

SJMLS-3(1)-013

**Placental Malaria and the *Plasmodium falciparum* Erythrocyte Membrane Protein (VAR2CSA).**Okungbowa, M. A.<sup>1</sup> and Madumere, R. J.<sup>1</sup>Department of Medical Laboratory Science, School of Basic Medical Sciences, College of Medical Sciences, University of Benin<sup>1</sup>.

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**Summary**

Malaria is a major global health problem. Pregnant women are susceptible to infection regardless of previously acquired immunity. Placental malaria is caused by parasites sequestered in the placenta. This is mediated by VAR2CSA, a parasite antigen that interacts with chondroitin sulfate A (CSA). The adhesion of infected erythrocytes (IEs) to vascular endothelium or placenta is the key event in the pathogenesis of severe *P. falciparum* infection. In pregnant women, the parasites express a single and unique member of the *P. falciparum* erythrocyte membrane protein 1 (PfEMP1) family named VAR2CSA, which is associated with the ability of the IEs to adhere specifically to chondroitin sulphate A (CSA) in the placenta. One vaccine strategy is to block this interaction with VAR2CSA-specific antibodies. The aim of this review is to give an overview of the role of the VAR2CSA, a member of the PfEMP1 family, as the mediator of placental sequestration and as a key target for PAM vaccine development. Diagnosis of placenta malaria includes microscopy of peripheral thick blood film, histidine Rich protein 2 (HRP2) and Polymerase chain reaction (PCR). Prevention and control for typical areas of high *P. falciparum* transmission have promoted the use of anti-malarial chemoprophylaxis to prevent placental infection and its associated adverse perinatal outcome.

**Key words:** *Placental Malaria, Plasmodium falciparum, Erythrocyte Membrane Protein (VAR2CSA).*

**Introduction**

Malaria is a life-threatening blood disease caused by parasites transmitted to humans through the bite of the *Anopheles* mosquito. Once an infected mosquito bites a human and transmits the parasites, those parasites multiply in the host's liver before infecting and destroying red blood cells.

There are more than 100 types of *Plasmodium* parasites (Turner *et al.*, 2013). which can infect a variety of species. Scientists have identified five types that specifically infect humans; *P. falciparum*, *P. vivax*, *P. ovale*, *P. malariae* and *P. knowlesi*.

*Anopheles* mosquitoes lay their eggs in water, which hatch into larvae, eventually emerging as adult mosquitoes. The female mosquitoes seek a blood meal to nurture their eggs. Each species of *Anopheles* mosquito has its own preferred aquatic habitat; for example, some prefer small, shallow collections of fresh water, such as puddles and hoof prints, which are abundant during the rainy season in tropical countries.

Transmission is more intense in places where the mosquito lifespan is longer (so that the parasite has time to complete its development inside the mosquito) and where it prefers to bite humans rather than other animals. The long lifespan and strong human-biting habit of the African vector species is the main reason why nearly 90% of the world's malaria cases are in Africa.

Human immunity is another important factor, especially among adults in areas of moderate or

intense transmission conditions. Partial immunity is developed over years of exposure, and while it never provides complete protection, it does reduce the risk that malaria infection will cause severe disease. For this reason, most malaria deaths in Africa occur in young children, whereas in areas with less transmission and low immunity, all age groups are at risk.

Symptoms of malaria can reoccur after varying symptom-free periods. Depending upon the cause, recurrence can be classified as either recrudescence, relapse, or reinfection. Recrudescence is when symptoms return after a symptom-free period. It is caused by parasites surviving in the blood as a result of inadequate or ineffective treatment (Water Meyer *et al.*, 2016). Relapse is when symptoms reappear after the parasites have been eliminated from blood but persist as dormant hypnozoites in liver cells. Relapse commonly occurs between 8–24 weeks and is commonly seen with *P. vivax* and *P. ovale* infections. *P. vivax* malaria cases in temperate areas often involve overwintering by hypnozoites, with relapses beginning the year after the mosquito bite. Reinfection means the parasite that caused the past infection was eliminated from the body but a new parasite was introduced. Reinfection cannot readily be distinguished from recrudescence, although recurrence of infection within two weeks of treatment for the initial infection is typically attributed to treatment failure. People may develop some immunity when exposed to frequent infections. (Warncke *et al.*, 2016).

