Chapter 3

Malaria in Pregnancy

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Additional information is available at the end of the chapter

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Abstract

Malaria infection during pregnancy is an important public health problem with substantial risks to both the mother and foetus. Pregnant women are the most vulnerable group of malaria-associated morbidity and mortality. A pregnant woman has an increased risk (up to four times) of getting malaria and twice the chances of dying from malaria, compared to a non-pregnant adult, becuase the immune system is partially suppressed during pregnancy. Malaria in pregnancy not only affects the mother but also has a dangerous sequel for the developing foetus, resulting in premature delivery or intrauterine growth retardation. Diagnosis of malaria in pregnancy remains a challenge due to the low parasite density and placental sequestration of *Plasmodium falciparum*. Thus, there is an urgent need for new diagnostic methods to detect malarial parasites in the pregnant women. Though antimalarial drugs are available, which can be safely given in the pregnancy, increasing drug resistance of malarial parasite may pose a big problem in the future. In this chapter, we review the burden of pregnancy-associated malaria (PAM), its pathogenesis, diagnostic issues during pregnancy and recent guidelines for chemoprophylaxsis and treatment.

Keywords: malaria, pregnancy

1. Introduction

Pregnancy-associated malaria (PAM) is a major health problem, which not only affects mother but also affects the developing foetus. Worldwide, 50 million women are at risk of PAM per annum [1, 2]. Depending upon the transmission pattern of malaria, PAM has been studied in two different geographical regions: one with a high and stable transmission rate (Africa) and another one with a low and unstable transmission rate (Asia-Pacific region). The majority of

the studies are from Sub-Saharan Africa, where *Plasmodium falciparum* causes the majority of the cases. Approximately 25 million pregnant women are at risk of *P. falciparum* infection, and 25% women had evidence of placental infection at the time of delivery [3]. Due to the high endemicity of malaria in these regions, adults develop natural immunity due to repeated infections; thus, PAM rarely results in fever and remains undetected and untreated. On the other hand, Asia-Pacific region has a low transmission of *P. falciparum* and women have little acquired immunity against malaria. In Asia-Pacific region, most pregnant women are at a risk of *Plasmodium vivax* infection. Asia-Pacific region consists of WHO South-east Asia and Western Pacific regions [3]. Approximately, 75 million women became pregnant in the Asia-Pacific region in 2007 [4]. Majority of these cases were from India and China. In low transmission settings, malaria in pregnancy is associated with anaemia, an increased risk of severe malaria and it may lead to spontaneous abortion, still birth, prematurity and low birth weight. In such settings, all pregnant women are affected irrespective of the number of times they have been pregnant. Infection with *P. vivax*, as well as with *P. falciparum*, leads to chronic anaemia and placental infection, resulting in birth weight reduction and increased neonatal mortality. However, reduction in birth weight in *P. vivax* is only two-third as associated with *P. falciparum*. Effect of *P. vivax* appears to increase with successive pregnancies [5].

One should be cautious while accessing the burden of malaria as there are many gap holes in the knowledge of epidemiology and burden of malaria in pregnancy. Long-term prospective studies are required for accessing the true incidence of PAM. Study designs and methodology should also be kept in mind while calculating the estimates of the burden of malaria [6–8]. Recently, verbal autopsy has been used in a study published in *The Lancet* [7], in which authors have interviewed the relatives of a person who has recently died to determine a cause of death. The results are astonishing in terms of numbers as there is a great disparity between malaria death rates of Lancet group estimates and WHO estimates [8]. The Lancet study has projected the estimates of 1.24 million deaths worldwide which includes 7,14,000 deaths under the age of 5 as compared to WHO estimates of 6,55,000 deaths worldwide which includes 5,63,300 deaths under the age of 5 [8]. The reliability of these findings is a matter of debate, and there is an urgent need to review these findings involving a broader group of experts, so that malaria control programs can be reformulated with newer targets. In Africa with stable transmission, the median prevalence of maternal malaria infection (defined as peripheral or placental infection) in all gravidae has been estimated to be 27.8% [1, 9]. These are the minimum estimates as they are based on single-point prevalence and are based upon light microscopy, which cannot detect the sub-microscopic parasitemia of pregnancy. So, more studies are required which can detect malaria with high sensitivity and specificity such as *Plasmodium* DNA detection by polymerase chain reaction (PCR) and placental histology. In a low-transmission African setting, the median prevalence of peripheral and placental parasitemia has been estimated to be 13.7 and 6.7% respectively [10]. However, outside Africa regions with low-transmission have respective estimates of 6.2 and 9.6% [10]. It has been estimated that placental infection in regions of stable transmission in Africa are identified more frequently in dry seasons as infection acquired during rainy season may persist for several months in placenta [11, 12]. Thus, during the low-transmission season also one can get the PAM with a higher frequency.

