



Epidemiology of Malaria in Pregnancy and Associated Risk Factors in Nigeria: a Review

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This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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ABSTRACT

Each year, an estimated number of 300–500 million people are infected with malaria parasite, with an undesirable effect of over one million deaths. Pregnant women as well as young children, non-immune travellers visiting malaria-endemic zones are at the highest risk of suffering or experiencing life - threatening malaria infection. Maternal immunity, parasite density, parity, inadequate antenatal care services, drug misuse and abuse as well intermitted preventive treatment drug failure cum resistance are the most associated risk factors of malaria in pregnancy

obtainable in endemic regions of sub-Saharan Africa. Identification and understanding of these factors will play a major role in reducing the burden as well as eliminating malaria disease among pregnant women living in endemic regions.

Keywords: Malaria; illness; parasite; maternal immunity; protozoa.

1. INTRODUCTION

1.1 Overview of Malaria Disease

Malaria is a complicated illness caused by the Plasmodium protozoan parasite that has a broad range of epidemiology as well as clinical manifestations depending on where you live [1].

It is a sickness that has been around for nearly 4,000 years and has definitely impacted human societies and civilization to a significantly large extent [2].

Charles Louis Alphonse Laveran, a French army physician serving in Constantine, Algeria, became the first to observe parasites in the blood of a malaria patient on November 6, 1880, and this earned him a Nobel Prize in 1907 [3].

Another remarkable finding in the world of malaria is the differentiation of malaria disease by Camillo Golgi, an Italian neurophysiologist in 1886. He discovered that there were at least two different types of the illness, one with tertian recurrence (fever every other day) and the other with quartan recurrence (fever every third day). He also noticed that different quantities of merozoites (new parasites) are generated at different stages of development, and that fever corresponded to the rupture and discharge of merozoites into the bloodstream. For his discoveries in neurophysiology, he was awarded the Nobel Prize in Medicine in 1906 [2].

However, in the mid-1950s, the World Health Organization (WHO) started a huge international drive to eradicate malaria. The WHO program initially, started with insecticide spraying and the use of drug treatment. There was a spectacular success in these program as of that time. In some areas, malaria was conquered completely, benefiting more people previously threatened by malaria disease [4-5]. The discovery that malaria was transmitted by mosquitoes enlightened the public on the health measures that could be taken to stamp out malaria. These efforts were aimed at both the insect's larval (which flourish in calm waters like wetlands) and adult phases.

Draining wetlands and altering land use practices were quite successful in reducing mosquito populations in some regions.

The majority of malaria deaths in Africa occur in children, but in regions without much transmission and inadequate immunity, all age groups are at risk [6]. This disease is one of the major problems of public health especially in tropical and subtropical areas of the world and in sub-Sahara Africa, where malaria vectors are commonly found [7-8]. According to figures provided by the World Health Organization, malaria occurs in over 90 countries worldwide [9]. In 2015, an estimated 212 million (ranging from 148-304 million) cases of malaria were reported globally, with 429,000 deaths, the majority of whom were children in Africa. In 2016, an estimated 216 million cases of malaria were reported in 91 countries, an increase of approximately 5 million cases from 2015 [9]. In 2016, there were an estimated 216 million cases of malaria in 91 countries, an increase of nearly 5 million cases over 2015 [7-8].

WHO facts report 36 percent of the world's population lives in areas where malaria transmission is a risk, 7 percent lives in areas where malaria has never been effectively controlled, 29 percent lives in areas where malaria was once transmitted at reduced numbers sometimes not, but now with a significant re-established transmission [10].

The most vulnerable and studied cohorts include pregnant women, children less than 5 years of age (Nema et al., 2020). Pregnant women remain highly susceptible to malaria because pregnancy minimizes immunity to the disease, thereby increasing the risk of illness, severe anaemia, acute pulmonary edema, renal failure, puerperal sepsis, postpartum hemorrhage, as well as death [11]. Furthermore, malaria during pregnancy causes negative impact on pregnancy including spontaneous abortion, neonatal mortality, and low birth weight and poor cognitive growth of the new born.