#### **Life cycle of Malaria Parasite.**

The life cycle of malaria parasites. A mosquito causes an infection by a bite. First, sporozoites enter the bloodstream, and migrate to the liver. They infect liver cells, where they multiply into merozoites, rupture the liver cells, and return to the bloodstream. The merozoites infect red blood cells, where they develop into ring forms, trophozoites and schizonts that in turn produce further merozoites. Sexual forms are also produced, which, if taken up by a mosquito, will infect the insect and continue the life cycle. In the life cycle of *Plasmodium*, a female *Anopheles* mosquito (the definitive host) transmits a motile infective form (called the sporozoite) to a

vertebrate host such as a human (the secondary host), thus acting as a transmission vector. A sporozoite travels through the blood vessels to liver cells (hepatocytes), where it reproduces asexually (tissue schizogony), producing thousands of merozoites. These infect new red blood cells and initiate a series of asexual multiplication cycles (blood schizogony) that produce 8 to 24 new infective merozoites, at which point the cells burst and the infective cycle begins a new (Brabin *et al.*, 2005).

Other merozoites develop into immature gametocytes, which are the precursors of male and female gametes. When a fertilized mosquito bites an infected person, gametocytes are taken up with the blood and mature in the mosquito gut. The male and female gametocytes fuse and form an ookinete a fertilized, motile zygote. Ookinetes develop into new sporozoites that migrate to the insect's salivary glands, ready to infect a new vertebrate host. The sporozoites are injected into the skin, in the saliva, when the mosquito takes a subsequent blood meal.

Only female mosquitoes feed on blood; male mosquitoes feed on plant nectar and do not transmit the disease. The females of the *Anopheles* genus of mosquito prefer to feed at night. They usually start searching for a meal at dusk and will continue throughout the night until taking a meal. Malaria parasites can also be transmitted by blood transfusions, although this is rare.

#### **Pregnancy-Associated Malaria**

Pregnancy-associated malaria (PAM) or placental malaria is a presentation of the common illness that is particularly life-threatening to both mother and developing foetus. PAM is caused primarily by infection with *Plasmodium falciparum*, the most dangerous of the four species of malaria-causing parasites that infect humans. During pregnancy, a woman faces a much higher risk of contracting malaria and of associated complications. Prevention and treatment of malaria are essential components of prenatal care in areas where the parasite is endemic (Menendez *et al.*, 2011).

Placental malaria is one of the major features of

malaria during pregnancy and has been widely used as a standard indicator to characterize malaria infection in epidemiologic investigations. Although pathogenesis of placental malaria is only partially understood, placental sequestration of *Plasmodium falciparum* results in the accumulation of parasitized erythrocytes in the intervillous space, infiltration by inflammatory cells, and release of pro-inflammatory mediators, which cause pathologic alterations that could impair materno-foetal exchanges, often resulting in adverse pregnancy outcome.

The average adult citizen of an endemic region possesses some immunity to the parasite (Meeusen *et al.*, 2001). Pregnancy causes complications that leave the woman and foetus extremely vulnerable. The parasite interferes with transmission of vital substances through the foetal placenta, often resulting in stillbirth, spontaneous abortion, or dangerously low birth weight. The tragedy of malaria in developing countries receives abundant attention from the international health community, but until recently PAM and its unique complications were not adequately addressed.

*Plasmodium falciparum* infections of the placenta remain a major medical challenge among pregnant women in sub-Saharan Africa. A number of factors influence the prevalence of placental malaria in pregnant women, including maternal age, gravidity, use of prophylaxis, nutrition, host genetics, and level of antiparasite immunity, as well as parasite genetics and transmission rates. Maternal anaemia has been shown to be one of the major complications of placental malaria in sub-Saharan Africa. The mechanisms by which malaria causes anaemia are fairly well understood.