Although *P. vivax* has been known to be associated with malaria in pregnancy for the quite long time, its impact has been accessed only recently [13]. Studies from India, Thailand and Papua, Indonesia showed that low birth weight neonates and anaemia are more pronounced as compared to non-infected pregnant women, but severity was less as compared to *P. falciparum* associated malaria in pregnancy [14–16].

2. Risk factors

2.1. Gravidity

Primigravidae are at increased risk of infection in high-transmission areas, whereas they are less marked in low-transmission areas as women of all gravidities are susceptible to severe maternal and foetal outcome. Thus, parity specific immunity plays an important role in PAM.

2.2. Maternal age

Younger age group is an independent risk factor for PAM. Thus, age-specific immunity protects an individual from PAM.

2.3. HIV infection

HIV increases the risk of acquiring malaria in pregnancy by weakening the immunity. It also hampers the cytokine responses to malaria. These patients have decreased IL-12 levels, which in turn lead to decreased interferon-γ leading to increased susceptibility to placental malaria in HIV. Malaria increases HIV viral load in pregnancy and also increases the expression of CCR5, which is an important co-receptor for HIV cell entry. Malaria and HIV are linked in other ways also, that is, *The DARC gene* which protects against *vivax* malaria might increase susceptibility to HIV [8, 17].

2.4. Effect of *Plasmodium* species

All the four species of Plasmodium can infect pregnant women, but the prevalence and effect of *Plasmodium ovale* and *Plasmodium malariae* in pregnancy are currently unknown. *Plasmodium knowlesi* is the commonest cause of malaria in Malaysia, but it is relatively rare during pregnancy [18]. Pregnant women are at increased risk to both *P. vivax* as well as *P. falciparum* infection, but the risk is more for *P. falciparum* due to placental cytoadherence. Mixed infections can also occur in pregnancy, but the prevalence of mixed infections decreases with increasing age and gravidity. Differences in between *P. vivax* and *P. falciparum* are important for understanding pathogenesis of malaria in pregnancy due to different species. *P. vivax* infects reticulocytes after binding of merozoites with Duffy antigen receptor, which is lacking in African population leading to protection against *P. vivax* [15]. This also helps in limiting the parasitemia in *P. vivax* infections as compared to *P. falciparum* infections where mature RBCs are invaded leading to relatively high parasitemia [11]. Infected RBCs with *P. vivax* do not express erythrocyte surface proteins required for sequestration, which is well documented in

P. falciparum infections [11, 19]. This heavy sequestration in placenta is discussed below that is associated with high parasitemia in placenta leading to low birth weight neonates and anaemia. Lastly, relapsing hypnozoite forms characteristics of *P. vivax* may complicate the clinical course of infection. This suggests that systemic infection in mother is playing an important role in pathogenesis of PAM due to *P. vivax* as compared from *P. falciparum* where placenta is heavily infected by malaria parasite.

3. Pathogenesis

3.1. Placental changes associated with malaria

Infected erythrocytes tend to lodge in much higher densities in intervillous space as compared to the peripheral circulation [20]. Due to sequestration of infected erythrocytes, trophozoites and shizonts are absent in peripheral blood [21]. PAM is also associated with increased numbers of phagocytic cells in the intervillous space along with the deposition of malarial pigment (haemozoin). Precise and accurate diagnosis requires an examination of histological sections of placenta. Based upon parasitized erythrocytes and haemozoin, placental changes have been categorized into four classes (**Table 1**).

S. no.	Category	Description
1.	Not infected	No evidence of parasitized erythrocytes or malarial pigment
2.	Active-acute	Parasitized erythrocytes present, with no or minimal pigment deposition in fibrin
3.	Active-chronic	Presence of parasitized erythrocytes along with substantial amount of pigment in cells or in fibrin
4.	Past	Absence of parasites but presence of pigment

Table 1. Description of placental pathology in PAM (adapted from Ismail et al. [67]).

