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The Malaria Concept in Pregnancy and the Mechanism of Evading the Immune System by the Malaria Parasite (Review)

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Authors' contributions

This work was carried out in collaboration between all authors. Author OAD designed the study. Authors CCI, DO, ROI, OO and POJ wrote the first draft of the manuscript. Author SC managed the literature searches. All authors read and approved the final manuscript.

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ABSTRACT

Malaria during pregnancy is a complex issue when considering the public health and an important contributor to maternal and infant morbidity and mortality in malaria-endemic countries. Malaria can be regarded as one of the leading cause of maternal deaths with regards to the sub-Saharan Africa. A minimum of 6 million women around the world stand the risk of being infected with malaria during pregnancy. Maternal deaths as a result of malaria occur at an approximate figure of 10, 000 per year while a minimum of 200, 00 babies also die on annual basis. Malaria remains a life threatening disease to the mother and her unborn child. The impact of the disease will depend on the strength of the mother, her immune system and the severity of the malaria. The people who are most at risk from malaria are women, who are experiencing their first pregnancies, and who are living in areas where stable malaria infections already exist. The protozoan parasites belong to the genus *Plasmodium.* Some relevant spp are *P. falciparum*, *P. vivax*, *P. malariae*, *P. ovale*, and extremely

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rarely *P. knowlesi* which causes malaria in macaques but can also infect humans. They are transmitted by the bite of a sporozoite-bearing female anopheline mosquito. After a period of pre-erythrocytic development in the liver, the blood stage infection, which causes the disease, begins. Parasitic invasion of the erythrocyte consumes haemoglobin and alters the red cell membrane. Malaria contributes to complications that can occur during pregnancy and these complications include anaemia, constant abortion, fetal deaths and prematurity. The first and second pregnancies experience the worst of this case. The World Health Organization with governmental support over the years have put in great effort in tackling the menace of malaria in pregnancy. The major objective of the collaborative effort is the public sensitization on the use of insecticide treatedmosquito nets (ITN), Intermittent preventive malaria treatment (IPT) and adequately treating acute mamalia infections that occurs during pregnancy, while the combination of Sulfadoxine-Pyrimethamine as regarding the IPT has proven to be of a great importancein the prevention of chronic malaria cases that can occur during pregnancy. The introduction of the Artemisinin-Combination Therapy (ACT) by the World Health Organization serving as a first-line treatment less complicated cases of malaria occurring during pregnancy has also provent to be of high benefit. Recently, the administration of soluble of chondrointin sulphate A (CSA) to pregnant women has proven to drastically reduce parasite adhesion. The administration of chondroitinase can effectively reduce parasite by 90%, thereby reducing chances of the foetus being exposed to the parasite. It is very important to make confirmations before proceeding to the treatment of malaria and enforcing therapy completions should be encouraged.

Keywords: Phosphatase; transaminases; arterioscleorosis; albumin; oxidase.

1. INTRODUCTION

Malaria can be linked to underdevelopment and the state of poverty. This has made the disease a serious public health challenge causing death rates that ranges in millions annually [1]. The sub- Saharan African region has been the most affected because the malaria infection in this region has been greatly linked to the most effective and dangerous malaria parasite which is the *Plasmodium falciparum* and the most effective malaria vector — the mosquito *Anopheles Gambiae* — which spreads the most and the control also has proven difficult [2]. Deaths as a result of malaria is most common among children and in regions where the malaria infection has been known to be common, a semi-immunity protection is acquired in the early stages of life and that ranges between 10 to 15 years [3]. However, contrary to the low malaria prevalence in the older generation, pregnant women in endemic regions are major victims of malaria infection, and the disease is most frequent and severe in pregnant women [4,5]. In the state of pregnancy, there is an occurrence of a transient reduction in immunity, which is cell-mediated, and the responses of cells antigens of the *P. falciparum* antigens experiences depression in pregnant women.

