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Review

Malaria during pregnancy: consequences and treatment - A review

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ABSTRACT:

Malaria during pregnancy (MP) is one of the main public health problems around the world. The World Health Organization (WHO) reports have shown that about 50% of the world's populations are at malaria risk particularly in sub-Saharan Africa where approximately twenty five million pregnant women are at high risk of *Plasmodium falciparum* infection each year. In Africa, Low Birth Weight (LBW) induced by malaria causes about 3-17 deaths per 1000 live births every year. This review summarizes the immunopathology, consequences, treatment, and prevention of this disease. At the end of review, the new drugs for malaria and vaccines that are still in clinical trials were also mentioned.

Keywords:
Immunity, Malaria, *Plasmodium*, Pregnancy.

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INTRODUCTION

Malaria during pregnancy (MP), caused by *Plasmodium* sp, is one of the major problems threatening public health throughout the world especially in Africa and the risk of malaria is more in pregnant women than in non-pregnant women (Takem *et al*., 2013). In 2009, about 225 million cases were diagnosed with malaria; therefore, malaria still has great burdens worldwide (Wilby *et al*., 2011). In sub-Saharan Africa, the WHO reports that around 25 million pregnant women are at high risk of infestation by *Plasmodium falciparum* each year. The malaria burden is mostly focused on children younger than five years and on pregnant women (Sevene *et al*., 2010; Desai *et al*., 2007).

There are two types of malaria transmission

Stable transmission

Transmission of this type is relatively high and stable which occur mainly in sub-Saharan Africa. Adults, including pregnant females, in this area have gained immunity toward malaria. Those pregnant women have the ability to control, cannot totally clear malaria infection (O'Meara *et al*., 2008; Ceesay *et al*., 2008; Ceesay *et al*., 2010). As a result, asymptomatic infection is common among these women whereas clinical disease is relatively rare. The estimated prevalence of malaria (based on the published studies in sub-Saharan Africa from 2000 till 2011) in pregnant women was 29.5% in Southern and east Africa, and 35.1% in Central and West Africa. Accordingly, about one of the four pregnant women in stable transmission areas of Africa has malaria infection evidence at delivery (Desai *et al*., 2007).

Unstable, low, and seasonal transmission

Transmission of this type is low with the main incidence reported throughout South America and in Asia-Pacific region. Pregnant women are more likely to develop many clinical diseases because they have lower acquired immunity than sub Saharan African women. In the Asia-Pacific region, the estimated prevalence of women with placenta malaria was 11%, while that of peripheral infection was 15.3% (Rijken *et al*., 2012). For South and Central America, less data on MP is available (Takem *et al*., 2013).

Pathogenesis of malaria

Malaria is a serious human disease caused by a parasite called *Plasmodium.* It has a complex life cycle and the disease pathology is due to the asexual blood parasite infection. The vector for the parasite is the female *Anopheles* mosquitoes. The life cycle (Figure 1) begins when the mosquito bites a human and the sporozoite forms are transferred to the blood. These forms are then transported to the liver and reach the hepatocytes, where division occur for the production of multinucleated schizonts. In case of *P. vivax and P. ovale,* a quiescent stage of hypnozoites can be seen in the liver. Then, rupture of the hepatic schizonts occur and merozoites are released into blood circulation. Merozoites penetrate (although it is a rapid penetration but it is the only chance for our immune system to be exposed to the parasite) into the Red Blood Cells (RBCs) where they grow into trophozoites and mature schizonts. As a result, the infected red blood cells will rupture releasing merozoites to will invade new erythrocytes. The asexual blood stage form gametocytes which are taken up by a feeding mosquito and then mature to form female and male gametes within the mosquito's gut.

Development of the fertilized zygote then occurs to form an ookinete and an oocyst and eventually sporozoites migrate to the salivary glands. Five *Plasmodium* species are able to infect human: *P. malariae, P. vivax, P. falciparum, P. ovale,* and *P. Knowlesi*. The most virulent species is *P. falciparum*. Most studies on MP have been directed to *P. falciparum* and *P. vivax*. Mostly, morbidity and mortality are associated with *P. falciparum* but the greatest disease burden has been attributed to *P. vivax* (Cowman *et al*., 2012; Sevene *et al*., 2010). Pregnant women are more vulnerable to malaria due to several reasons:

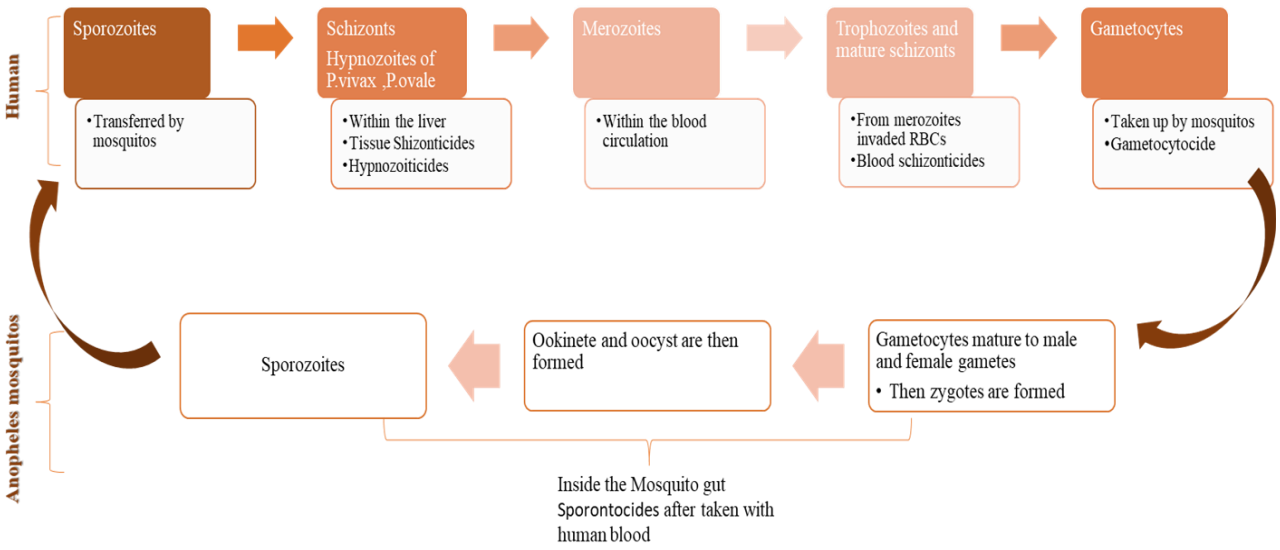

Figure 1. Life cycle of *Plasmodium* parasite and targets of antimalarial drugs

Hormonal factors

Among the key hormonal factors regulating immune response in human are cortisol and prolactin, where cortisol suppresses while prolactin stimulates immune response. It has been found that cortisol concentration increased during pregnancy due to placental production of corticotrophin-releasing hormone with the highest levels found in primigravidae and *Plasmodium*-infected women. During pregnancy, plasma cortisol level steadily increases reaching about three times non-pregnant values. Additionally, cortisol levels are found to be higher in primigravidae than in multigravidae. Studies have demonstrated a relationship between cortisol, parity and infection as the highest cortisol levels were found in the blood of primigravidae with *P. falciparum*-infection compared to infected multigravidae. Such an elevation of blood cortisol levels associated with reduced circulating white blood cells that are crucial in controlling infection (Bouyou-Akotet *et al*., 2005; Takem *et al*., 2013; Mavoungou, 2006). Additionally, high cortisol levels have been linked to depressed cytotoxicity of Natural Killer (NK) cells cytotoxicity versus *P. falciparum*-parasitized RBCs and enhanced sensitivity to malaria. Furthermore, cortisol decreases the surface expression of natural cytotoxic receptors (namely, NKp30 which is essential in stimulating NK cytotoxic activity versus infected RBCs. On the other hand, prolactin (which enhances NK cytotoxicity) levels have been reported to be higher in multigravidae thus increasing infection resistance. The higher plasma cortisol level and lower prolactin levels in primiparous women compared to multiparous women are the main hormonal reasons behind the increased susceptibility of pregnant women to malaria (Bouyou-Akotet *et al*., 2005; Rogerson *et al*., 2007b; Takem *et al*., 2013; Mavoungou, 2006). Moreover, the plasma prolactin concentrations are higher in multiparous women have less susceptibility to MP because they have higher prolactin concentration which means they are gaining immunity against the parasite (Duffy *et al*., 2003).

Physiologic and behavioural factors

Pregnant women are more attractive to the mosquito because of several physiological and behavioural factors occurring during pregnancy. Physiologic changes include elevated abdominal temperature making pregnant women easily detectable by the mosquitos (Ansell *et al*., 2002). Also, changes in the splenic functions induced by pregnancy making primigravidae susceptible to malaria as early as eight weeks' gestation (Brabin *et al*., 1988). Additional behavioural change

that occur during pregnancy is urinary frequency where pregnant females urinate two times more than non-pregnant female, therefore their chance of being exposed to the mosquitos is more as they leave their insecticide treated bed-nets (Lindsay *et al*., 2000).