Recently, studies have shown that chronic infections are associated with lower maternal haemoglobin and low birth weight due to foetal growth retardation, whereas preterm births are more closely associated with acute infection having high parasitemia.

3.2. PAM is not always associated with pathology

It has been seen that microscopic examination of blood smears is not a sufficient diagnostic tool to detect the sub-microscopic infections. These are mainly detected by polymerase chain reaction, and a study by Mankhambo et al. [22] has shown that sub-microscopic infections are not associated with low birth weight or with lower maternal haemoglobin. Thus, it is the density of the parasites which matters a lot and women might not suffer from adverse effect of PAM, in whom density of the parasites is under control. Therefore, PAM is common but is not always associated with adverse outcomes.

3.3. Plasmodium infected erythrocytes that cause malaria in pregnant versus non-pregnant women

Placental-infected erythrocytes with *P. falciparum* differ in a number of ways as compared to infected erythrocytes from non-pregnant women (**Figure 1**) [19]. Placental-infected erythrocytes adhere to glycosaminoglycan receptors throughout the intervillous space [23, 24]. Chondroitin sulphate A has been considered to be the most predominant receptor placental adhesion receptor, which is present as a glycosaminoglycan side chain [25] of tissue thrombomodulin [26] and also as a part of secreted low-sulphated aggrecan in intervillous space. In contrast, infected erythrocytes of non-pregnant women do not use this receptor, and sequestration occurs near to vascular wall in other tissues. Another important difference is that rosettes formation does not occur among placental infected erythrocytes, which is a common feature of infected erythrocytes of non-pregnant women [27, 28]. Placental erythrocytes can adsorb IgM [29], and the adhesion ligands vary in their sensitivity to trypsin digestion [30]. On the other hand, infected erythrocytes of non-pregnant women can adsorb IgM on their surface. Thus, parasite antigens causing adhesion of infected erythrocytes to chondroitin sulphate A are different from those antigens that are expressed on infected erythrocytes during non-placental *P. falciparum* infections. All these surface expressed antigens are collectively known as variant surface antigens (VSAs).

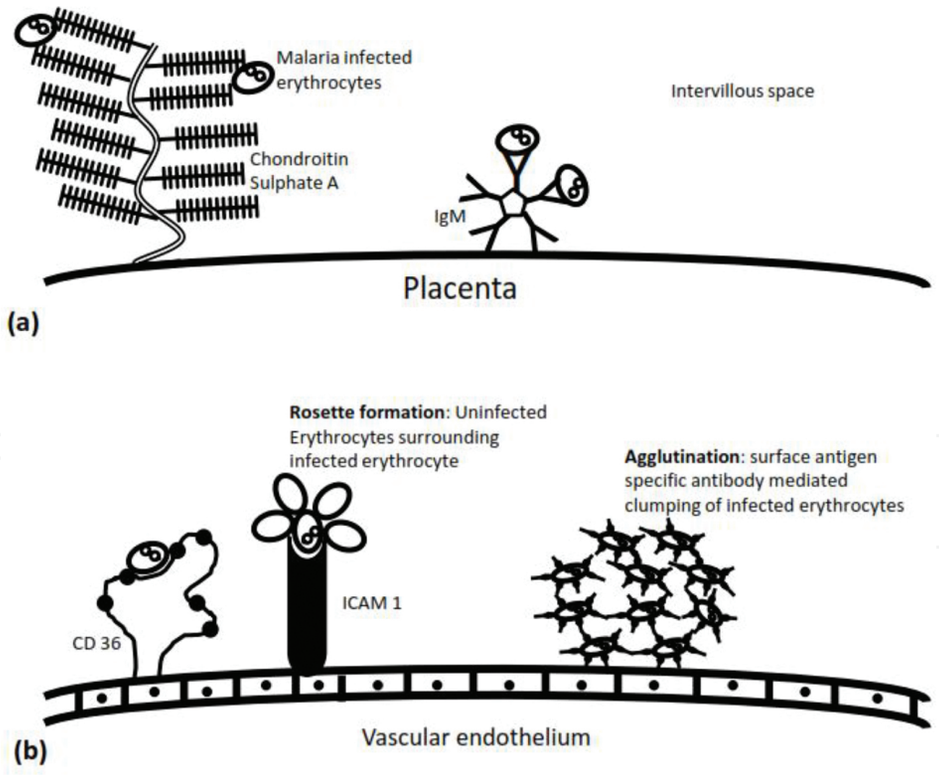

Figure 1. Comparison of malaria-infected erythrocytes in pregnant women (a) versus non-pregnant individuals (b). In pregnant women, infected erythrocytes adhere to chondroitin sulphate A receptor present in intervillous area of placenta, whereas in non-pregnant women infected erythrocytes adhere to CD36 or ICAM1 and also exhibit rosette formation and agglutination [19].

