A brief review on features of falciparum malaria during pregnancy

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Abstract

Malaria in pregnancy is a serious public health problem in tropical areas. Frequently, the placenta is infected by accumulation of *Plasmodium falciparum*-infected erythrocytes in the intervillous space. Falciparum malaria acts during pregnancy by a range of mechanisms, and chronic or repeated infection and co-infections have insidious effects. The susceptibility of pregnant women to malaria is due to both immunological and humoral changes. Until a malaria vaccine becomes available, the deleterious effects of malaria in pregnancy can be avoided by protection against infection and prompt treatment with safe, effective antimalarial agents; however, concurrent infections such as with HIV and helminths during pregnancy are jeopardizing malaria control in sub-Saharan Africa.

Introduction

Malaria is the cause of significant morbidity and mortality worldwide. In 2015, an estimated 212 million cases of malaria occurred globally, with 429 000 deaths. Most cases occurred in tropical countries (90%), mainly among children under 5 years of age.[1] Most cases of malaria are caused by either *Plasmodium falciparum* or *P. vivax,* but almost all deaths are due to falciparum malaria.[2] Malaria can have devastating consequences on both the mother and the developing foetus. The effects of malaria in pregnancy, due to either *P. falciparum* and *P vivax*, include maternal anaemia, spontaneous miscarriage, stillbirth, preterm delivery and foetal growth retardation, which increase morbidity and mortality in infancy.[3-6] In 2007, Dellicour and collaborators estimated that approximately 85 million pregnancies occurred in areas with *P. falciparum* transmission, 54.7 million of which were in areas with stable falciparum malaria, and 31 million were in Africa.[7]

The consequences of falciparum malaria during pregnancy are mediated through a number of mechanisms, and chronic or repeated infections and co-infections have insidious effects. The susceptibility of pregnant women to malaria is due to both immunological and humoral changes,[8,9] on which research on a malaria vaccine are focused. The adverse effects of malaria in pregnancy vary geographically by malaria transmission intensity. This is thus an important preventable infection, and access to safe, effective antimalarial drugs remains essential. The aim of this study was to synthesise the empirical literature in order to obtain a comprehensive understanding of the pathophysiology, histology and immunology, clinical manifestation and epidemiological features of malaria during pregnancy and also effective antimalarial agents, prevention and co-infections in tropical areas of Africa. A literature search was performed to identify reports on malaria and pregnancy, comprising original research and systematic reviews. No restriction was set on time of publication, but only peer-reviewed publications in English in Medline and PubMed were accessed. The terms used were: malaria AND pregnancy OR malaria AND pregnant OR plasmodium AND pregnancy malaria AND pregnant AND pathophysiology OR histology OR immunology OR clinics OR epidemiology OR antimalarial OR prevention OR HIV AND/OR helminths. Articles were screened on the basis of title and abstract. The flow of retrieval is shown in Figure 1. Recommendations and health policy with regard to malaria during pregnancy were retrieved from the WHO library.

Pathophysiology and histology of placental malaria

P. falciparum can parasitise red blood cells (RBCs) and then adhere to the linings of small blood vessels, thus obstructing perfusion in organs including the heart, lung, brain, liver, kidney, subcutaneous tissues and placenta.[10,11] Sequestration in the placenta is different from that in other organs, as the RBCs accumulate in the intervillous space[12] such that the parasite density is often higher than in peripheral blood.[10] The sequestration allows parasite maturation on the placental endothelium, where mature trophozoites and schizonts are often observed.[13,14] Sequestration is probably possible only from the fourth month of pregnancy, when the anatomical structures of the placenta are already formed.[15] Lacunar formations in the trophoblast appear between the 10th and 21st day but do not contain maternal blood until the 12th week of pregnancy.[15,16] The pathophysiological processes that cause adverse foetal effects of malaria in pregnancy are due mainly to accumulation of parasitised RBCs in placental intervillous spaces.