Placental sequestration *of P. falciparum and P. vivax-infected RBCs*

Syncytiotrophoblast, that line the placental intervillous spaces through which maternal blood circulates, expresses a receptor called Chondroitin Sulphate A (CSA) to which erythrocytes infected with *P. falciparum* are bind (Duffy *et al*., 2003). The *P. vivax* -infected RBCs attach to two receptors: CSA and the intracellular adhesion molecule (ICAM-1) (Carvalho *et al*., 2010; Chotivanich *et al*., 2012).

Adhesion of *Plasmodium falciparum* in the placenta

P. falciparum parasites have the ability to sequester in the placenta leading to placental malaria, which may lead to death of the mother and the child. The most dangerous among *Plasmodium* species is *Plasmodium falciparum* because it is able to adhere to the endothelium and sequester within the vascular beds of several organs (Duffy *et al*., 2003). During pregnancy, several parasite antigens act as ligands to facilitate binding of *P. falciparum* infected RBCs to CSA. These antigens are collectively referred to as Variant Surface Antigen Pregnancy Associated Malaria (VSAPAM) which differ from the surface antigens of infected RBCs in the non-pregnant women. A lot of studies have been done to identify VSAPAM and these studies focused on *P. falciparum* Erythrocytes Membrane Protein 1 (PfEMP1), which is a highly variant antigen encoded by var2CSA gene form the var family of genes .Two variants of PfEMP1 are identified: one is known as VAR1CSA which is unlikely to be responsible for CSA binding and the second is var2CSA which is more likely to be responsible for binding and has many of the characteristics of variant surface antigens involved in pregnancy associated malaria (Rogerson *et al*., 2007a).

When *P. falciparum* invades the RBCs, it starts exporting proteins to the cell surface, such as adhesins (like PfEMP1) that bind to various host receptors such as CSA. This binding enables the parasite to attach to the vascular beds and avoid clearance by the spleen. The parasitic sequestration in the brain and the placenta is the reason behind the disease and death that occur due to cerebral malaria and MP, respectively (Duffy *et al*., 2003; Rogerson *et al*., 2007b). Not only the mature form of *P. falciparum* bind to and thus accumulate in placenta, but also during the ring stage where studies demonstrated that a proportion of parasite that bind to CSA during their mature stages will also attach to syncytiotrophoblast during their ring stages by different mechanism not involving CSA and PfEMP1. Two proteins called ring-stage surface proteins (RSP-1 and RSP-2) were identified as the ones responsible for the placental adhesion of ring-stage parasites. However, the mature form of the parasite constitute the major part of sequestered parasites and smaller part of the ring-stage parasite (Duffy *et al*., 2003).

Adhesion of *Plasmodium vivax* in the placenta

P. vivax infected RBCs (Pv-RBCs) also adhere and sequester in the placenta using CSA (Carvalho *et al*., 2010, Chotivanich *et al*., 2012), Hyaluronic acid (Chotivanich *et al*., 2012), and ICAM-1 (Carvalho *et al*., 2010) as receptors. The adhesion of Pv-RBCs is partly mediated by VIR proteins which are encoded by *P. vivax* variant genes (vir) superfamily which (unlike var gene family of genes for *P. falciparum* where are only 59 members*)* consists of about 350 members subdivided into 10 subfamilies. Although the cytoadhesion of Pv-RBCs is about 10 folds lower than that of *P. falciparum* infected RBCs, the interaction strength is the same with the receptor (Carvalho *et al*., 2010). *P. vivax* differs from *P. falciparum* because it infects reticulocytes (immature erythrocytes), reducing the densities of the parasite. Additionally, there is activation of the liver hypnozoites leading to *P. vivax* relapse. On the other

hand, *P. vivax* species do not frequently express variant surface antigens, so that placental sequestration does not occur frequently. Accordingly, the effects on birth weight, and the higher risks of miscarriage and preterm delivery associated with *P. vivax* is probably due to systemic rather than local effects. Even though the mechanism for this is incompletely discovered (Takem *et al*., 2013).

Immunological changes in pregnancy malaria and development of immunity

Placental changes in response to malaria

Placental sequestration of infected RBCs induces maternal mononuclear cells to produce β-chemokines (chemotactic factors, such as macrophage-inflammatory protein-1α and β, interferon-inducible protein 10, and monocyte chemoattractant protein that recruit macrophages and monocytes. Macrophage migration inhibitory factor which aids in macrophage retention and activation, has been reported to be increased in concentrations in placental malaria. As a result of placental macrophage activation, where they present antigens to T cells (Rogerson *et al*., 2007a). Studies reported significant elevation in Tumor Necrosis Factor (TNFα), Interleukin (IL) 1β, interferon γ, and interleukin 2 in the placental blood or tissue during infection with malaria (Rogerson *et al*., 2007b). These cytokines work together to increase the macrophage phagocytic activity, secreting nitric oxide and reactive oxygen intermediates and induce proliferation of T cells; thus assisting in parasites removal from the placenta. It also has been reported that there is upregulation of interleukin 10 in the intervillous space with placental malaria which might help to reduce pathological effects of pro-inflammatory cytokines (Moore *et al*., 1999).