3.4. Humoral immune response to variant surface antigens in pregnancy

VSAs are the main targets of IgG which provides the protective immunity in response to repeated episodes of *P. falciparum* infections in non-pregnant individuals. Thus, if VSA is different among pregnant and non-pregnant individuals, then susceptibility to infection with *P. falciparum* in previously clinically immune women when they become pregnant could easily be explained. This would also explain the increased chances of PAM in women of low gravidity in areas with high transmission. A study by Fried et al. [31] has provided an evidence which shows that VSA expressed by placental infected erythrocytes are immunologically distinct. They have shown that IgG derived from multigravidae who were exposed to *P. falciparum*, inhibit the adhesion of infected erythrocytes to chondroitin sulphate A that are obtained from primigravidae [32]. Whereas, adhesion of infected erythrocytes to chondroitin sulphate A is not inhibited by serum from either primigravidae or men. IgG1 is known to be the predominant subclass of IgG against VSA in PAM [33, 34].

3.5. Humoral immune response to other antigens in pregnancy

Humoral immune response to other blood stage antigens have also been known to provide immunity in PAM. Thus, young age is an independent risk factor for PAM. The relative protection from severe malaria has also been observed in the area of high exposure to malaria prior to pregnancy. However, humoral immune response to pre-erythrocytic antigens/blood stage antigens other than VSA is not sufficient to provide adequate immunity in PAM [32].

3.6. Protective antibodies in PAM

There is an inverse relationship between gravidity and PAM. Protective levels of antibodies against VSA inhibiting adhesion to chondroitin sulphate A have an inverse relationship to low birth weight, preterm delivery and low maternal haemoglobin levels [35, 36]. More studies are required to identify the other targets of protective immune response in pregnancy.

3.7. Increase in monocyte infiltrates in placental intervillous space

Maternal mononuclear cells are stimulated by sequestrated infected erythrocytes in placenta. Activated mononuclear cells secrete β-chemokines that are chemotactic for macrophages and monocytes. Macrophage migration-inhibitory protein (MIF) helps in retention and activation of macrophages [37, 38]. Thus, induction of these cytokines helps in increase of monocytes and macrophages in the intervillous space in PAM. These cells also act as antigen presenting cells to T cells [39].

3.8. Placental cytokines in PAM

During normal pregnancy, cytokine balance is shifted towards Th2-type immune response [40], and Th1-type immune response is associated with adverse maternal and foetal outcomes such as maternal anaemia, spontaneous abortions and premature deliveries. The Th1-type of immune response aids in clearing the parasites from the placenta. The various mechanisms documented include increase in phagocytic activity of macrophages and increase in nitric

oxide activity. In addition to that, oxygen-free radicals along with stimulation and proliferation of T-cells also play an important role in clearing the parasites. Thus, Th1-type immune response helps in fighting against the malaria infection, but its overproduction is harmful as it can terminate the pregnancy. The ill effects of pro-inflammatory cytokines are counterbalanced by IL-10 and have been shown to be up-regulated in intervillous space. Thus, it is the delicate balance between Th1 and Th2 immune response which provides immunity in PAM.

3.9. Role of innate cells in PAM

Macrophages, dendritic cells, natural killer (NK) cells, γδ T cells are the arms of innate immune response, which helps in shaping the adaptive immune response to malaria. They help in early production of cytokines which determine the response to infection by modulating the immune response. Placental macrophages help in eliminating the parasites. Infected erythrocytes also adhere to NK cells to produce interferon-γ. Adherence to dendritic cells is mediated by CD36 which further helps in antigen presentation to T cells [41, 42]. NK T cells have been shown to be protective against blood-stage malaria infections in athymic mice. Toll-like receptors (TLRs) help in recognition of asexual-stage of *P. falciparum* by innate cells. Polymorphism in TLR 4 and TLR 9 is known to be associated with low birth weight, foetal growth retardation and maternal anaemia [43, 44]. There are few studies available which confirm the specific roles of innate immune response in PAM, so more studies are required to unveil the role of innate immune response in PAM among humans.