2. MALARIA DISEASE PATHOLOGY

Malaria is transmitted through various ways, which include injection of sporozoite via bites of female *Anopheles* as well as a blood transfusion from semi-immune individuals without clinical symptoms which may contain malarial parasites [1]. In congenital malaria, infected mothers transmit parasites to their children before or during birth [12].

The malaria parasite always has two hosts in its life cycle: a mosquito vector and a vertebrate host particularly human being [13]. Transmission of malaria occurs through a vector, the female *Anopheles* mosquito. This mosquito ingests gametocytes, the sexual form of the parasite when feeding on the blood of an infected human being. Within the guts of the mosquito, the male and female gametocytes mate and undergo meiosis to form a motile zygote called ookinetes. These ookinetes thereafter migrate through the midgut wall of the mosquito onto the exterior of the gut membrane where they develop into oocysts. The oocysts grow, rupture, and release thousands of sporozoites, which make their way to the salivary gland of the mosquito [2].

During a blood meal, a malaria-infected female *Anopheles* mosquito inoculates sporozoites into the human host. The bulk of sporozoites from a biting female mosquito's saliva simply happen to be injected into the host's subcutaneous tissue, from whence they move into the host's capillaries. The sporozoites go through the bloodstream to the liver, where they infiltrate the hepatocytes. During the hepatic development, the parasite hides from the immune system, undergo numerous divisions (mitosis), multiply in numbers and forms schizonts. In *P. vivax* and *P. ovale*, some injected sporozoites may differentiate into stages known as hypnozoites which may remain inactive in the liver cells for a while before undergoing schizogony which triggers a recurrence of illness when the red blood cells are infected [14]. When a person is bitten by an infected female mosquito, within one to two weeks, the proliferating parasites induce burst of the infected liver cells. Consequently, merozoites will be discharged into vesicles that circulate in the bloodstream. During the erythrocyte stage of the infection, the merozoites invade the red blood cells, performs multiple divisions to yield trophozoites and schizonts which are released into the blood stream upon rupture. There is a repeat of the erythrocytic stage, starting from the release of merozoites

and reinfection of the blood cells. This forms the basis for regular fever symptoms. Few merozoites escapes the repeat cycle of the erythrocytic stage and eventually develop to gametocytes that gets ingested by a mosquito during blood meal. A summary of the life cycle of plasmodium species affecting man is represented in the Fig. 1 below

2.1 Malaria Diagnosis

At the moment, there are just a few ways for diagnosing malaria. Clinical diagnosis based on history and physical examination, observational diagnosis based on the existence of fever in endemic regions, and the use of light microscopy to analyze stained peripheral blood smears are generally acceptable diagnostic techniques for malaria infection. Nucleic acid amplification techniques (PCR), according to Wilson, play practically little significance in malaria diagnosis since these techniques are restricted to a few big public health facilities. Just like other endemic infectious diseases, a variety of rapid diagnostic tests referred to as MRDTs (Malaria Rapid Diagnostic tests), have been designed to aid diagnosis in malaria [15]. The use of florescent Microscope has also been considered useful in malaria diagnosis though its use is limited due to non-availability of the microscope, techniques and high cost [16] However, it is important to note that in malaria-endemic areas, microscopy is and has always been the standard method recommended by WHO for malaria diagnosis.

2.2 Treatment and Prevention of Malaria in Pregnancy

Today a range of options exist once it comes to prevention and treatment of malaria infections. These options include all the techniques employed to prevent mosquito bites, proper implementation of a medical prophylaxis and application of diverse treatment options using drugs in case a malaria infection occurred.

2.2.1 Chemotherapy

Nowadays, the chemotherapeutic agents for malaria therapy is restricted to three major groups of compounds: quinolines, antifolates, and artemisinin derivatives.: quinolines, antifolates and artemisinin derivatives [17] For over a decade, the preferred therapy is based on combining existing drugs with artemisinin derivatives (artemisinin combination therapies, or