Development of immunity

Function of innate cells in developing immunity to MP

Dendritic cells, macrophages, and NK cells work together to determine the nature of adaptive immunity against malaria infection by cytokine production and antigen presentation (in case of dendritic cells) (Rogerson *et al*., 2007a). Among the first responders to *P. falciparum*-infected RBCs are the NK cells by producing IFN-γ where they are activated during the first eighteen hours, an activation that is dependent upon IL 12 and IL 18. As previously mention that cortisol levels are elevated during pregnancy and they are higher in the first pregnancy compared to multiple pregnancies, an elevation that results in downregulation in NKp30 expression and explains the higher susceptibility of primiparous women to malaria (Mavoungou, 2006).

Response of T cells and B cells during pregnancy

Recent studies have shown that memory T-cells are sequestered rather than distributed in peripheral blood and thus decreasing the response of proliferative T-cells due to the absence of trafficking memory T-cells from peripheral blood (Hviid *et al*., 1991). Additionally, T-cell proliferative responses and cytokine production (IL4, IL2, IL10, and interferon γ) were found to be higher in multiparous than in primiparous women. As a response to MP, VSAPAM-specific IgG are produced at high concentration, and in recently gestating multigravidae, the frequency of VSAPAM-specific memory B cells reaches 1 in 4000 B cells (Fievet *et al*., 2002).

Consequences of malaria in pregnancy

The consequences of MP depend on the intensity of transmission which determines the degree of acquired immunity (Takem *et al*., 2013). MP can cause serious health-related problems to the mother and to their offspring during their childhood and even later in their life.

Maternal effects

In stable malaria transmission areas, most infections are asymptomatic but with substantial risk of severe maternal anemia with a prevalence of about 26% and about 1 in 4 cases of anemia can be prevented with adequate Intermittent Preventive Treatment (IPT) of MP (Tagbor *et al*., 2010; Bouyou-Akotet *et al*., 2003;

Huynh *et al*., 2011). Malarial anemia occurs due to the breakdown of infected RBCs and dysfunction of bone marrow dysfunction. Placental sequestration of pigmented monocyte occurs during placental malaria leading to maternal anemia which may occur as these monocytes secrete TNF that inhibits erythropoiesis or may lead to oxidative stress, affecting RBCs membrane function resulting in increased RBC destruction (Rogerson *et al*., 2007a). In unstable and low transmission areas, malaria can result in higher rate of maternal anemia in primigravidae compared to multigravidae and more in *P. falciparum* infection compared to *P. vivax* infections. MP commonly lead to abortion in unstable transmission areas because in these areas most infections associated with fever; however, little is known about whether this happens in stable transmission areas (Poespoprodjo *et al*., 2008; Guyatt *et al*., 2001).

A causal relationship has been reported between malaria and miscarriage during the first three months of gestation and the abortion risk is higher in symptomatic and asymptomatic women compared to malaria-free women during their first trimester (McGready *et al*., 2012). Maternal death also has been reported as one of the consequences of MP in several studies (Anya, 2004; Romagosa *et al*., 2007).

Perinatal effects

Malaria increases the risk of Low Birth Weight (LBW) (a birth weight of less than 2.5 kilogram) particularly in primigravidae and this risk is about four times higher in pregnant women with placental malaria (Christensen *et al*., 2011; Desai *et al*., 2007). In stable transmission areas, happens as a result of Intra-Uterine Growth Retardation (IUGR) rather than pre-term delivery. On the other hand, in low transmission areas, LBW occurs due to pre-term delivery. In Africa, to about 3-17 deaths per 1000 live births each year occur due to malaria induced LBW (Desai *et al*., 2007). Malaria prevention by using IPT or insecticide-treated bed nets associated with 21% reduction in LBW. In unstable transmission areas, preterm deliveries, still births and neonatal deaths have been reported (Poespoprodjo *et al*., 2008). Placental insufficiency during chronic malaria is a possible explanation for fetal growth retardation. Additional factors including cellular infiltration of the placental intervillous space thus reducing placental efficiency, elevated cytokines production reducing nutrient transport, weakened placental blood flow, and the sequestration of infected RBCs, and the accumulation of monocytes and fibrin which mechanically decrease placental blood flow (Christensen *et al*., 2011; Rogerson *et al*., 2007a; Imamura *et al*., 2002).