3.10. T and B cell response in PAM

During pregnancy, very delicate immunological balance is maintained so that mother's immune system must remain tolerant to the developing foetus but provide protection against invading pathogens on another side. Earlier studies have shown that pregnancy predisposes the women to severe disease due to the suppression of cell-mediated immune response [45]. However, these days submicroscopic parasitemia is well documented in which slides for peripheral smear are negative, but PCR is positive. It has been postulated that decrease in T-cell proliferative responses might be caused by the absence of memory T cells due to sequestration as compared to earlier concept of immunosupression [46].

Fievet et al. [47] investigated the immune response to *P. falciparum* antigen in Cameroonian primigravidae, evolution after delivery and during the second pregnancy. They have shown that levels of antibodies to Pf155/RESA are lower during the pregnancy in comparison to levels of antibodies after the delivery. However, levels of *P. falciparum* asexual blood stages are higher during the pregnancy than after delivery. This increase during pregnancy has remained unexplained and has not been reported earlier. It has been proposed that due haemodilution and passive transfer of IgG to developing foetus, there occurs a decrease in maternal IgG levels during pregnancy. It has also been postulated that immunosuppressionwhich occurs during pregnancy may impair the T-cell subsets differentially leading to impairment of IL-2 cellular response,but proliferative responses, IL-4, IFN-γ responses are either not affected or moderately increased. This suppression of IL-2 has been linked to the hypothesis supporting the transient depression of Th1 immune response during pregnancy. However, the suppression

of IL-2 is not parallel with the reduction of IFN-γ, suggesting Th1 subset might be differential affected by the PAM [48, 49]. Fievet et al. [49] have shown that cellular immune response is related to previous placental infection and parity even after the pregnancy in relation to *P. falciparum* infections. They have shown that T-cell proliferative responses and cytokine production (IL-2, IL-4, IL-10 and IFN-γ) is significantly higher in multigravidae as compared to primigravidae when cells are stimulated with chondroitin sulphate A-adhering RP5 strains of *P. falciparum* but not with other strains which lack adherence to chondroitin sulphate A. These findings will be useful in designing the vaccine for malaria in pregnancy, if parity-dependent stimulation of cytokine production is important in PAM. In PAM, high levels of IgGspecific against VSA has been documented along with higher number of VSA-specific memory B-cells. Surface-exposed epitopes of VAR2CSA are the main target of antibody production [49].

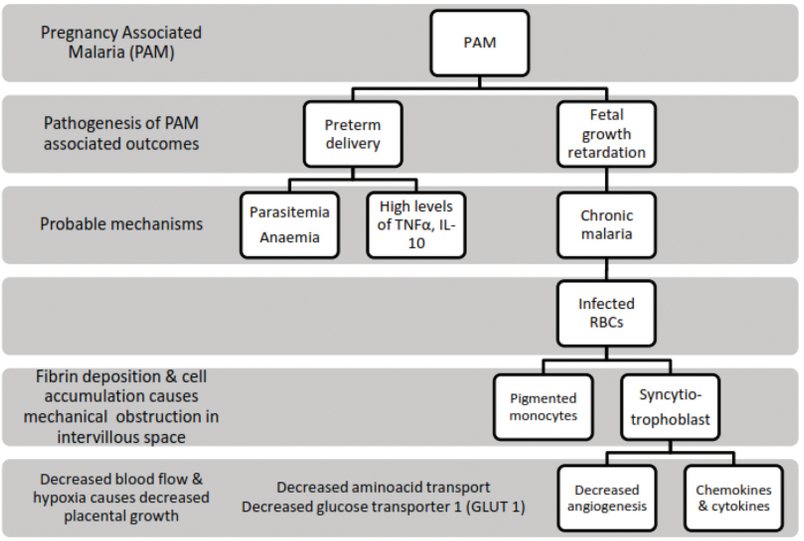

Figure 2. Probable mechanisms by which pregnancy-associated malaria can cause preterm delivery or foetal growth retardation [19].