Placental malaria is recognized as a common complication of malaria in pregnancy in areas of stable transmission, and is particularly frequent and severe in primigravidae. Many hypotheses, based on a systemic or local failure of the immunological response to malaria, have been proposed to explain the 'preference' of the parasites for replication in the placenta with a particular focus on the discovery of an

uncommon subpopulation of *Plasmodium falciparum* which can adhere and massively sequester in the placenta. Histologically, placental malaria is characterized by the presence of parasites and leucocytes within the intervillous spaces, pigment within macrophages, fibrin deposits and trophoblasts, proliferation of cytotrophoblastic cells and thickening of the trophoblastic basement membrane. The exact mechanisms leading to placental changes and determining the observed impairment of materno-foetal exchange are incompletely understood. Parasites are unlikely to be directly responsible for the placental pathology, but leucocytes, through the production of non-chemotactic cytokines, might be associated with the thickening of the trophoblastic basement membrane, and might cause a mechanical blockage of oxygen and nutrient transport across the placenta. There is sound epidemiological evidence that placental malaria determines low birth weight, mainly mediated by intrauterine growth retardation, and increases the risk of death and disease during the first year of life. Antimalarial chemoprophylaxis significantly reduces placental malaria and prevents the development of low birthweight. It is likely that, in areas of high endemicity, the placenta is where the drama of maternal malaria is mostly played. A deeper understanding of the mechanisms involved in this process is of key importance in the design of protective interventions which are effective and acceptable during the gestation period.

Pregnant women are particularly vulnerable to malaria because *Plasmodium* parasites, usually resident in red blood cells, readily respond by switching tissue tropism to colonize the placenta, where heavy infections develop with malign consequences for mother and child. Infected red blood cells display adhesive parasite ligands, encoded by the *var* genes, on their surface. These ligands mediate attachment to vascular epithelium, thus ensuring the parasites are sequestered and can avoid clearance via the spleen. The adhesive ligands mediate tissue tropism and, like many *Plasmodium* proteins, have a huge capacity for variation, another means of immune evasion. Malaria parasites respond to pregnancy by switching expression to

a surprisingly conserved gene, *varcsa*, encoding a ligand for chondroitin sulfate A, which is present in the placenta have shown that, unlike most subtelomeric genes, *varcsa* is transcribed in the opposite direction to other *var* genes and is under the control of a distinct flanking element. These attributes might explain its conservation among genetically distinct malaria strains and might offer a route to therapy.

**Plasmodium falciparum erythrocyte membrane protein 1**

*Plasmodium falciparum* erythrocyte membrane protein 1 (PfEMP1) is a family of proteins present on the membrane surface of red blood cells (RBCs or erythrocytes) that are infected by the malarial parasite *Plasmodium falciparum*. PfEMP1 is synthesized during the parasite's blood stage (erythrocytic schizogony) inside the RBC, during which the clinical symptoms of falciparum malaria are manifested. Acting as both an antigen and adhesion protein, it is thought to play a key role in the high level of virulence associated with *P. falciparum*. An elusive protein, its chemical structure and molecular properties were revealed only after a decade, in 1995. It is now established that there is

not one but a large family of PfEMP1 proteins, genetically regulated (encoded) by a group of about 60 genes called *var*. Each *P. falciparum* is able to switch on and off specific *var* genes to produce a functionally different protein, rendering evasion from the host's immune system. RBCs carrying PfEMP1 on their surface stick to endothelial cells, which facilitates further binding with uninfected RBCs (through the processes of sequestration and rosetting), ultimately helping the parasite to both spread to other RBCs as well as bringing about the fatal symptoms of *P. falciparum* malaria.

It was established that when the parasite (both the trophozoite and schizont forms) enters the blood stream and infects RBCs, the infected cells form knobs on their surface. Then they become sticky, and get attached to the walls (endothelium) of the blood vessels through a process called cytoadhesion, or cytoadherence (Angeletti *et al.*, 2015). Such attachment favours binding with and accumulation of other RBCs. This process is known as sequestration. It is during this condition that the parasites induce an immune response (antigen-antibody reaction) and evade destruction in the spleen.