New born and infant effects

It has been found that placental malaria decreases the transfer, through the placenta, of maternal antibodies and cellular immune responses to other infections, like measles, tetanus, and *Streptococcus pneumoniae.* Placental malaria also increases the risk of anemia in infants and it is associated with neonatal and infant mortality (Moraes-Pinto *et al*., 1998; Okoko *et al*., 2001). In primi- and secundigravidae, the prevention of malaria by using IPT and Insecticide-Treated bed Nets (ITNs) decreases the risk of neonatal mortality by up to 18% (Eisele *et al*., 2012).

Later childhood, adolescence and adulthood effects

Some studies suggest that high proportion of LBW children due to placental malaria suffer later from cognitive impairment, learning disability, and behavioral problems due to sub-optimum development of the brain. Other studies have linked LBW to insulin resistance in skeletal muscle and future type 2 diabetes risk, probably occurred due to persistent skeletal muscle morphology modifications which eventually will lead to functional capacity and physical activity reduction in adult life (Christensen *et al*., 2011). Moreover, LBW is associated with adulthood short stature due to incomplete growth, which increased the possibility of delivering LBW children when these women become pregnant (Mohanty *et al*., 2006; Edouard *et al*., 2004).

Symptoms of malaria

It has been found that both the severity and frequency of MP depend on the level of acquired immunity to malaria before pregnancy, which mainly depend on the intensity of malaria transmission. In stable transmission areas, most women with *P. falciparum* infections are asymptomatic because those women are considered to be semi-immune, but they have high risk of severe anemia and LBW. In low transmission areas, MP frequently causes symptoms like fever, headache, malaise, and vomiting. If not treated, the infection may progress into severe complications, like cerebral malaria and pulmonary edema and may eventually cause maternal death (Sevene *et al*., 2010).

Diagnosis of malaria in pregnancy

Early diagnosis of MP is necessary to prevent its deleterious consequences on both the mother and her infant. Parasitological diagnosis of MP is usually done by one of the following methods:-

Microscopy

This is one of the most widely used methods for the diagnosis of malaria in pregnant and nonpregnant persons. It is possible to diagnose the density and species of the parasites by using the microscope. However, the problem is with the sensitivity of the microscope which cannot go below 10-15 parasites/µl. Thus, a significant proportion of pregnancy with malaria would not be diagnosed due to very low parasite densities or the parasites being sequestered in the placenta. It has been found that the sensitivity of peripheral blood microscopy in the diagnosis of MP, when using placenta histology as the reference test for *P. falciparum* infections, was 60% and that of placental microscopy 45% (Kattenberg *et al*., 2011).

Rapid diagnostic tests

This can detect circulating antigens of malaria. Shorter time for diagnosis and minimal training are required compared to microscopy. Rapid diagnostic test cannot detect the parasite density and the sensitivity in diagnosing MP is less than that of microscopy. When using microscopy as the reference test, the sensitivity of RDT is 81% for both placental and peripheral blood (Kattenberg *et al*., 2011).

Polymerase Chain Reaction (PCR)

Polymerase Chain Reaction (PCR) can detect DNA of the parasite and can be used for diagnosing malaria but it is availability is limited in health care facilities. In Africa, it has been found that PCR sensitivity was more than 80% when using microscopy as the reference test (Kattenberg *et al*., 2011).

Placental histology

After delivery is the only time when this test can be done and that is why it is not used for the management of infections occurring during pregnancy (Takem *et al*., 2013).

Treatment

Classification of antimalarial drugs

According to the mechanism of action

Antimalarial drugs can be classified according to their mechanism of action because they target different life cycle stages of the *Plasmodium* parasites which fall into five groups (Figure 1):

- **Tissue schizonticides:** These act against pre-erythrocytic schizonts like primaquine, atovaquone-proguanil and pyrimethamine.
- **Hypnozoiticides:** Which act against quiescent liver stage hypnozoites from *P. vivax* and *P. ovale* infections like primaquine.
- **Blood schizonticides:** This class called 'clinically curative' as they suppress symptoms of infection by eliminating the parasite's erythrocytic forms. Examples are atovaquone-proguanil, sulfadoxine, sulfones, quinine, mefloquine, and chloroquine.
- **Gametocytocides:** Effective against gametocytes in the blood, thus preventing mosquito infection like primaquine (which has activity against all *Plasmodium* species). Other examples are chloroquine and

quinine which have activity against *P. vivax* and *P. malariae.*

- **Sporontocides:** These prevent oocyst development and parasite multiplication in the gut of the mosquitos when ingested with the blood of human host as the mosquito bites the human. Examples are primaquine, chloroguanide and pyrimethamine.

Malaria treatment typically should include drugs with tissue and blood schizonticidal effects, in addition to gametocytocidal activities (Sevene *et al*., 2010).