3.11. Pathogenesis of foetal growth retardation in malaria

Foetal growth retardation is known to be associated with chronic malaria. Whether it occurs due to mainly due to events occurring near the delivery (e.g. cytokines, impaired uteroplacental blood flow or biochemical imbalance in the placenta) or due to chronic infection which slowly compromise the foetal growth, are still unknown. Malaria is known to impair uterine spiral arteries remodelling during trophoblast invasion, leading to decreased placental circulation [50]. Mechanical obstruction of intervillous space by infected erythrocytes, monocytes and deposition of fibrin are also known to compromise the placental circulation [51]. Cytokines released by monocytes could directly or indirectly affect nutrient transport mechanisms. Thus, decreased blood flow, impaired placental development and impaired nutrient transport are the probable mechanisms by which foetal growth retardation occurs (**Figure 2**).

3.12. Pathogenesis of preterm delivery due to malaria

Preterm birth occurs delivery before 37 weeks of gestation, and it is known to be closely associated with high parasitemia, maternal anaemia, increased levels IL-10 and TNF-α [38]. But how it occurs is still unknown.

3.13. Pathogenesis of anaemia in malaria

Anaemia in malaria is a multifactorial, caused by a combination of erythrocyte destruction (both infected and uninfected erythrocytes) and bone marrow dysfunction. Other associated factors such as hookworm infection, HIV infection, chronic inflammation, iron and folic acid deficiency, accumulation of pigmented monocytes and their inflammatory mediators are known to suppress the erythropoesis [52, 53].

4. Role of hormones in PAM

Malaria in pregnancy has been associated with an increase in cortisol levels, which may reflect a stress response to malaria. It has also been postulated to suppress the immune system, but exact mechanism how it occurs is still a matter of debate. In late pregnancy, it is also associated with reduced oestradiol levels [54, 55].

5. Maternal outcomes in malaria

The maternal outcome in malaria depends upon the degree of immunity acquired by the pregnant women. Thus, epidemiological transmission has an important effect on maternal outcome. In areas of high transmission, only few individuals get the clinical signs and symptoms of malaria and same applies to pregnant women [10]. In Africa, malaria is responsible for approximately 26% of severe anaemia cases among pregnant women of all gravidities [2]. Hospital-based studies have shown that malaria-related maternal mortality rate among pregnant women, varies from 0.5 to 23.0%, whereas it varies from 2.9 to 17.6% among community-based studies [56]. However, in areas having low, unstable and seasonal transmission, women are more susceptible to develop the severe disease. In India, malaria-related maternal mortality rate among pregnant women varies from 7.0 to 66.6%, and in Thailand it varies from 10 to 27% [57]. Targeted treatment approach is required to curtail these figures of mortality.

6. Child outcomes in malaria

Malaria has the devastating effects on the developing foetus resulting in various outcomes (**Figure 3**). Low birth weight is an independent risk factor for the increase in infant mortality

rate [12, 58]. Risk of low birth weight doubles in primigravidae having placental malaria. Malaria in pregnancy is responsible for 20% of low birth weight deliveries in Sub-Saharan Africa [9]. In areas of high transmission, women have good-level immunity acquired due to repeated infections, thus decreasing the episodes of febrile illness, an important predisposing factor which causes preterm delivery. Furthermore, it is the intrauterine growth retardation which is the major cause of low birth weight babies as compared to areas having low rates of unstable transmission where preterm delivery is likely to be a more important cause of low birth weight due to poor levels of acquired immunity [10]. Malaria in pregnancy is also responsible for increased neonatal deaths, stillbirths, spontaneous abortions and anaemia. Steketee et al. [1] have reviewed the similar factors in Sub-Saharan Africa and estimated low birth weight, preterm delivery and stillbirth attributable to malaria in pregnancy, to vary from 8 to 14%, 8 to 36% and 13 to 70% respectively.

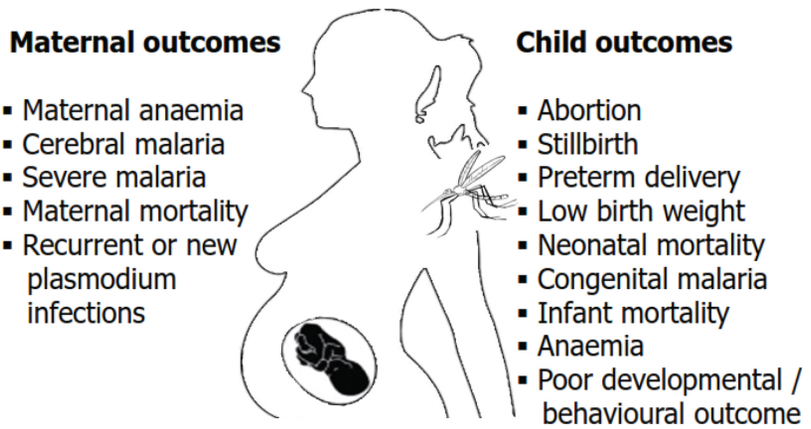

Figure 3. Maternal and child outcomes associated with malaria in pregnancy [10].