**Structure of *Plasmodium falciparum* erythrocyte membrane protein 1**

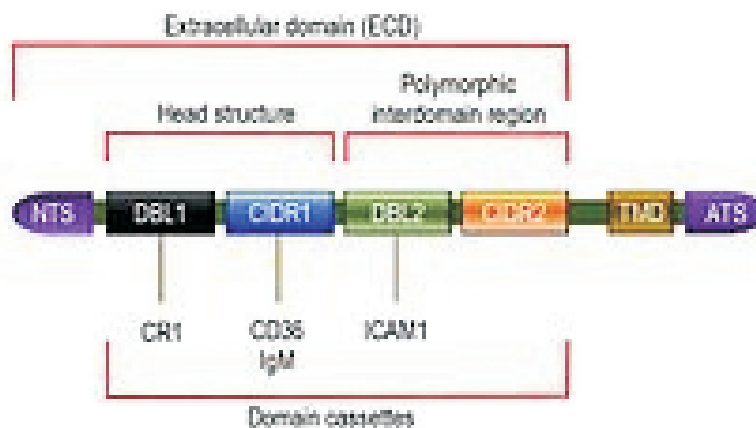


Figure 1: Typical structure of PfEMP1. NTS = N terminal segment. TMD = transmembrane domain. ATS = intracellular acidic terminal segment (Pasternak *et al.*, 2009).

PfEMP1 is a large family of proteins having high molecular weights ranging from 200 to 350 kDa (Antinori *et al.*, 2012). The wide range of molecular size reflects extreme variation in the amino acid composition of the proteins. But all the PfEMP1 proteins can be described as having three basic structural components, namely, an extracellular domain (ECD), a transmembrane domain (TMD) and an intracellular acidic terminal segment (ATS). The extracellular domain is fully exposed on the cell surface, and is the most variable region. It consists of a number of sub-domains, including a short and conserved N terminal segment (NTS) at the outermost region, followed by a highly variable Duffy-binding-like (DBL) domain, sometimes a Ca<sup>2+</sup>-binding C2 domain, and then one or two cysteine-rich interdomain regions (CIDRs).

Duffy-binding-like domains are so named because of their similarity to the Duffy-binding proteins of *P. vivax* and *P. knowlesi*. There are six variant types of DBL, named DBL $\alpha$ , DBL $\beta$ , DBL $\gamma$ , DBL $\delta$ , DBL $\epsilon$  and DBL $\zeta$ . CIDR is also divided into three classes: CIDR $\alpha$ , CIDR $\beta$  and CIDR $\gamma$ . Both DBL and CIDR have an additional type called PAM, so named because of their specific involvement in pregnancy-associated malaria (PAM). In spite of the diverse DBL and CIDR proteins, the extracellular amino terminal region is partly conserved, consisting of about 60 amino acids of NTS, one each of DBL $\alpha$  and CIDR1 proteins in tandem. This semi-conserved DBL $\alpha$ -CIDR1 region is called the head structure. The last CIDR region joins the TMD, which is embedded in the cell membrane. The TMD and ATS are highly conserved among different PfEMP1s (Howell *et al.*, 2007).

VAR2CSA is atypical in having a single domain cassette that consists of three N terminal DBL<sub>PAM</sub> domains followed by three DBL $\epsilon$  domains and one CIDR<sub>PAM</sub>. The seven domains always occur together. The usual NTS is absent. The protein specifically binds to chondroitin sulphate A (CSA); hence the name VAR2CSA.