According to the chemical structure

Antimalarial drugs can be classified according to chemical structures into seven classes including 4-aminoquinolines as chloroquine and amodiaquine, 8-aminoquinolines as primaquine, aryl amino alcohols as mefloquine, antifolates as sulfonamides and biguanides, peroxides as artemisinin derivatives, respiratory chain inhibitors as atovaquone and antibiotics as clindamycin, tetracycline, doxycycline, azithromycin, and fluoroquinolones (Sevene *et al*., 2010).

Antimalarial drugs indicated for use in MP

Most antimalarial drugs are considered as category C with respect to pregnancy risk which means that reproduction studies in animals have demonstrated fetal adverse effects in the absence of well controlled studies in humans, but the potential benefits may necessitate using these drugs in pregnancy in spite of the potential risks (Sevene *et al*., 2010). Thus, antimalarial drug selection is made according to risk-benefit criteria and the patient assessment due to the limited availability of human data. The currently recommended antimalarial drugs for treating MP are listed below.

Aminoquinolines

Chloroquine (ChQ)

This drug has both schizonticidal and gametocytocidal activities. It has activity against *P. vivax, P. ovale*, *P. malariae,* and sensitive *P. falciparum* parasites. The problem with ChQ is the increase in resistance among *P. falciparum* parasites and also there is some resistance among *P. vivax* parasites. ChQ also has anti-inflammatory and antipyretic activities (Kalia *et al*., 2007). Alone or in combination with proguanil, ChQ can be used for chemoprophylaxis for people travelling to endemic areas (Sevene *et al*., 2010).

Safety: ChQ is well tolerated with some mild Side Effects (SE) like nausea, headache, and dizziness can occur. ChQ causes pruritus especially in black population (AlKadi, 2007). Long term use of high ChQ doses may cause retinopathy and neuromyopathy. ChQ is considered to be safe in all pregnancy trimesters and can also be used in breast-feeding women (Steketee *et al*., 1996).

Amodiaquine (AQ)

AQ has activities similar to ChQ even the antipyretic and anti-inflammatory effects. It is effective in *P. falciparum* infections resistance to ChQ.

Safety: SE are similar to those of CQ but pruritus is less common. AQ can cause fatal agranulocytosis and toxic hepatitis after prophylactic use. Thus, AQ is contraindicated for chemoprophylaxis and in persons with hepatic disorders. It has been found by recent studies that AQ is safe during second and third trimester of pregnancy (Thomas *et al*., 2004).

Piperaquine (PIP*)*

PIP was frequently used as monotherapy for treatment and prophylaxis leading to resistance development. Thus, it use was abandoned in 1980s. Recently, the use of PIP has revived. It is currently used in combination with dihydroartemisinin and its use is under registration by USA regulatory agencies to be prescribed to children and nonpregnant adults (Ashley *et al*., 2004). It has similar safety to ChQ.

Arylaminoalcohols

Quinine (QN)

For the treatment of uncomplicated malaria, QN sulphate is given orally. However, QN hydrochloride is given intravenously for treating complicated or severe malaria. QN is given in combination with tetracycline or clindamycin in areas where multi-drug resistance malar-

ia is common like in Asia and South America. QN is not used for prophylaxis (Sevene *et al*., 2010).

Safety: QN is highly toxic drug with the majority of its SE being dose-dependent. Cinchonism is a unique syndrome of QN use. It is characterized by reversible tinnitus, headache, nausea, and dizziness (AlKadi, 2007). QN may cause prolongation of the QT interval. Also, it stimulates insulin secretion increasing the risk of hypoglycemia. In addition, it may causes hemolytic anemia in patients with G6PD deficiency. QN is considered to be safe for use in pregnancy though its use may increase the risk of hypoglycemia in pregnant women (Sevene *et al*., 2010).

Mefloquine (MQ)

MQ is used together with Artemisinin (AS) for malaria treatment in multi-drug resistant areas. MQ is recommended for chemoprophylaxis. One study has shown that MQ was safe and effective drug for treating ChQ-resistant malaria in pregnant women (Adam *et al*., 2004).

Safety: MQ can cause mild gastrointestinal and neurological adverse effects. When used prophylactically, sever central nervous system SE occur in 1:10,000 patients. Adverse effects of MQ are dose-related. MQ can be considered safe even when given in the first trimester because there is no increase in birth defects or fetal loss when it is used during pregnancy (Schlagenhauf *et al*., 2012).

Lumefantrine

This drug is only found in combination with Artemether (AL). The combination is not recommended for prophylaxis and it has been shown to be safe in pregnancy by a study carried out in Thailand among 125 pregnant women. Lumefantrine is well tolerated with reversible adverse effects as nausea, diarrhea, pruritus, and skin rashes (McGready *et al*., 2008; Tarning *et al*., 2009).

