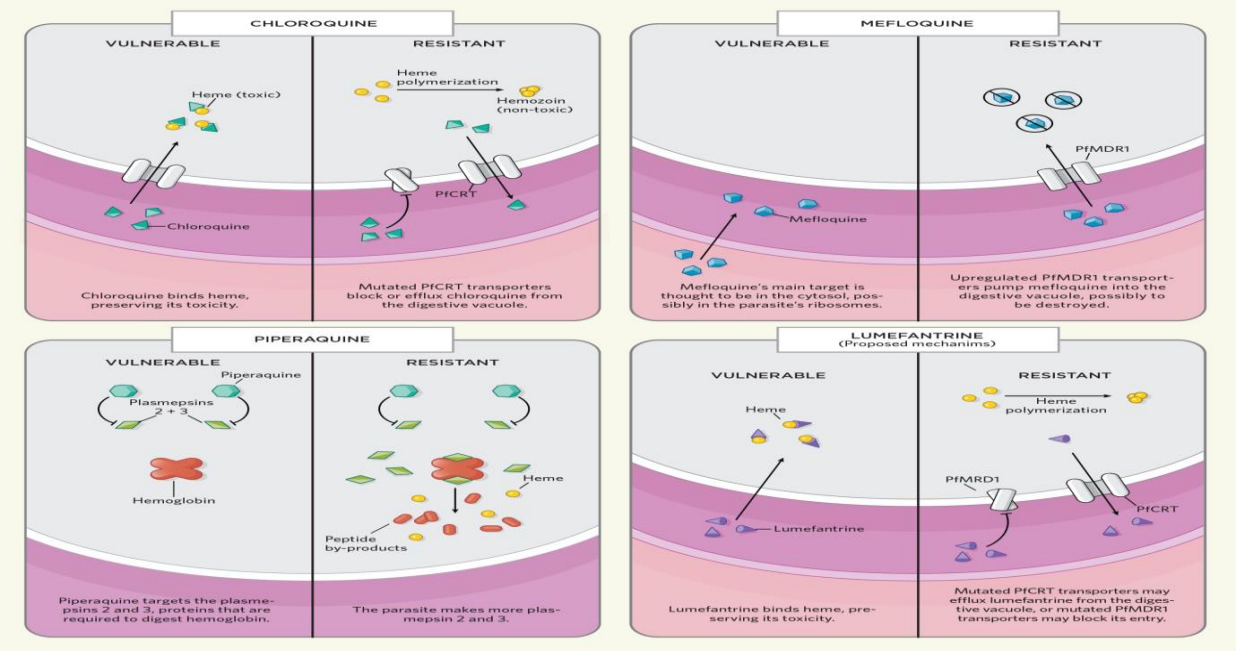

Figure 1: *P. falciparum* resistance to antimalarial drugs (Slivinski, 2019).

P. falciparum, the parasite responsible for the most severe form of malaria, has shown varying degrees of resistance to several antimalarial drugs as shown in Fig 1.:

1. Chloroquine: Once highly effective against *P. falciparum*, resistance to chloroquine has become widespread in many parts of the world, particularly in sub-Saharan Africa and Southeast Asia.
2. Sulfadoxine-pyrimethamine (SP): Resistance to SP has also emerged in many regions, limiting its effectiveness. Resistance to SP often arises due to mutations in the genes responsible for the targets of this drug.
3. Artemisinin-based Combination Therapies (ACTs): ACTs are currently the frontline treatment for uncomplicated P. falciparum malaria. However, there have been reports of emerging resistance to artemisinin, the core component of these combinations, particularly along the Thailand-Cambodia border. This resistance is associated with mutations in the kelch13 gene.
4. Mefloquine and Atovaquone-Proguanil: These drugs are also used in combination therapies but may face challenges due to resistance, albeit to a lesser extent compared to other drugs.
5. Piperaquine: This drug, often used in combination with dihydroartemisinin, is facing increasing resistance, particularly in Southeast Asia. (Slivinski, 2019).

Efforts to combat drug resistance include combination therapies, where multiple drugs with different modes of action are used simultaneously to reduce the likelihood of resistance emergence. Continued surveillance, research into new drug candidates, and efforts to prevent malaria transmission are also crucial in the fight against drug-resistant malaria. Additionally, the World Health Organization (WHO) and various national health agencies regularly monitor and update treatment guidelines to address emerging resistance patterns. (Slivinski, 2019).