ACT), the only antiplasmodial drug for which no clear resistance has been published but for which alarming reports of tolerance in the field has been reported [18]. During pregnancy, attempts have been made to prevent malaria through the use of antimalarials drugs which are regularly administered throughout pregnancy in order to sustain protective blood levels. WHO has recommended chemoprevention techniques (i.e., providing drugs which block infections) in selected population cohorts at high risk of infection (pregnant women, children, and travelers) and for specific contexts like elimination. This involves the practice of intermittent preventive treatment with Sulfadoxine -pyrimethamine (IPTp) or Seasonal Malaria Chemoprevention (SMC) with Sulfadoxine Pyrimethamine (SP) to combat incidence and clinical manifestation of malaria. Chemoprevention technique has been reported to reduce the incidence of moderate-to-severe anemia in pregnancy among first- and second-time mothers, living in endemic regions [19]. Recent reports suggest that a good number of eligible pregnant women in Nigeria receive the minimum three recommended doses of

intermittent preventive treatment with Sulfadoxine -pyrimethamine (IPTp-SP), although full coverage is yet to be achieved [20-21]. Prophylaxis with chloroquine was formerly considered a safe and effective method of prevention, however it has since been discontinued in some endemic regions due to drug-resistant parasites. WHO strongly encouraged intermittent preventive therapy in pregnancy (IPTp) using sulfadoxine-pyrimethamine to protect women staying in African regions of moderate to high malaria transmission. In 2016, an approximated 19 percent of eligible pregnant women in the 23 African nations that reported on IPTp distribution levels got the required three or more doses of IPTp, compared to 18 percent in 2015 and 13 percent in 2014 [12].

It must be noted that drug-resistant *Plasmodium falciparum* parasites are rendering the few medicines known to be safe during pregnancy ineffective, and the introduction of novel therapies or other treatments is hampered by worries about fetal safety.

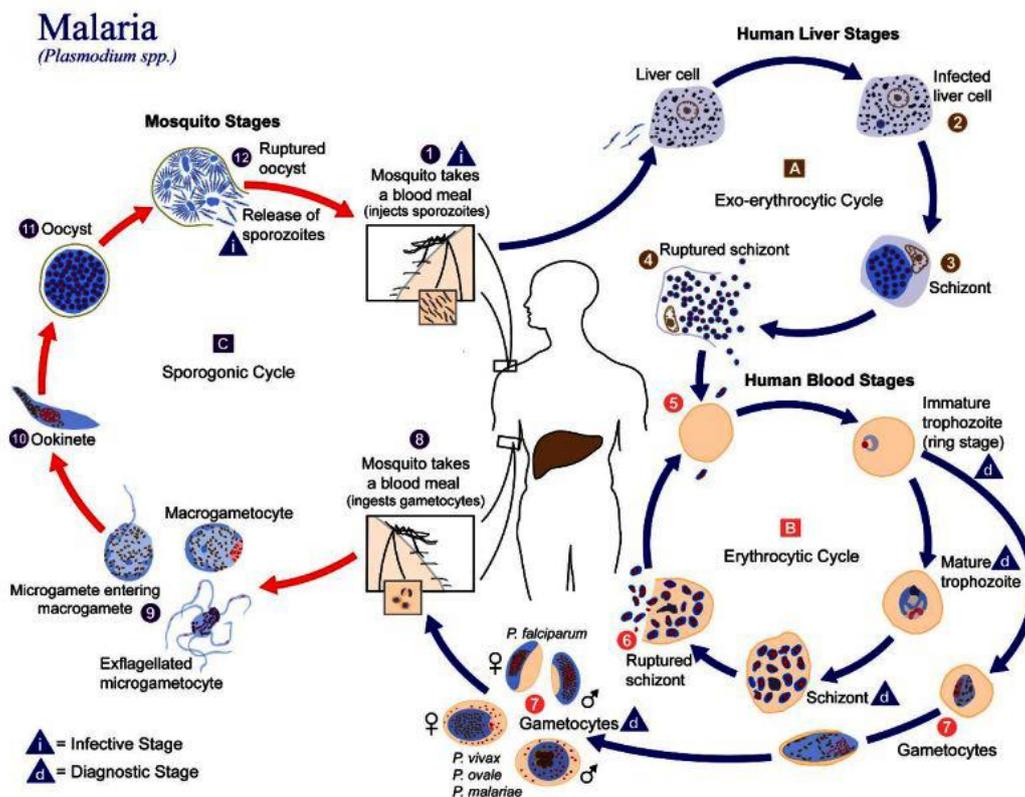


Fig. 1. Detailed life cycle of plasmodium species affecting man

Source: [2]