### **Function of *Plasmodium falciparum* erythrocyte membrane protein 1**

The primary function of PfEMP1 is to bind and attach RBCs to the wall of the blood vessels. The

most important binding properties of *P. falciparum* known to date are mediated by the head structure of PfEMP1, consisting of DBL domains and CIDRs. DBL domains can bind to a variety of cell receptors including thrombospondin (TSP), complement receptor 1 (CR1), chondroitin sulphate A (CSA), P-selectin, endothelial protein C receptor (EPCR) and heparin sulfate. The DBL domain adjacent to the head structure binds to ICAM1. CIDRs mainly bind to a large variety of cluster determinant (CD36). These bindings produce the pathogenic characteristics of the parasite, such as sequestration of infected cells in different tissues, invasion of RBCs, and clustering of infected cells by a process called resetting (Hviid *et al.*, 2012).

### **VAR2CSA Protien**

VAR2CSA is unique in that it is mostly produced by the placenta during pregnancy (the condition called pregnancy-associated malaria, PAM, or placental malaria). The majority of PAM is therefore due to VAR2CSA (Kraemeret *et al.*, 2006). Unlike other PfEMP1, VAR2CSA binds to chondroitin sulphate A present on the vascular endothelium of placenta. Although its individual domains can bind to CSA, its entire structure is used for complete binding. The major complication in PAM is low-birth-weight babies. However, women who survived the first infection generally develop an effective immune response. In *P. falciparum*-prevalent regions in Africa, pregnant women are found to contain high levels of antibody (immunoglobulin G, or IgG) against VAR2CSA, which protect them the placenta-attacking malaria parasite. They are noted for giving birth to heavier babies.

### **Mechanism of VAR2CSA Protien.**

*P. falciparum* expresses proteins on the surface of parasite-infected erythrocytes (IE) helping them bind to an unusually low-sulfated form of chondroitin sulfate A (CSA) in the placental intervillous space. By this process, the parasite avoids being filtered through the spleen where it would be cleared from the bloodstream and killed. When selected in-vitro for CSA-binding, the only upregulated gene expressed in the *P. falciparum* parasites was the var2csa gene (Maier *et al.*, 2008). Parasite clones where the

*var2csa* gene was disrupted lost the ability to adhere to CSA by blocking the binding of IE. Its protein, VAR2CSA (Variant Surface antigen 2-CSA), belongs to the *Plasmodium falciparum* erythrocyte membrane protein 1 (PfEMP1) family and contains six Duffy binding-like (DBL) domains. The regions that mediate binding to CSA have not been defined, but DBL2, DBL3, and DBL6 have shown the highest affinity for CSA binding when testing with recombinant single-domains.

### Clinical Significance of VAR2CSA Protein

In a normal human immune system, malaria parasite binding to RBCs stimulates the production of antibodies that attack the PfEMP1 molecules. Binding of antibody with PfEMP1 disables the binding properties of DBL domains, causing loss of cell adhesion, and the infected RBC is destroyed. In this scenario, malaria is avoided (Pasternak *et al.*, 2009). However, to evade the host's immune response, different *P. falciparum* switch on and off different *var* genes to produce functionally different (antigenically distinct) PfEMP1s. Each variant type of PfEMP1 has different binding property, and thus, is not always recognized by antibodies. By default, all the *var* genes in the malaria parasite are inactivated. Activation (gene expression) of *var* is initiated upon infection of the organs. Further, in each organ only specific *var* genes are activated. The severity of the infection is determined by the type of organ in which infection occurs, hence, the type of *var* gene activated. For examples, in the most severe cases of malaria, such as cerebral malaria, only the *var* genes for the PfEMP1 proteins DC8 and DC13 are switched on. Upon the synthesis of DC8 and DC13, their CIDR<sub>α1</sub> domains bind to EPCR, which brings about the onset of severe malaria. The abundance of the gene products (transcripts) of these PfEMP1 proteins (specifically the CIDR<sub>α1</sub> subtype transcripts) directly relates to the severity of the disease. This further indicates that preventing the interaction between CIDR<sub>α1</sub> and EPCR would be good target for a potential vaccine. In pregnancy-associated malaria, another severe type of falciparum malaria, the gene for VAR2CSA (named *var2csa*) is activated in the placenta. Binding of VAR2CSA to CSA is the primary cause of premature delivery, death of

the foetus and severe anaemia in the mother (Quad *et al.*, 2012) This indicates that drugs targeting VAR2CSA will be able to prevent the effects of malaria, and for this reason VAR2CSA is the leading candidate for pregnancy associated vaccine.