Pyronaridine

This drug has shown to be useful in multi-drug resistant *P. falciparum* malaria (Chavalitshewinkoon-Petmitr *et al*., 2000). Not known whether it is safe in pregnancy or not.

Antifolates

Sulfadoxine and pyrimethamine (SP)

A fixed dose combination used only for treating malaria. SP is highly effective blood schizonticide against *P. falciparum* but it has less activity against other species. SP is well tolerated with the most serious SE being hypersensitivity to the sulfa components which differ in severity from mild skin rash to Stevens-Johnson syndrome. This combination considered to be safe in pregnancy and can be used for prevention of malaria in pregnant women (Sevene *et al*., 2010).

Chloroguanide and proguanil

Proguanil is used nowadays only for prophylaxis. It can be used in combination with ChQ for prophylaxis in non-immune pregnant women.

Safety: Proguanil may cause mouth ulcers, hair loss, and gastrointestinal upset. Proguanil should be avoided in patients with renal or hepatic problems. Currently, there are no studies to prove that this drug is harmful to pregnant women when used prophylactically (Sevene *et al*., 2010).

Peroxides (artemisinin derivatives)

Artemisinin derivatives are antimalarial drugs with the fastest onset of action among antimalarial drugs with potent and rapidly acting schizonticidal activity, clearing the parasite more rapidly than ChQ or QN and resulting in rapid symptomatic responses. Artemisinin derivatives can halt gametocyte development and, as a result, can reduce transmission (Meshnick, 2002).

Safety: SE include nausea, vomiting, fever and itching. In addition, bleeding with dark urine and some cardiac changes have been reported. Artesunate (AR), an artemisinin derivative, is used in combination with MQ for treating malaria. Both embryolethality and limb long bone malformations are increased with AR. MQ was toxic to the mother and enhance fetal variation. AS and

MQ combination did not increase their toxicity compared to the toxicity of either drug given alone. Embryotoxicity of AR was decreased when it is given together with MQ (Boareto *et al*., 2012). However, safety data are still limited in human pregnancy (Sevene *et al*., 2010).

Other drugs with antimalarial activity

Clindamycin

It is an antibiotic with blood schizontocidal activity which is a slowly acting drug. It is usually given in combination with QN for treating *P. falciparum* in areas of decreased QN sensitivity (McGready *et al*., 2001). Limited data available on its use during pregnancy but its use has not been associated with adverse effects on the pregnant women (Sevene *et al*., 2010).

Azithromycin (AZ)

A macrolide antibiotic with activity versus *P. falciparum*. It acts synergistically with QN against *P. falciparum* and their combination is effective and safe against drug resistant *P. falciparum* malaria. AZ also can be used in combination with ChQ, a combination that is effective against infections with *P. falciparum* and *P. vivax* species. These combinations are under evaluation to see whether they can be used for treatment and prevention of malaria in both pregnant and non-pregnant patients. Azithromycin is interesting not only because of its safety in pregnancy but also because of its activity against sexually transmitted diseases which are common in areas where malaria is endemic (Sevene *et al*., 2010).

Contraindicated antimalarial drugs in pregnancy

Tetracycline and doxycycline are combined with QN or AS to be used in multi-drug resistance malaria but they are contraindicated in pregnancy due to irreversible discoloration of fetal teeth and decreasing fetal bone growth. Primaquine is also contraindicated because its use has been associated with maternal and fetal intravascular hemolysis (Sevene *et al*., 2010).

Guidelines for treatment of MP

- CQ is the safest drug in pregnancy but the emergence of resistant *P. falciparum* makes it much less useful (Sevene *et al*., 2010).
- The drug should be selected according to the severity of the disease, the gestational age, the infecting *Plasmodium* species, and pattern of resistance (Sevene *et al*., 2010).
- Combination therapies containing artemisinin are considered first line in treating *P. falciparum* in malaria endemic areas, including during pregnancy according to WHO (Sevene *et al*., 2010).
- 1st trimester of pregnancy: - Clindamycin, ChQ, QN and proguanil are considered safe during this trimester. For uncomplicated malaria during first trimester, it is recommended to use a combination of QN plus clindamycin for seven days. For severe malaria, it is suggested to use parenteral antimalarial drugs. However, as the treatment cannot be delayed and because AR can reduce the risk of death, both AR and QN (parenterally) can be considered as options.
- 2nd and 3rd trimesters of pregnancy: - Combination therapies containing artemisinin are relatively safe on the fetus when used during these trimesters. For uncomplicated malaria during the 2nd trimester, a combination of AR and clindamycin for seven days, or QN with clindamycin for seven days can be used. AQ also can be used. AL is safe and well tolerated in high transmission areas such as Uganda where pregnant women have developed acquired immunity. Atovaquone-proguanil combined with AR has been shown to be relatively safe in small clinical trials in Thailand (Takem *et al*., 2013).