2.2.2 Use of insecticide

Insecticides contribute significantly in mosquito vector management and will continue to do so in the future. Mosquitoes are considered public health foes due to the biting irritation and noisy nuisance, insomnia, allergic reaction, and disease transmission, particularly malaria, caused by their bite. One method for controlling mosquito-borne diseases is to kill or prevent mosquitos from biting humans and animals, hence disrupting disease transmission [22]. The WHO pesticide assessment method now recommends 12 insecticides for indoor residual spraying (IRS) against mosquitoes, with only dichloro-diphenyltrichloroethane (DDT) having the longest residual impact of more than 6 months, but not yet being utilized in Nigeria due to environmental concerns [22]. For over a decade, Anopheles vector control method is primarily reliant on pyrethroid insecticides, which are a single type of pesticide. These are the only insecticides that have been licensed for use on insecticide-treated bed nets, and they are growingly being used in Africa's indoor residual spray (IRS) programs and long-lasting insecticide-treated nets (Ranson *et al.*, 2011). However, there are fears that progress towards vector control is threatened by the emergence of mosquitoes that are resistant to pyrethroids [23].

2.2.3 Windows and door nets

As previously noted, one of the widely recognized techniques for controlling mosquito-borne illnesses is to disrupt disease transmission by killing or preventing mosquitos from feeding on human and animal blood. Due to negative consequences on non-target species, increasing environmental and human health concern of synthetic organic chemicals as well as reported cases of resistance of mosquitoes to synthetic insecticides, humans have resorted to environmentally safe, low cost, non-insecticidal methods of mosquito control [22]. The use of windows and Door nets has proven to be an environmentally safe and low-cost method of mosquito control in endemic regions. Houses with exposed eaves, no screens, and no doors and/or windows within malaria-endemic regions have a higher risk of human–vector interaction and are strongly linked with increased malaria transmission. [24]. In locations where residents are particularly exposed to malaria vectors due to a variety of factors, especially communities and refugee camps where poor housing prevails, malaria transmission and occurrence might be

reduced by using nets to screen doors, windows, and eaves, as well as constructing ceilings, repairing roofs, and sealing cracks in walls [25]. Apart from insecticide treated nets (ITNs), windows and door nets provide protection and are efficient against attacking vectors that bite late at night and indoors [26]. In Nigeria, window/door net screens were used more frequently than other vector control techniques, such as pesticide spraying and the usage of bednets, despite the fact that they appear to be less effective when compared to others [27].

2.2.4 Treated bed nets

Sleeping beneath an insecticide treated bed nets (ITNs) is one of the most frequent ways to avoid mosquito bites. ITNs are regarded as a kind of personal protection that works by providing both a shield to mosquitoes and the deadly impact of pesticides contained on the bed net material. In Sub-Saharan Africa, ITNs have been proven to lower malaria incidence rates in a variety of settings, as well as malaria death rates in pregnant women and children aged below five years [28].

Household ownership of ITN a minimum one, rose in Sub-Saharan Africa from 50% in 2010 to 80% in 2016 [12]. However, at 43% in 2016, the fraction of families having enough nets, one net for every two persons, remained insufficient. According to WHO reports, more individuals in Africa who are at risk of malaria are sleeping beneath an ITN. This strategy protected 54 percent of the population in 2016, compared to 30 percent in 2010. Also Also, producers reported delivering a total of 582 million insecticide-treated mosquito nets (ITNs) globally between 2014 and 2016 [12]. In Sub-Saharan Africa, 505 million ITNs were distributed, compared to 301 million bed nets in the previous three-year period between 2011 and 2013 [9]. Additionally, figures from African national malaria control programs (NMCPs) show that 75 percent of ITNs were given through wide spread distribution outreach between 2014 and 2016. [12]. Between 2014 and 2016, 16 nations accounted for more than 80% of distributions in Sub-Saharan Africa. These countries in decreasing order of number distributed include Nigeria, Democratic Republic of the Congo, Uganda, Ethiopia, United Republic of Tanzania, Ghana, Mozambique, Côte d'Ivoire, Kenya, Senegal, Burkina Faso, Mali, Sudan, Cameroon, Madagascar and Malawi [12].