Placental malaria is also known to reduce the maternal antibodies to the foetus resulting in other infections such as measles and *Streptococcus pneumonia* [59, 60]. Recent studies have reported a rise in congenital malaria whose prevalence varies from 8 to 33% [61–63]. The increase may attributed to increase in drug resistance, HIV, increase in virulence and increased detection rates. Data is lacking which can provide direct evidence of malaria in pregnancy affecting development of the child in the long term. However, study from Malawi [64] has shown that placental malaria is an independent risk factor for anthropometric status in infancy. Other risk factors such low birth weight, anaemia can hamper the development of the brain and may result in cognitive disorders.

7. Diagnosis of PAM

Diagnosis of malaria in pregnancy is challenging as *P. falciparum* parasites are either absent or undetectable in peripheral blood, due to the sequestration of parasites in placenta [65]. This is due to the fact that infected erythrocytes are sequestered in the intervillous space [23]. Infections having a low parasite density may also affect the pregnant women and her devel-

oping foetus [66]. Thus, early diagnosis is essential for the timely initiation of treatment. Although, it is considered to be a gold standard for histological examination of the placental malaria, it is not applicable for routine diagnosis [67, 68]. However, placental examination is not possible before the delivery and thus, antenatal placental infection can only be inferred by peripheral blood smear examination.Although polymerase chain reaction (PCR) has the potential to diagnose malaria in pregnancy with higher sensitivity and specificity. A recent study by Mayor et al. [69] have shown that among the PCR positive for *P. falciparum* in peripheral and/or placental blood samples, 71.3, 61.5, 60.7 and 58.2% were negative by peripheral microscopy, by HRP2 ELISA in plasma, by HRP2 RDT in plasma and by histology respectively. However, molecular techniques are costly and are not available everywhere. Studies [70, 71] have shown a marked underestimation of malaria infection in pregnant women when diagnosed by standard microscopy in peripheral and placental blood as compared to molecular techniques such as polymerase chain reaction (PCR). Thus, there is an urgent need for more accurate diagnostic tools to detect malaria in pregnancy to prevent the negative clinical impact of hidden infection in pregnancy.

8. Prevention and management of PAM

Prevention of PAM is an important public health issue. Mainly, three-pronged approach has been advised for reducing the burden of PAM which are as follows [72]:

1. Effective case management
2. ITNs: use of insecticide-treated nets (ITNs)
3. IPT: intermittent preventive therapy in areas of stable transmission

In areas with low or unstable transmission of malaria, PAM can be controlled by timely diagnosis, and treatment of acute cases as IPT will be not very useful as it is in high transmission areas. Malaria in non-immune pregnant women are prone to severe disease, thus early initiation of antimalarials along with supportive management is very useful. Use of ITNs is useful in high transmission areas as its use will decrease the exposure to infective mosquito bites, thus decreasing the risk of placental malaria, low birth weight, still births and furthermore, continue to protect the newborn baby during infancy, since most babies sleep with their mothers [73]. However little is known about their effect in decreasing the clinical malaria and low birth weight in low transmission areas [74].

PAM in high transmission areas may be associated with placental parasitemia, causing maternal anaemia even in the absence of documented peripheral parasitemia. Therefore, it is recommended to treat presumptively whenever pregnant women present with severe anaemia, whether or not she has a history of fever and whether or not peripheral parasitemia is present [75, 76]. It is also recommended to give iron and folic acid supplementation to all pregnant women as a part of routine antenatal care. A study from Western Kenya has shown a dramatic reduction of 38% in the incidence of malaria parasitemia, 47%

reduction in anaemia and 28% reduction in the prevalence of low birth weight babies in those pregnant women who regularly used ITNs [77].