Immunology of Malaria during Pregnancy

P. falciparum malaria can run a turbulent and dramatic course in pregnant women. Pregnancy appears to interfere with the immune processes in malaria, a disease that itself alters immune reactivity (Perlmann and Troye-Blomberg, 2002). The physiological changes of pregnancy and the pathological changes due to malaria have synergistic effects on each other, thus making life difficult for both the mother and the child (Steketee *et al*., 2001). In pregnancy, malaria tends to be more atypical in presentation. This could be due to hormonal, immunological and haematological changes during pregnancy (Plebanski and Hill, 2000). The prevalence of clinical malaria is more and with a higher severity in pregnant women than non-pregnant women, especially in highly endemic malarious areas such as Nigeria, where semi-immune adults usually have significantly acquired resistance to local strains of *Plasmodium* (Uko *et al*., 1998). It has been reported also that pregnant women with *Falciparum* malaria are significantly more anaemic than non-infected pregnant women or infected non-pregnant women (Mockenhaupt *et al*., 2000). *Falciparum* infection is higher during pregnancy, more so in primigravidae and is usually associated with anaemia or reduced haemoglobin levels (Mockenhaupt *et al*., 2000). Anaemia is the trademark of malaria, especially with *P. falciparum* infection. The mean haematocrit level is lower in primigravidae when compared with secundigravidae and multigravidae in malaria endemic areas (Nosten *et al*., 1991). Cell-mediated immune responses to malaria antigens are more markedly suppressed at first than in subsequent pregnancies (Brabin, 1996).

Risk Factors for Malaria in Pregnancy

Presumably less affected by malaria are the multigravidae, and this is because immunological memory from the first pregnancy is retained (Brabin, 1996). Another independent risk factor for malaria in pregnancy is young maternal age ((Takem and D'Alessandro, 2013)

Because of the continuous development of malaria immunity in older women, young primigravidae and multigravidae are at greater risk of malaria and its adverse effects than older primigravidae and multigravidae respectively (Dicko *et al*., 2003). Human Immunodeficiency Virus (HIV) infection increases susceptibility to malaria, resulting in more prevalent and higher infection, and a relative loss of gravid-dependent immunity Roberds et al. (2021). A common complication of severe *P. falciparum* infection is cerebral malaria which has a high mortality rate during pregnancy (Brabin, 2000). Good knowledge of the effects of malaria on pregnant women is important because, with sufficient knowledge, the women can properly understand the issues facing them and can better improve their well-being (Iriemenam *et al*., 2011). An increase in knowledge is also important for proper use of prevention methods (Ouattara *et al*., 2011). Many studies have been done in Nigeria to evaluate the knowledge of pregnant women on the health effects of malaria. In a cross-sectional study in Ibadan, Nigeria, 37% of the women had high knowledge of malaria in pregnancy (Aluko and Oluwatosin, 2012). In another study done in Ekiti state, Nigeria, which evaluated the

knowledge of pregnant women attending an antenatal clinic, they found that knowledge of malaria was very good (among 1.0%), average (among 78.9%), and poor (among 20.1%) of the participants (Iriemenam *et al*., 2011).

A study in Edo State, Nigeria, concluded that 69% of the pregnant women had good knowledge of malaria, however, 2.3% of the women knew how malaria affected the fetus (Wagbatsoma and Aigbe 2010). Another study was done in Edo, which found that 89% of their respondents knew mosquito bites caused malaria and 75% of them considered malaria a significant health risk during pregnancy. They also evaluated their knowledge on malaria and found that the women had poor knowledge about the consequences of malaria, with a mean score of 3.5 on a scale of 0-7, 59% of the participants scored between 3 and 4. They also concluded that the women had poor belief about the means of preventing malaria with insecticide-treated nets and intermittent preventive therapy (Enato et al., 2007: Ogba et al., 2023)

These studies found general knowledge of malaria to be average and the knowledge of the consequences of malaria to the mother's health and fetus' health to be very low. Many of the studies evaluated knowledge and bed net use separately; very few studies analyzed the association between knowledge and bed net use. A study was carried out in the capital of Nigeria, Abuja, and found that 43.7% of their participants had excellent knowledge of malaria and how to prevent it, 12.9% had good knowledge, 14.9% had average knowledge, 13.9% had fair knowledge and 14.6% had poor knowledge. They also found that there was no statistically significant association between knowledge of malaria and the use of ITN. The reasons their participants gave for not sleeping under the bed net included heat from the bed net, and fear of suffocation, and many of the participants thought that the bed net was not effective at preventing malaria (Akaba *et al*., 2013). Another study in Ekiti State, Nigeria, found that knowledge significantly influenced the use of insecticide-treated nets and out of the 69% of the participants who knew about bed net use, 95% of them scored "good" on knowledge (Akinleye *et al*., 2011). Both studies analyzed the association between knowledge and bed net use but their conclusions were different.

Conclusion

In conclusion, malaria remains a pressing global health concern, especially for pregnant women and their unborn children. The intricate interplay between malaria and pregnancy underscores the urgent need for targeted interventions to prevent and manage the risks associated with this condition. By embracing multifaceted approaches recommended by organizations like the World Health Organization, including IPTp, and timely diagnosis and treatment, we can significantly reduce the burden of malaria-related complications during pregnancy. Understanding the complexities of malaria and pregnancy is pivotal in devising effective strategies to safeguard maternal and neonatal health, thereby advancing toward the overarching goal of malaria elimination and promoting the well-being of mothers and children worldwide.

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