In Nigeria, insecticide treated bed nets have been reported to be an effective measure of malaria prophylaxis. Possession and usage of long-lasting insecticidal nets (LLIN) are among the tried-and-true approaches used by Roll Back Malaria (RBM) partners in Nigeria to combat the high prevalence of malaria [29]. The use of LLIN has been linked to a reduction in the frequency of infective mosquito attacks by 70–90%, malaria hospitalization by 50%, neonatal death by 27%, the occurrence of malaria parasitaemia by 40%, and anaemia by almost 50%. [29]. Nonetheless, using insecticide-treated nets has certain advantages, such as prevention of low birth-weight due to placental malaria [26].

2.3 Epidemiology of Severe Malaria in Pregnancy

According to Azuonwu and his colleagues, generating a reasonable estimate of the worldwide burden of malaria infection in pregnancy is challenging, owing to weak numerator (number of women diagnosed of malaria during pregnancy) and denominator (people at risk) datasets (Azuonwu *et al.*, 2011). However, statistics indicate that about 125 million women in malaria-endemic countries get pregnant each year and need infection prophylaxis to avoid illness and death for themselves as well their children [30].

P. falciparum is the leading cause of malaria in pregnant women (Alakuand Abdullahi, 2015). In African region, twenty-five million pregnant women are thought to be at risk of malaria infection each year, with 25% showing signs of placental infection at the time of birth (Azuonwu *et al.*, 2011, [31]. In areas of stable *P. falciparum* malaria transmission, where approximately 50 million pregnancies occur each year, women are semi-immune and often carry their infections with few or no symptoms [30].

In a study conducted in Nigeria to determine the prevalence of positive asymptomatic *Plasmodium falciparum* parasitemia amongst pregnant women, it was reported that 30% (60/200) of the recruited women has asymptomatic *P. falciparum* infection [32]. Malaria susceptibility rises throughout pregnancy, making pregnant women a major parasite reserve in the population. *Plasmodium falciparum* biology and clinical manifestations in semi-immune women make diagnosis difficult during pregnancy, making targeted treatments ineffectual [26]. Because pregnant women

frequently carry gametocytes, potentially as a result of prolonged parasitaemia, infection for mother and child generally develops slowly. This may hypothetically enhance the spread of resistant strains [33].

2.4 Associated Risk Factors of Malaria in Pregnancy

2.4.1 Maternal Immunity

The modulation of pregnant women's immune systems to endure fetal and placental tissues produces an internal environment favourable to infectious agent growth and development, rendering them more vulnerable to infection. According to some specialists, this modulation indicates a higher incidence of malaria illness, a larger parasite density, and more problems in pregnant women (Piñeros *et al.*, 2013).

Over the course of their pregnancies, women normally develop resistance to malaria parasites by acquiring antibodies against parasitized red cells that bind chondroitin sulfate A in the placenta [34]. Fried and Duffy reasoned that due to induced immunity generated by prolonged exposure to *Plasmodium* parasites in pregnant women, overall parasite burden may be low and difficult to identify using conventional techniques such as blood smear microscopy.

First-time mothers are vulnerable to parasitemia and chronic infections caused by *P. falciparum* because they lack immunity against CSA-binding parasites [26].

Generally, in endemic region, a particular level of immunity generated before entering the reproductive age together with the immunity developed over the course of pregnancy, and the effect of prophylaxis (IPTP) taken during ANC on parasite density affects the clinical manifestation of malaria in pregnancy [35].

The combination of pregnancy-specific immune and malaria-specific responses with certain parasite types that sequester in the placenta particularly *Plasmodium falciparum*, increases the probability of pregnancy complications, anemia, low birth weight, preterm, and most importantly, maternal and newborn death [36].