Pregnancy related malaria is therefore a major challenge in the sub-Saharan Africa, and this affects approximately 24 million pregnant women on yearly basis. Although the infection by *P. falciparum* in the state of pregnancy is usually asymptomatic, it contribute to unfavourable perinatal results with a great risk for child mortality, particularly in regions where malaria infection cases are less common [6,7]. Pregnancies in women who reside in areas known for a high malaria infection rates usually have a high *P. falciparum* parasitemia density and frequency, with high rates of maternal morbidity, which includes abortion, fever, severe anaemia, and placental malaria [8,9]. Annually, figures ranging between 75,000 and 200,000 infant deaths are recorded to malaria infection in pregnancy worldwide.

2. PLASMODIUM CYCLE IN THE VECTOR

Just like many protozoa, plasmodia pass through some basic stages in the course of their two-host life cycle. The infective stage for humans is the uninucleate, lancet-shaped sporozoite [10]. The sexual reproduction produces the Sporozoites in the midgut of vector anopheles mosquitoes and move to the salivary gland. When an *Anopheles* mosquito that is already infected gets to bites a human, it injects along with saliva into small blood vessels the sporozoites. Sporozoites have been observed to enter the liver parenchymal cells within 30 minutes of inoculation. In the cells of the liver, the parasite develops into a spherical, multinucleate liver-stage schizont containing 2,000 to 40,000 uninucleate

merozoites. This process fast multiplication is regarded as exoerythrocytic schizogony. This exoerythrocytic or liver phase of the infection is normally completed between 5 and 21 days, depending on the *Plasmodium* species. However, in infections related to *P vivax* and *P ovale*, there might be a delay in the maturation of liver-stage schizonts for close to 1 to 2 years [11]. These inactive liver-phase parasites are regarded as hypnozoites. Irrespective of the required time for development, the mature schizonts gets to rupture eventually, and it releases into the bloodstream thousands of uninucleate merozoites. Each merozoite has the ability to infect a red blood cell. The merozoite in the red blood cells develops to form either an erythrocytic-stage (blood-stage) schizont (by the process of erythrocytic schizogony) or a spherical or banana-shaped, uninucleate gametocyte. The mature erythrocytic-stage schizont is made up of 8 to 36 merozoites, which are being released into the bloodstream at the rupturing of the schizont. These merozoites goes ahead to infect another red blood cell generation [11].

The *plasmodium* sexual stage which is the gametocyte, is infectious for mosquitoes that ingest it in the process of feeding. Within the mosquito, the development of the gametocytes into female and male gametes (macrogametes and microgametes, respectively) is observed and their fertilization commences for their development into sporozoites which has the human infection ability and this takes place within a time frame of 2 to 3 weeks [12].

3. PATHOGENESIS

The cause of clinical illness is linked to the erythrocytic stage of the malaria parasite [13]. The earliest signs and symptoms of malaria has to do with erythrocytes rupturing when erythrocytic-stage schizonts mature. The release of these materials from the parasites is assumed to trigger the immune response from the host. The cytokines, reactive oxygen intermediates, and other cellular products released during the immune response play a important role in pathogenesis, and might be responsible for the feeling of fever, chills, sweats, weakness, and other symptoms that can be linked to malaria [14]. In cases of *falciparum* linked malaria (the form leading to most mortality), erythrocytes that has been infected gets to adhere to the endothelium of capillaries and post capillary venules, which leads to a stoppage in the microcirculation and anoxia in local tissues. Cerebral malaria is caused in the brain through this. It also leads to acute tubular necrosis and renal failure in the kidney; and can cause ischemia and ulceration in the intestine, which can leading to gastrointestinal bleeding. The parasite experiences protection from attack by the body's immune system because it lives in the liver and blood cells for most part of its human life cycle, and is relatively not visible to surveillance by the immune system [14]. However, the spleen gets to destroy circulating infected blood cells. To prevent this eventual occurrence, the *P. falciparum* parasite shows proteins with adhesive attributes on the surface of infected blood cells, which causes the sticking of the blood cells to small blood vessels walls, thereby inhibiting the parasite from passing through the general circulation and the spleen [15].