Histologically, inflammatory remodelling is characterized by infiltration of phagocytic cells (monocytes).[17-21] Sequestration of infected erythrocytes in the placenta triggers beta-chemokine secretion by maternal mononuclear cells,[22-24] and macrophages and monocytes, attracted by chemotaxis, predominate in the intervillous space, resulting in modification of the spiral microvessels.[25]

These histological changes form a mechanical barrier that reduces intra-placental blood flow and may lead to foetal hypoxia.[26] The process has been suggested as a cause of intrauterine growth retardation and therefore low birth weight,[27-29] although it may not be solely responsible,[30] as disturbance of the transport of nutrients into the placenta by inflammatory lesions may also play a role.[31-34]

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Placental malaria is determined either on stained slides prepared from placental blood or in stained placental biopsies, a much more sensitive method for detecting placental parasitaemia,[35] which can detect infections preceding delivery by up to one month by observation of the product of digestion of haemoglobin by the parasite - malaria pigment or haemozoin in histological sections. The pathological classification proposed for the phases of placental infestation[18] is: i) no infection: parasites and malaria pigment absent; ii) acute infection: parasites present, malaria pigment absent; iii) chronic infection: parasites and malaria pigment present; and iv) past infection: no parasites, malaria pigment present.

Immunological changes related to malaria during pregnancy

Specific humoral immunity to malaria in pregnant women

All women are not equally susceptible to malaria. The frequency and severity of malaria are greater during a first pregnancy than in subsequent ones,[36,37] and parasitaemia decreases with parity and maternal age.[38] People living in malaria-endemic areas who are repeatedly bitten by mosquitoes infected with *Plasmodium* develop a certain antigenic reaction and immunity due to immunoglobulins G (IgG), which targets surface antigens of infected erythrocytes known as variant surface antigens VSAs), which are produced by the parasites. They are encoded by a number of genes, organized into multigene families in the parasite chromosomes, and are involved in the adhesion of infected mature erythrocytes (over 18 h after invasion) in the tissues. The gradual acquisition of partial immunity with repeated exposure to *P. falciparum*-infected mosquito bites (in areas where malaria transmission is stable and intense) is due mainly to acquisition of IgG directed against the most numerous VSAs present in the parasite population.[39,40] In pregnant women, the VSA expressed by parasitised RBCs that mediate adhesion to chondroitin sulphate A (CSA) and hyaluronic acid on the syncytiotrophoblasts that line the placental intervillous spaces have unique antigenic properties;[14] they are fundamentally different from the corresponding antigens expressed on the infected erythrocyte surface in nonplacental *P. falciparum* infections, and are the main target of IgG.[9,41]

The parasite ligand that mediates adhesion of parasitised RBCs to CSA is a conserved antigen, the recognition of which requires a significant change in plasma IgG,[42] which pointed to the existence of pregnancy-specific VSAs (VSA_{PAM}).[43] The dominant VSA on the surface of parasitised RBCs is *P. falciparum* erythrocyte membrane protein 1 (PfEMP1), which is encoded by the *var2* multigene family.[14,26] These VSA_{PAM} are also collectively referred to as VAR2CSA;[14,26,44-46] other receptors could be involved.[45,47] Several studies have demonstrated the integral role of VAR2CSA in placental malaria (reviewed in [48]). The extracellular region of VAR2CSA includes an N-terminal sequence, six cysteine-rich Duffy binding-like domains and interdomain regions that increasingly appear to play a key role in the adhesion and immunogenicity of recombinant VAR2CSA protein fragments.[49,50]

In non-pregnant women and in men, the antibodies do not recognize VSA_{PAM},[43,51] and women living in malaria-endemic areas during their first pregnancy do not yet have specific antibodies and are therefore highly susceptible to malaria infection. In subsequent pregnancies, exposure to VSA_{PAM} induces the production of specific IgG,[42,43,52-54] which is detectable at 20 weeks in the first pregnancy but appears earlier and more rapidly in subsequent pregnancies, decreasing after childbirth.[55,56] It has been shown experimentally that the serum of multigravidae women exposed to *P. falciparum* malaria inhibits adhesion to CSA of infected erythrocytes from pregnant women, while no inhibition was observed with sera from primigravidae women in early pregnancy or from men.[42]

Others immunological changes related to the susceptibility of pregnant women to malaria

Pregnancy is associated with decreased immunity. The high protein requirements associated with nutritional deficiency explain a failure of gamma-globulin production, and immunosuppression due to increased cortisol levels in maternal blood has also been proposed.[57-60] The decrease in cellular immunity during pregnancy makes women susceptible to the infections that are usually controlled by this type of immunity,[61,62] including malaria.[63] The frequency of malaria attacks and hyper-parasitaemia during pregnancy have been linked to the state of transient immunosuppression, while humoral immunity against malaria is not affected.[64,65]