IPT has replaced the previous policy of chloroquine chemoprophylaxsis given weekly [78], as it was associated with poor patient compliance and increased chances of developing drug resistance [79]. Curative treatment dose of effective anti-malarial drug is given at predefined intervals during the course of pregnancy. As shown in **Figure 4**, all women should receive at least two doses of IPR in the second and third trimesters of pregnancy with the aim of clearing the placenta from parasites at the time of rapid foetal growth [80]. Though a single dose is also beneficial,yet one should aim for giving 2–3 doses. Sulphadoxine-pyrimethamine (SP) is the most common drug used in IPT, due to its long half-life and good safety profile in pregnancy [75, 81]. However, SP resistance in *P. falciparum* is prevalent throughout the Sub-Saharan Africa. The Queen Elizabeth Central Hospital Epidemiology of Resistance in Pregnancy-Associated Malaria (QuEERPAM) study [82] has shown promising results regarding the antenatal use SP and concluded that it does not exacerbate PAM despite the expansion of drug-resistance *P. falciparum*. Thus, in areas with substantial resistance, SP can be used as a component of antenatal care because pharmacologically, SP in the presence of partial host immunity can clear the resistant parasites, with limited placental inflammation. Thus, artemisinin-based combination therapy in IPT must now be evaluated along with priority-based research on evaluating the effectiveness and safety profile of newer antimalarial drugs [83, 84]. Recently, artemisinin-based chemotherapy has been found to be safe for the treatment of *P. falciparum*-associated malaria in pregnant females during first trimester. In near future, quinine-based antimalarial therapy during first trimester might be replaced by artemisinin combination therapy due to the encouraging results shown by Moore et al. [85].

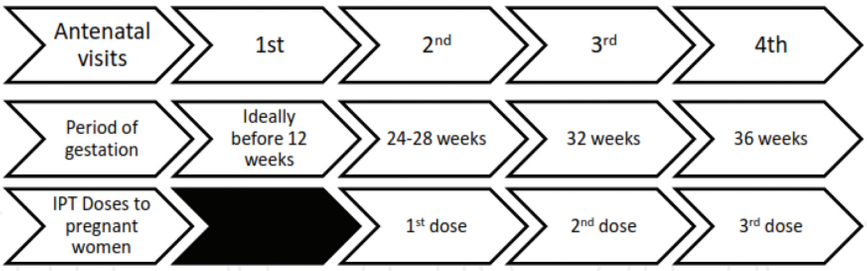

Figure 4. Intermittent preventive treatment (IPT) dosing schedule as recommended by World Health Organization. All women should receive at least two doses of IPT after quickening, as it helps in clearing the parasites at the time of rapid foetal growth. IPT may also be given at fourth visit, if not received the requisite number of doses. Maximum benefit is derived from 2 to 3 doses.

9. Conclusion

Malaria in pregnancy is an important public health problem. It not only affects mother but also hampers the growth of developing foetus. In areas with high transmission rate of ma-

laria, population is relatively immune and patients do not present with symptomatic malaria, which delay the diagnostic workup. Moreover, predominant *Plasmodium* species in such areas is *P. falciparum* that is known to cause sequestration of infected RBCs in placenta leading to compromise in normal physiology of placenta. In areas of low-transmission area, *P. vivax* is the predominant species causing malaria in pregnancy. It mainly causes systemic ill effects as compared to *P. falciparum* infection. Moreover, relapse of malaria could occur due to hypnozoites that could further complicate *P. vivax* infection in pregnancy. The variation in *Plasmodium* species among these two regions is mainly attributed to lack of Duffy-binding proteins that are absent among majority of African population making them resistance to *P. vivax* infection as this protein is required by the parasite to invade reticulocytes.

Diagnosis is established by microscopic examination of peripheral blood smear and by rapid antigen detection kit. However, parasitemia is difficult to establish by microscopy due to sequestration of infected malarial parasite in placenta. Thus, molecular techniques such as PCR, real-time PCR are promising tools that can be utilized in future. Major disadvantage of molecular techniques is that these are costly and require sophisticated laboratory equipment. However, loop-mediated isothermal amplification (LAMP) could provide an answer to such a problem as it can be performed in simple water bath and does not require gel-documentation system as amplified products can be visualized by naked eye.

As majority of pregnant females suffering from malaria are asymptomatic, intermittent preventive chemotherapy is advocated in high transmission areas. However, due to increase in emergence of drug resistance, safety and efficacy of artemisinin-based combination therapy and newer antimalarials should also be established in near future along with implementation of other vector control measures. Research is also required to develop new antimalarials, which are safe in pregnancy for the radical cure of *P. vivax* infection.

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