4. MALARIA IN PREGNANCY

Pregnant women stands three times more likely chance to suffer more from severe ailment resulting from malarial infection when compared with their counterparts who are not pregnant, and their rate of death from chronic disease also approaches 50% [16,17]. In areas where malaria infection is common, the estimation is that a minimum of 25% of pregnant women are infected with malaria, with the group with the highest infection and morbidity risk are the prim-gravidas, children, and co-infected HIV patients [18]. The highest infection rate occurs during the second trimester, giving credence to the importance of antenatal care as part of the effort in the prevention and treatment of malaria. There are hypothesis that the most of the pregnancy consequences are because of two main factors: the immune-compromised pregnancy state and cases of having infected red blood cells being sequestered in the placenta [18]. Immunosuppression in pregnancy poses special problems. It makes malaria more common and more severe. In addition, to add to the woes, malaria itself suppresses immune response. Hormonal changes of pregnancy, reduced function of reticule-endothelial system are the causes of immunosuppression in pregnancy. This results in loss of acquired immunity to malaria, making the pregnant more prone for malaria [16].

5. CONGENITAL MALARIA

Malaria during pregnancy may result in fetal exposure to malaria if parasites are transmitted

across the placenta and could result in congenital malaria [19]. The most dangerous type of malaria, *P. falciparum*, also seems very able to infect cells in the placenta, leading to a higher intensity infection, and reducing oxygen delivery to the baby. This, combined with the mother's illness and anaemia, can lead to low birth weight, anaemia and other complications in the child once it is born [20]. *P. falciparum* has the unique ability of cytoadhesion. Chondrointin sulphate A (CSA) has been identified as the adhesion molecule for parasite attachment to placental cells. The administration of soluble of CSA to pregnant women has proven to drastically reduce parasite adhesion. The administration of chondroitinase can effectively reduce parasite by 90% [21].

Malaria can also pass through the placenta, or be transferred to the baby through blood during childbirth. Most babies are thought to remain unharmed if the mum-to-be has malaria, as long as the malaria is treated promptly and effectively [22].

6. EFFECT OF MALARIA ON THE FOETUS

1. Intra-uterine Growth Retardation: This may occur as a result of pyrexia and transplacental infection in susceptible woman. Erythrocytes infected with *P. falciparum* congregate in the maternal placental vascular space, where the parasites replicate. Malaria-infected placentas are frequently observed to carry antibodies, cytokines, and macrophages, which are indicative of an active immune response. This immune response may stimulate early labour, though the precise effect of malaria-parasitized placentas on prematurity is not clear [23]. The IUGR effect appears to relate to nutrient transport to the foetus. First, a high density of parasites and chronic parasite infection in the placental blood and the associated cellular immune response may result in consumption of glucose and oxygen that would have gone to the foetus. Malaria-associated maternal anaemia may also contribute independently to IUGR, most likely through a reduction in oxygen transport to the foetus. Until recently, the mechanism through which parasite sequestration occurs in the placenta has been unclear [5].

2. Low Birth Weight (LBW): Low birth weight is the single greatest risk factor for neonatal and infant mortality. Low birth weights due to malaria may result from IUGR or premature delivery, it can also be influenced by many factors, including genetics, multiple pregnancies, placental abnormalities, maternal nutrition, maternal age, gravidity, and history of smoking, and a range of viral, bacterial, and parasitic infections. Infant mortality is three times higher for LBW babies than for those of normal weight. This is due to placenta parasitation, which interferes with placenta blood circulation and impairs the growth of the foetus [24].

3. Neonatal Death: Congenital malaria may cause death in the neonatal period of the baby of a susceptible woman but it is very rare in endemic area because the antibody that fights against malaria crosses the placenta and the infant becomes passively immunized [25].