2.4.2 Parasite density

The parasite density tells you how serious an infection is and how well a patient is responding to therapy. The asexual stages of all the species

of *Plasmodium* are counted during this process. Parasite density has become the only approach for measuring malaria infection that is commonly and technically available (WHO, 2010). It is achieved by evaluating the ratio of counted parasites within a particular set of microscopic fields to either countable white blood cells (WBCs) or recorded red blood cells (RBCs) within the same field, and then multiplying that ratio by the determined or predicted number of the patient's actual WBCs or RBCs [37].

Mean parasite density gives a reliable assessment of how an individual handles a single infection. It is important to keep in mind that, in addition to age and immunity, congenital blood diseases may have an effect on parasite density in general [17]. Nevertheless, age has often been used to define acquisition of immunity against malaria parasite [17]. Transmission intensity and inflammatory responses during acute malaria infection, has been considered factors that influence the levels of parasitemia at clinical presentation [38]. In an effort to clarify relationships between age, transmission regions, and parasitemia levels, Roucher and colleagues asserted that measurements are usually much higher in newborns than in older children and adults, and discrepancies between age groups are greater in holoendemic areas than in meso and hypoendemic areas [39].

Parasite density has been positively associated with the number of clinical episodes. This was first described in the works of Rogier and colleagues, whose findings suggested that persons who have frequent *P. falciparum* clinical attacks lacks the ability to regulate parasite density, which regularly exceeds the value required to provoke a clinical attack (Rogier et al., 1996). Another study identified a connection between the capacity to tolerate large parasite burdens asymptotically and the number of clinical malaria episodes. Some findings, have implicated a molecular (genetic) effect on the ability to control parasite density, and thus the frequency of clinical episodes [17]. In other words, high parasite counts without symptoms appear to protect against clinical episodes (Lopera-Mesa et al., 2013). One scientific explanation is the development of effective concurrent clinical immunity, which reduces the chance of developing clinical malaria even in the presence of a considerably high parasite burden (Mueller et al., 2013).

The aggregation of parasites in the placenta is a notable characteristic of *P. falciparum* malaria during pregnancy, although parasite density in the peripheral circulation is low and sometimes difficult to detect [40-41]. Because mature parasites could be hidden away in deep organs, parasite density in the circulating blood as calculated by microscopic examination of giemsa - stained blood smears does not always reflect the full parasite load, which demonstrates why the existence and density of *P. falciparum* parasitemia at any particular point in time do not automatically equate to clinical disease, particularly in holoendemic areas [42]. Furthermore, Doolan and colleagues explained that individuals may have elevated parasite burdens without symptoms, or they may become ill even with low parasite density. Several studies have estimated parasite cut-off densities in different settings depending on age, season and endemicity. One of such studies is that of Afrane and colleagues that reported maximum parasite densities of 500 parasites per μl of blood in children less than five years of age and could be used to identify the malaria-related fever cases in this cohort. In the same study, malaria related fever cases were defined using a parasite density of 1,000 parasites per micro liter of blood in children aged 5–14. The cut-off parasite density for those above the age of 14 was 3,000 parasites per micro liter of blood [43].

2.4.3 Parity

When a woman is pregnant, she is at an elevated risk of infection and disease including malaria. However, the risk of infection with malaria reduces with the number of times they have given birth. Numerous reports suggests that placental malaria resulting from consecutive pregnancies can regulate immunological responses to malaria parasites during pregnancy [44]. Parity has repeatedly been proven to lower vulnerability to malaria infections during pregnancy, particularly in *P. falciparum* endemic regions [45] Furthermore, available evidence from scientific research suggests that malaria vulnerability in primigravidae might be attributed to the absence of antibodies capable of blocking infected erythrocytes adherence to placental chondroitin sulfate A (CSA) [45]. Immunity against CSA-binding parasites can be totally reliant on gender and parity in particular, with antibodies increasing throughout subsequent pregnancies, and consequently a decreased risk of placental parasitemia, negative pregnancy outcome [46-47,44,38].