Clinical manifestations of malaria in pregnant women

In regions with high rates of transmis-

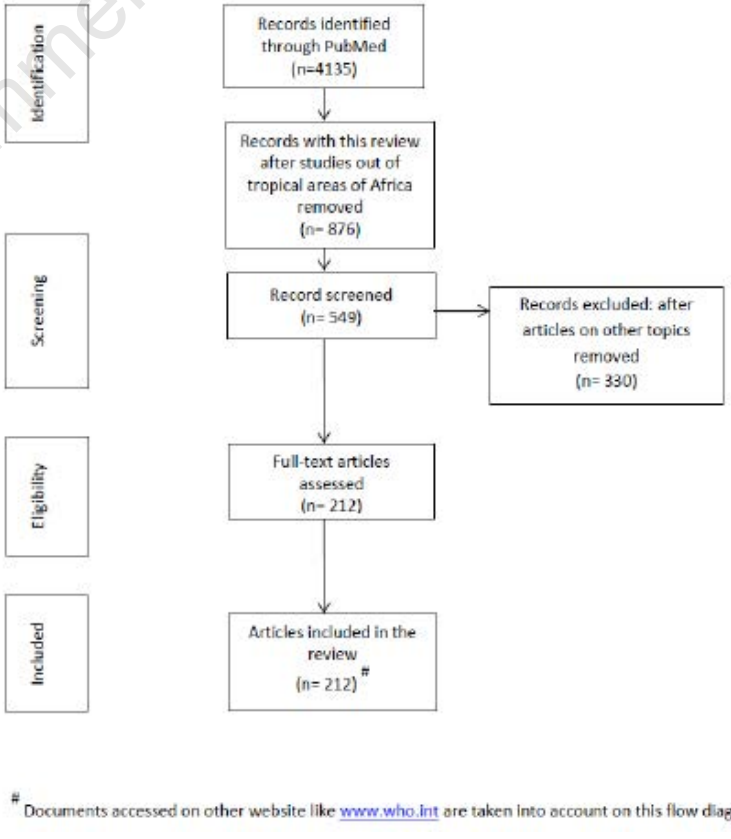

Figure 1. Flow diagram of the numbers of articles reviewed.

sion of malaria, women have considerable immunity to malaria by the time they reach child-bearing age. Nevertheless, they are susceptible to placental malaria during their first or second pregnancy and less so with subsequent pregnancies.[66] Pregnant women malaria infection more frequently have a higher density of parasites, more malaria episodes, anaemia, severe malaria and mortality. The negative effects on infants include low birth weight due to in utero growth retardation, premature birth, abortion, intrauterine death, neonatal mortality, infant mortality and congenital malaria. Some of the consequences of malaria in pregnancy were described at the beginning of the 20th century[67,68] and then later.[69-74] Malaria makes a normal pregnancy a pathological pregnancy,[75] although its effects manifest differently by gestational age.

Low birth weight and maternal anaemia are major public health problems. At national level, the indicators of malaria control for pregnant women are the percentage of children with a low birth weight and the percentage of women with anaemia during the third trimester of pregnancy.[76] Anaemia due to malaria in pregnant women is defined by a haemoglobin concentration ≤11 g/dL.[77] The syndrome is multifactorial, and its mechanism is still poorly understood but is due to both the destruction of infected and uninfected erythrocytes and inhibition of erythropoiesis. *P. falciparum* induces the production of mediators and inhibitors of erythroid precursors,[78-80] such as macrophage migration inhibitory factor,[81] which is increased in the placenta of infected pregnant women and leads to suppression of the formation of erythroid colonies. It acts synergistically with TNF-α and interferon-γ, which also inhibit haematopoiesis.[82]

In endemic countries, a low birth weight is often associated with intrauterine growth retardation and premature delivery (<37 weeks of gestation).[5,83,84] Malaria and high placental parasitaemia increase the risk for preterm delivery.[85-87]

Epidemiological features of malaria in pregnant women

It has long been recognized that the clinical manifestations of malaria in a community are determined by the degree of endemicity of the infection in the local environment and by the age-specific levels of immunity acquired through exposure to infection.[65] Tables 1 and 2[88-104] detail some of the prevalence of malaria in pregnant women in high-transmission and in lower-transmission areas are, respectively.