7. THE MALARIA PARASITE'S MECHANISM FOR EVADING THE IMMUNE SYSTEM

Plasmodium, the parasite responsible for malaria, infects red blood cells. It produces proteins in the red blood cells that bind to the surface of the host cell. These are known as adhesion proteins [17]. They prevent the red blood cells from circulating correctly in the blood capillaries, and trigger the symptoms of severe malaria. The parasite has 60 genes coding for 60 different adhesion proteins, only one of which appears on the surface of the red blood cell at any one time. In this way, the various adhesion proteins are presented in turn, and the parasite keeps one step ahead of the host's immune system, which must learn to recognize and then destroy infected cells [26].

8. CONTROL OF MALARIA IN PREGNANCY

Intermittent Preventive Treatment in Pregnancy. WHO recommends IPTp with sulfadoxine-pyrimethamine (IPTp-SP). In September 2012, the WHO Malaria Policy Advisory Committee reviewed the most recent evidence on efficacy and effectiveness of IPTp-SP and issued new policy recommendations that promote the increased uptake of IPTp-SP in all areas of Africa with moderate-to-high transmission of *Plasmodium falciparum* malaria.

Use of insecticide treated nets (ITNs). The second component of WHO's prevention

approach, the use of ITNs**,** benefits pregnant women and their families. In areas of stable transmission, ITNs reduce the risk of malaria, which in turn produces significant protection against maternal anaemia and low birth weight [27].

Prompt diagnosis and case management of malaria illness. Malaria case management is another essential component of malaria control during pregnancy. Pregnant women with symptomatic malaria are at higher risk of foetal loss, premature delivery, and death, and they need urgent treatment. The goal in treatment of malaria during pregnancy is to cure the infection completely; any level of parasitemia has consequences for mother and foetus [28].

9. TREATMENT OF MALARIA

It has been recommended by the World Health Organization (WHO) now recommends that women in experiences subtle *P. falciparum* malaria in their second or third trimester period of pregnancy should be treated with artemisinin-based combination therapy. In as much as the therapy seems to be short acting, it remains potent and effective due to the artemisinin component (i.e., artemether, artesunate, or dihydroartemisinin) which greatly reduces the parasite number during the first 3 days of administration [27]. The more sustainable partner drug (i.e., lumefantrine, piperaquine, amodiaquine, or mefloquine) which is acts longer removes the remaining parasites, and as such preventing recrudescent malaria. The longer-acting partner drug is also has also been implicated as being responsible for the prophylactic effect that occurs after treatment, and this blocks the chances of new infections while concentration of the drug in the blood exceeds the minimum required for the inhibition of the parasite. Thus, the time range of the post-treatment prophylactic effect is as a result of the potency and half-life for the elimination of the drug [16]. The same mode of action is used in the preventive treatment, where repeated curative anti-malarial treatments removes potential asymptomatic infections and blocks the possibility of the occurrence of new infections. However, artemisinin-based combination therapy is not currently recommended in pregnancy for intermittent preventive treatment. The current recommendation from the WHO is for all women in regions with high risk of getting infected with malaria in Africa to receive intermittent preventive treatment with sulfadoxine-pyrimethamine as part of their antenatal care [17].

10. CONCLUSION

Malaria is increasingly becoming one of the hardest infectious diseases to eradicate in Africa. The overall burden of the infection is devastating youth, women, and the health systems as a whole. It has affected human resources of Africa and lowered directly the economic growth that should have been experiences annually. It not only weakens the workforce, but also stops children from learning in school, prevents pregnant women from taking good care of their families effectively, and reduces the chances of having a health outcome after pregnancy. Malaria during pregnancy results in foetal exposure to malaria parasite. This combined with the mothers illness can lead to low birth weight, anaemia another complications in the child once it is born. Governments and donors haven recognized this extraordinary toll and have put in more commitment towards the prevention, treatment, and eradication of the disease. The reduction in the ITN tariffs thereby making them cheaper and more affordable has also been successful, including the incorporation of programs to sensitize against infectious disease in reproductive health, and intermittent preventive treatment.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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