Prevention

Strategies for preventing MP that are widely used include IPT and ITNs, such as Long-Lasting Insecticidal Nets (LLINs). It has been found that ITNs signif-

icantly reduced morbidity and mortality caused by malaria in children. Additionally, maternal parasitaemia reduced by about 38%, LBW incidence reduced by about 28%, and maternal anemia reduced by about 47%. IPT includes administering therapeutic doses of antimalarial drugs. The WHO recommends the administration of at least two doses of SP during the last two trimesters of pregnancy, regardless of the presence of malaria. Several sub-Saharan African countries have included this recommendation in their prevention strategies to control malaria. In spite of the development of resistance to SP, a study in Benin has shown that SP was effective even in the presence of resistance but to certain level. Accordingly, it is highly important to find other therapeutic options to SP in case of resistance. MQ may be a good alternative to SP owing to the fact that it has half-life of elimination which provides a prolonged prophylactic period after treatment. Additionally, MQ has been found to be more effective in preventing placental malaria and maternal anemia at delivery compared to SP, but its LBW reducing effect was similar to SP (Takem *et al*., 2013).

Future drugs

Isoquine

This is an AQ derivative which has the advantage of not producing the toxic quinone-imine metabolites that are toxic to the liver and neutrophils (Casagrande *et al*., 2008). Short-chain analogues of ChQ with improved activity versus ChQ resistant parasites were also investigated. Fosidomycin, which acts by inhibiting 1-deoxy-D-xylulose 5-phosphate reductoisomerase (one of the enzymes of the non-mevalonate isoprenoid synthetic pathway that is found in many pathogens but not in human) has also been tested in some patients and produced modest cure rates. A combination of fosmidomycin and clindamycin been investigated in a 70-patient study with acute uncomplicated malaria due to *P. falciparum* and the results have shown that it was well tolerated with a cure rate of more than 95% (Ruangweerayut *et al*., 2008).

The most recent antimalarial drug class is quinolone -3-diarylethers

This class of drugs has been shown to be selectively potent cytochrome bc1 complex inhibitor of the parasite's mitochondria. Thus, it is highly effective against the human malaria that is caused by *P. falciparum* and *P. vivax*. Additionally, these drugs are active against the parasite's blood and liver stages, the gametocytes, the zygote, the ookinete, and the oocyst. ELQ-300 has been chosen as preclinical candidate because of its good oral bioavailability at the tested effective doses in mice, its metabolic stability, and its high activity in blocking transmission in the tested models of malaria. Because of its predicted low dose and long half-life in patients, ELQ-300 has the potential to be one of the new drugs for the prevention, treatment, and even eradication of malaria (Nilsen *et al*., 2013).

Ozonides

These are new interesting group of antimalarial drugs derived from spiro adamantine-shielded 1,2,4-trioxolane which has very good oral bioavailability and efficacy. OZ439 is a member of these drugs which reaches phase 2 trials with an elimination of half-life of about 30 hours in preclinical investigations and resulted in complete cures after the administration of single oral dose to mice infected with *P. berghei*. The result of this study indicated that OZ439 (combined with other drug) may be effective for single-dose malaria treatment (Miller *et al*., 2013).

NITD609

A spiroindolone drug that is found to inhibit gametocytogenesis and block transmission of *P. falciparum* to the vector. It reaches phase II trials (Pelt-Koops *et al*., 2012).

Vaccination

A lot of researches have been done to develop vaccines against malaria and the only available vaccine now is RTS,S which is in phase 3 trials. This vaccine

target *P. falciparum* circumsporozoite protein which is the major coat protein of the parasitic invasive sporozoite stage (Riley *et al*., 2013).

CONCLUSION

This review sheds some light on both old and new concepts relating to malaria in pregnancy. As much as possible is covered about this major public health problem from epidemiology to immunopathology and treatment. Since the information on safety of the antimalarial drugs are limited and based on few studies, more researches have to be done to find the safest and the most effective combination of drugs to help control this maternal and fetal threatening disease. Also trials are underway to find the best IPT, because if we can prevent malaria in pregnancy then we can prevent its consequences on the newborn which will lead to long life complications like metabolic disease and type II diabetes mellitus that can occur in adults born with LBW. Finally, it would be interesting if somebody can develop more vaccines against *Plasmodium falciparum*. If this happens, var2CSA seems likely to be a good target for this vaccine based on data related to the acquired immunity among pregnant mothers.

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