In areas of intense, stable transmission of *P. falciparum*, partial immunity leads to clinically latent malaria during pregnancy. Infection is suspected from maternal anaemia and a low-birth-weight infant.[105-107] The best epidemiological indicator of malaria during pregnancy is the prevalence of placental infestation with *P. falciparum*.[99,108] Nevertheless, the existence of a correlation between parasite load in peripheral blood and cord blood remains controversial. For example, Brabin and Rogerson[109] reported a correlation between these values, while Ismail and colleagues[18] reported no parasitaemia in 69% of samples of peripheral blood but evidence of infection in placental samples. The differences in the results are due partly to geographical variations in malaria epidemiology and partly to the laboratory methods used. In a meta-analysis of 20 studies of peripheral blood and placental parasitaemia, 9% of placentas and none of the peripheral blood samples were infected.[109] The sensitivity of microscopy for detecting parasites in the placenta is, however, much lower than that of polymerase chain reaction methods.[110]

The incidence of malaria episodes and the parasite density decrease with the number of pregnancies, and less excess malaria is observed with subsequent pregnancies.[111-115] In low-transmission areas, women of all gravidities are susceptible to symptomatic, severe maternal disease: miscarriage, stillbirth and congenital malaria are common complications, and malaria is an important cause of low birthweight.[116,117]

Safety and efficacy of antimalarial agents in pregnant women

The choice of antimalarial drug for pregnant women depends on their tolerance and on the absence of toxicity. The choice should also take into account the period of pregnancy and local efficacy against *P. falciparum*

Chloroquine

Chloroquine has been widely used to treat *falciparum* malaria during pregnancy. In 1986, WHO recommended that pregnant women living in malaria-endemic areas receive chloroquine chemoprophylaxis.[118] Subsequently, alarming evidence of resistance of the malaria parasite to this drug emerged. Steketee and colleagues[119] reported a 42% treatment failure in Siaya District, Kenya, in 1986 and a 46% failure 10 years later.[120] In the United Republic of Tanzania

Table 1. Median prevalence of maternal malaria parasitaemia in peripheral blood during pregnancy in areas with stable transmission.

Study period	Country	Sample size	Prevalence (%)	References
2006-2008	Burkina Faso	1034	39.2	88
2010	Burkina Faso	579	18.1	89
1999-2001	Cameroon	770	32.8	90
2005-2006	Gabon	203	34.4	91
1992	Gambia	537	27%	92
2009	Ghana	363	28.4	93
1994-1996	Kenya	713	45	94
2002-2003	Malawi	1869	20.1	95
1996	Uganda	853	62.1	96
1994-1995	United Republic of Tanzania	1177	35.2	97
1993	United Republic of Tanzania	389	65.5	98
1989	Central African Republic	229	35.6	99

Table 2. Median prevalence of maternal malaria parasitaemia in peripheral blood during pregnancy in areas with low transmission.

Study period	Country	Sample size	Mode of transmission	Prevalence (%)	Reference
1998	Uganda	537	Meso-endemic	8.6	100
2003-2004	Sudan	836	Meso-endemic	26.2	101
2000	Ethiopia	1774	Seasonal	2.3	102
2001	Sudan	175	Seasonal	17.4	103
2003	Sudan	744	Seasonal	13.7	104

in 1991, treatment failed in 35% of 49 pregnant women.[121] Curiously, chloroquine was reported to be 100% effective against falciparum malaria in a study in northern Nigeria in 1993.[122] In Malawi, Heymann *et al.*[123] found that 37% of pregnant women failed to eliminate *P. falciparum* after 4 weeks of supervised chemoprophylaxis with chloroquine. In 1990, 37.1% of women in the Central African Republic had placental *P. falciparum* malaria, despite chemoprophylaxis.[99] In Benin, chemoprophylaxis with chloroquine for 7 months during pregnancy did not prevent placental parasitaemia in 12.7% of women.[124] A study in Burkina Faso of the efficacy of chloroquine and sulfadoxine-pyrimethamine (SP) for the prevention of malaria in pregnancy showed a placental parasitaemia prevalence of 18.8% and 10.6%, respectively.[125]

Because of the increasing resistance of malaria parasites to chloroquine, WHO recommended in 2004 that SP be used as an alternative for the prevention of malaria during pregnancy.[126]

Sulfadoxine-pyrimethamine

SP is used in pregnant women even though knowledge about its safety is limited. The only suspected form of toxicity is kernicterus with neurotoxicity due to unconjugated bilirubin. Sulphonamides can de-conjugate bilirubin bound to albumin, which would theoretically increase the risk for kernicterus if SP were administered during the third trimester of pregnancy.[127]