2.4.4 Gestation age

Women who have been infected with malaria prior fertilization are more prone to malaria parasite infection during the first trimester, since early gestational age has been linked to malaria infection [48]. This phenomenon has been described in view of the fact that women were exposed to malaria at almost the same intensity before and after fertilization. Further explanations suggests that elevated malaria infection in the first trimester is a consequence of subpatent infections existing before conception that are below detectable limit of microscopy and rapid diagnostic test (RDT). The increased proportion of microscopic infections throughout pregnancy caused by subpatent infection which was before pregnancy is explained by changes in women's physiology and immunity during early pregnancy, thus increasing the vulnerability to infectious diseases [48-49].

Furthermore, pregnant women in their first trimester with little or no knowledge about malaria control and preventive measures are at highest risk of malaria infection. Late registration for ANC by pregnant women in their first trimester, and subsequent failure to receive Insecticide treated nets (ITNs) as well as IPTp early enough is a major contributor to this effect. This behavior is said to be common among pregnant women living in sub-Saharan Africa [50-51].

2.4.5 Drug misuse and abuse

Drug abuse or misuse resulting from self-medication prevalent among pregnant women is considered a significant public health concern across the globe. According to studies, only about 10% - 30% of clinical signs experienced by individuals are made known to a physician, and the majority of these clinical manifestations are either endured or self-medicated [52].

Self-medication is now seen as a threat to global public health due to the high prevalence of drug misuse and its associated problems such as addiction, adverse drug reactions and masking of disease, which can complicate diagnosis [53]. According to Babatunde and colleagues, the manifestation and effects of self-medication in pregnancy are different and may be influenced by the kind of drugs used and even the trimester of the pregnancy. Notably, the development of malaria parasite resistance, especially in the developing nations, where antibiotics and antimalarials can be procured over the counter

without prescription and proper diagnosis is of great concern. Pregnant women in rural areas are prone to self-medication and improper malaria therapy [54]. This has been ascribed to the high morbidity and mortality in children and pregnant women due to malaria in such settings, as well as the easy accessibility to antimalarials, which encourages mothers to self-medicate for themselves and their young one.

Self-medication is partly accountable for why pregnant women seek medical care late, thereby complicating their conditions and increases the incidence malaria and other malaria related complications.

2.4.6 Poverty

Poverty has been closely associated with malaria, with the risk of malaria greater in the least developed countries by two folds compared to people living in rich/developed countries [55]. Poverty refers to lack of good and quality resources to provide the necessities of life. It also extends to lack of access to quality health care like antenatal care. Recent reports suggest that 70% of women worldwide live-in poverty and this negatively impacts the health of women (especially pregnant women) and their children [56]. In poverty-stricken communities, people suffer from communicable diseases, nutritional deficiencies, poor housing, limited access to treatment and vector control measures [57]. Since healthy diet is key to successful pregnancy, malnourished mothers living in poverty are highly endangered with malaria complications and death during pregnancy after child birth. Poor housing of the poverty-stricken communities, facilitates mosquito bites among inhabitants and therefore may likely to develop malaria. Furthermore, the expenses of consulting and medications, as well as commuting to faraway health facilities, may be too expensive for low-income families [55]. Poverty can lead to taking up jobs in mining or agricultural establishments in the bush, where malaria vectors abound, and also relocation to underdeveloped and densely populated peri-urban regions with shoddy dwelling units, all of which promotes mosquito bites consequently malaria disease. Pregnant women living in such environment are in greater risk of developing malaria.

2.4.7 Inadequate antenatal care

The WHO has recommended that the first antenatal visit should start at 12 weeks in

focused antenatal care (ANC) and less than or equal to 14 weeks in traditional antenatal care with 4 visits and 7-16 visits respectively [58]. All of these serves to contribute to and improve the health and well-being of women throughout pregnancy, childbirth and the post-natal period. However, reports of late or no attendance have stalled the progress and in recent times defeated the purpose of the antenatal care program as increased maternal and neonatal death attributable to malaria disease has been observed [59].

Most studies have shown that mother and child deaths are preventable through antenatal care visits by directly observing and treating complications in early stages of pregnancy till delivery (Haftu *et al.*, 2018). Therefore, not attending, late visits and inadequate provision of the recommended services by health care providers during ANC visits may lead to adverse perinatal outcome.