### Current research

Each VAR2CSA domain has a potential affinity to CSA, but there are large areas not exposed to the immune system and appear to be buried in the quaternary structure (Rowe *et al.*, 2009). Data has indicated that these domains interact, forming a binding site that is specific for low-sulfated CSA found in the placenta. The binding of antibodies to one of these domains would prevent adhesion of parasitic IE in the placenta. Moreover, studies have shown that women acquire immunity to PAM through antibody recognition of the VAR2CSA domain, also known as VSA<sub>PAM</sub>, after exposure during their first pregnancy. By measuring circulating levels of IgG antibodies that presumably target VAR2CSA, the study demonstrated that subsequent pregnancies confer progressively greater protection to PAM. Thus, PfEMP1 proteins such as the VAR2CSA domain could prove attractive as potential candidates for vaccine targets.

### Characteristics of Malaria-Infected Placenta

The placenta is a complex, sophisticated organ with several important functions throughout gestation, with the primary purpose of providing sustenance for the developing foetus. The placenta is also a site for *P. falciparum* sequestration. Many hypotheses, based on a systemic or local failure of the immunological response to malaria, have been proposed to explain the "preference" of the parasites for replication in the placenta; some have been reviewed elsewhere. At term, the placenta is usually a circular-shaped structure measuring approximately 20 cm in diameter and 2.5 cm in thickness. The foetal portion of the placenta consists of the chorionic plate and its villi and the peripheral trophoblastic shell that surrounds the intervillous space and covers the maternal tissue. Anchoring villi contact the decidua basalis. The decidua basalis (maternal portion of the placenta) rests on the stratum basalis and is

characterized by large, polyhedral pale blue stromal (decidua) cells.

The placental sequestration of *P. falciparum* (placental malaria) results in the accumulation of parasitized erythrocytes in the intervillous space, infiltration by inflammatory cells, and release of pro-inflammatory mediators, which cause pathologic alterations. Histologically, placental malaria is characterized by the presence of intervillous parasites and leukocytes, malarial pigment within macrophages, fibrin deposits and trophoblasts, proliferation of cytotrophoblastic cells, and thickening of the trophoblastic basement membrane.

### Diagnosing Placental Malaria

The sequestration of malaria parasites in the placenta is one of the major features of malaria infection during pregnancy. In semi-immune women (i.e., those residing in areas of unstable malaria transmission), the proportion of parasitized erythrocytes is often higher in the placenta than in peripheral blood. Additionally, placental infection may be detected in the absence of peripheral blood parasitaemia and may persist after initiation of antimalarial treatment. Because not all malaria-exposed pregnant women in areas of malaria endemicity suffer from placental malaria and its serious consequences, a number of studies have assessed the prevalence and risk factors of placental malaria in sub-Saharan Africa, while others have attempted to elucidate protective immune responses against placental infection and/or immune pathogenesis. However, results from the various studies are often discordant, due in part to different techniques of sample collection and analysis in different studies, based on the differences in the definition of placental malaria (Othoro *et al.*, 2006). Some studies based their definition on the presence of malaria parasite and/or pigments in blood smears from placental blood. Others based their definition on histological findings (Mockenhaupt *et al.*, 2006), while yet others based their definition on the use of histidine-rich-protein-2 (HRP2) capture test and polymerase chain reaction (PCR). In various parts of sub-Saharan Africa, placental malaria prevalence rates ranging from 9.5 percent to 37.1 percent were obtained by placental blood smear

microscopy, 35 percent to 75.5 percent by placental histological examination, 41 percent to 43.1 percent by HRP2, and 51 percent to 59 percent by PCR (Singer *et al.*, 2004).

It is pertinent to state that most studies in sub-Saharan Africa relied on the results of the placental smear, the sensitivity of which is low compared with placental histopathology. Using a more reliable method of assessing placental infection, such as the histopathologic examination, might have changed the results (Shulman *et al.*, 2003). Although microscopy with placental blood is less sensitive than placental histology, it is considerably more sensitive in the diagnosis of maternal malaria than peripheral blood smears. For instance, in southern Ghana, the vast majority of *P. falciparum* infected delivering women were asymptomatic, and microscopy of thick films from peripheral blood missed more current infections than it detected, with roughly half of the women with microscopically proven placental parasitemia having a *P. falciparum* negative peripheral blood film. In Blantyre, Malawi, blood smear microscopically detectable *P. falciparum* peripheral and placental infection was more common in women with their first and second pregnancies than in multigravid women, but neither infection detected by histology only nor incidences of past infection differed with gravidity, and similar numbers of women were uninfected (Rogerson *et al.*, 2003).

Placental histology is therefore considered the "gold standard" of malaria diagnosis in pregnancy for epidemiological or biological study purposes, because it can show signs of active infection (presence of infected erythrocytes in the intervillous space), past or chronic infection (malarial pigment), or both. However, due to limited technical expertise, such testing is rarely available in endemic areas; examination of thick films of blood samples obtained by placental incision is comparatively easier. Although placental hemozoin is described as the clinically most relevant marker of infection, detection of hemozoin on placental thick blood films is likely influenced by difference in sensitivity.

The comparisons of microscopy, HRP2 (or other rapid diagnostic tests (RDTs), and PCR in placental malaria diagnosis are challenging to interpret because they detect infection in different ways: microscopy detects viable whole parasites in red blood cells, HRP2 detects specific parasite proteins, and PCR detects parasite DNA. Although the HRP2 and PCR are able to detect parasite debris present in the blood when viable parasites may be sequestered in the placenta or persist at very low densities, both parasite proteins and DNA can be detected after successful treatment, making the results of HRP2 and PCR potentially confusing in a clinical setting. PCR assays also detect low-level infections that produce no major foetal impairment; however, some studies have shown that sub-microscopic infections detected by PCR are associated with mild maternal anaemia and inflammation, and sub-microscopic infections detected by rapid diagnostic test are associated with maternal anaemia and low birth weight. A better understanding of the clinical and epidemiological relevance of detection techniques is imperative for proper interpretation.

### Conclusion

Despite considerable improvement in healthcare delivery services in the African continent, the control of malaria in pregnant African women, one of several child survival strategies applied through antenatal care, continues to be particularly challenging. Prevention and control recommendations for typical areas of high *P. falciparum* transmission have promoted the use of antimalarial chemoprophylaxis to prevent placental infection and its associated adverse perinatal outcome. This confirms prior findings. Other randomized trials show a protective effect of prophylaxis on placental infection or peripheral parasitaemia (Sharma *et al.*, 2001). However, persistently low program coverage coupled with diminishing intervention effectiveness has forced a re-evaluation of the relative importance of malaria in pregnancy. The prophylactic medicines include sulfadoxine pyrimethamine, proguanil, and pyremethamine, while the curative ones include artesunate, chloroquine, and amodiaquine. These drugs are relatively safe in pregnancy and are widely used

in malarious areas of sub-Saharan Africa

### Recommendations

Substantial reductions in maternal malaria, anaemia, and low birth weight can be achieved by intervention programs, including the use of preventive intermittent treatment, chemoprophylaxis, and the use of insecticide-treated nets. Interventions should also exist for maternal anaemia (e.g., good nutrition, iron and folate supplementation, and hookworm treatment) can be provided through antenatal care programs. More studies should be carried out on the VAR2CSA protein in order to develop a vaccine that can be effective against the *Plasmodium falciparum* and combat pregnancy associated malaria. Finally, collaboration between scientists, policy makers, and control programs should be strengthened and community-level research encouraged in order to guide programs, monitor and evaluate markers of success.

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**Citation:** Okungbowa, M. A. and Madumere, R. J. Placental Malaria and the *Plasmodium falciparum* Erythrocyte Membrane Protein (VAR2CSA). *Sokoto Journal of Medical Laboratory Science*;3(1): 119 - 128

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