Unfortunately, the utilization of ANC is very low in developing countries where malaria is endemic. This behavior has been attributed to financial constraints, ignorance on when to start an antenatal clinic, long-distance to a health facility, busy work schedules, not getting permission from the spouse, cultural and personal belief and non-satisfactory service provided by the health care facilities [58-59].

2.4.8 Drug resistance

Plasmodium parasite resistance to sulfadoxine-pyrimethamine (SP) is linked to mutations in the dihydrofolate reductase (dhfr) and dihydropteroate synthetase (dhps) genes. Three *Plasmodium falciparum* dhfr mutations, specifically N51I, C59R and S108N (generally referred to as the triple mutation) and *Plasmodium falciparum* dhps mutations at A437G and G540E (usually denoted as double mutation) together constitute the quintuple mutations that compromises the potency of SP [60-61]. The efficiency of IPTp-SP to avert low birth weight (LBW) declines with growing prevalence of mutations at specific codons in *Plasmodium falciparum* dhfr and dhps genes. Gutman *et al.* noted that IPTp-SP fails to prevent parasite growth in areas where the dhps A581G mutation has evolved alongside the dhfr and dhps quintuple mutant to produce 'sextuple' mutant parasites (Gutman *et al.*, 2015). As a result, the demographic prevalence of 581G has taken a center stage in IPTp-SP policy debates.

by Malaria Policy Advisory Committee to the WHO [60-61]. WHO has advised for the execution of SP for intermittent preventive treatment only if the frequency of the *Plasmodium falciparum* dhfr K540E mutation (as well as the quintuple mutation) is less than 50% (WHO, 2010). Later on, WHO recommended that IPTp-SP be stopped in areas where the frequency of mutation at K540E position in dhfr gene is greater than 95 % and mutation at A581G position in dhps gene is greater than 10 % as SP is likely to be inefficient (WHO, 2013).

Even though the A581G mutation is not common in Sub-Saharan Africa, the codon has been discovered in ten African nations (Naidoo and Roper, 2013). Furthermore, the presence of mutations at I164L position of dhfr gene and a higher incidence of the dhps A581G mutation have been related to greater therapeutic failure of SP in some African countries [62]. In West and Central Africa, a triple mutant genotype of dhfr (N51I, C59R, S108N) together with the A437G mutation in the dhps gene has been linked to treatment failure of SP (Berzosa *et al.*, 2017).

In south western Nigeria, dhfr (S108N), and dhps (K540E) resistant genes of *plasmodium* parasite have been observed among isolates from children, pregnant women and other adult cohorts [63]. Another report in Nigeria recorded a very high frequency of the *Plasmodium falciparum* dhfr triple-mutant alleles (N51I, C59R, and S108N) at 63% (38/60) while none of the isolates carried the I164L mutation [32]. In another study, the frequency of mutations at S436A, A437G, A581G and A613S positions in dhps gene of plasmodium parasite was 82.1% (23/28), 96.4% (27/28), 71.4% (20/28) and 71.4% (20/28) respectively having reported in the same study that the triple mutations in dhfr gene was almost fixed; S108N (100%), N51I (93%) and C59R (93%) [64]. Esu and his colleagues also noted that I164L and K540E mutations were absent. Generally, from the published literatures on resistance to SP in Nigeria, South western Nigeria has presented more data on high prevalence of molecular markers of resistance to SP than every other region [65-68].

3. CONCLUSION

In endemic regions of sub-Saharan Africa, pregnancies are threatened by malaria caused by *P. falciparum*. This review highlights some of the associated risk factors of malaria in pregnancy. Poverty remains one of the high-risk

factors that contribute to the morbidity and mortality of pregnant women infected with malaria parasite in sub-Saharan Africa. Precisely which precedes the other (malaria or poverty) continues to be the focus of debates in many quarters as a classical case of the chicken and the egg. However, one thing is clear; the obvious correlation between the two as WHO has estimated that up to 20% of people who die from malaria, die from ingestion of substandard antimalarials, a consequence of unaffordability of quality drugs. Through rigorous sensitization, efforts should be made to create awareness and improve the understanding, standard of living, and knowledge of pregnant women towards current prevention and control measures against malaria infection so as to reduce these risk factors and complications associated with malaria in pregnancy.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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