Two studies indicate that the SP clears parasites within 48-72 h.[128] In Malawi, Schultz and colleagues[129] demonstrated that two curative doses of SP (one in the second trimester and a second in the third trimester) significantly reduced placental parasitaemia. WHO currently recommends intermittent preventive treatment in pregnancy (IPTp) with SP, with two curative doses 1 month apart from the second trimester of pregnancy, the first dose being given between weeks 14 and 20 and the second at least 1 month after the first.[126] More recently, WHO recommended that IPT be given at every antenatal clinic visit if the visits are at least 1 month apart.[130]

Mefloquine

Mefloquine has a long half-life, making it useful for IPTp. In Malawi, administration of mefloquine in the second and third trimesters of pregnancy was effective, with good tolerance, although dizziness and abdominal pain were reported.[131] In Benin, however, a clinical trial showed that two doses of 15 mg/kg mefloquine in the second and third trimesters, although significantly more effective than SP, were often accompanied by side-effects such as vomiting, dizziness and physical asthenia; a case of neuropsychiatric disorder was also noted.[132]

Amodiaquine

Steketee and colleagues[133] observed a cure rate of 78% with amodiaquine among women who had parasitaemia under chloroquine chemoprophylaxis. The safety of amodiaquine in pregnancy and especially for the prevention of malaria is not documented.[134] The drug is considered to be well tolerated by pregnant women, but agranulocytosis, one of its serious side-effects, limits its use in prophylaxis.

Quinine

Quinine, which is considered to be well tolerated during pregnancy, is indicated only for curative treatment. The recommended doses must be respected to avoid abortive effects.[135-139] Quinine has replaced chloroquine in the treatment of malaria in pregnant women, but few clinical trials have been conducted. Harmful effects of quinine during pregnancy have been recognized for a long time, and induction of uterine contractions has been reported.[140]

A study of the safety and efficacy of quinine (30 mg/kg per day for 7 days) in Thailand showed side-effects such as dizziness in 42% of women,[141] with 4% parasitaemia on day 7 of treatment and 23% resurgence of malaria on day 28 of clinical monitoring. A study of the efficacy of the combination of quinine and clindamycin in the second and third trimesters resulted in a 67% cure rate (95% confidence interval, 43-91%) by day 67 of clinical monitoring.[142] A case of *P. falciparum* malaria resistant to quinine *in vivo* and *in vitro* was reported in 1988.[143] Hence, a combination of quinine (30 mg/kg per day) and clindamycin (15 mg/kg per day) for 7 days has been suggested for effective treatment of malaria.[143,144]

Artemisinin derivatives

Artemisinin derivatives are generally well tolerated by pregnant women. Use of drug combinations such as artemether–lumefantrine in the second and third trimesters of pregnancy did not increase the risks for spontaneous abortion, stillbirth or congenital abnormalities when compared with quinine.[145] The PREGACT study group conducted a randomized, open-label trial between June 2010 through August 2013 to compare the safety and efficacy of artemether-lumefantrine, amodiaquine–artesunate, mefloquine–artesunate and dihydroartemisinin-piperaquine in Burkina Faso, Ghana, Malawi and Zambia in women in the second or third trimester of pregnancy. Artemether-lumefantrine was associated with the fewest adverse effects and acceptable cure rates but provided the shortest post-treatment prophylaxis, while dihydroartemisinin–piperaquine was most effective and had an acceptable safety profile.[146]

It has been suggested that artemether-lumefantrine is safe during the first trimester.[147] A study of birth outcomes of women inadvertently exposed to this combination during the first trimester found no adverse outcomes.[148] Because of insufficient data on the safety of these drugs during the first trimester of pregnancy, however, WHO recommends their use only during the second and third trimesters.[126]

Dapsone and chlorproguanil

In a clinical trial in Uganda, minor side-effects (headache, nausea, sub-jaundice) were reported after use of dapsone–chlorproguanil during pregnancy.[149] A case of hyperbilirubinaemia due to dapsone administered to a pregnant woman for leprosy was reported.[150] Proguanil and chlorproguanil are well tolerated during pregnancy and have been recommended for prophylaxis against malaria for more than 40 years. Nevertheless, studies of pharmacokinetics showed altered metabolism of proguanil in pregnancy, suggesting that the dose should be increased for pregnant women,[151-153] which poses a problem of adjustment in the combination with dapsone. In Kenya, Keuter and colleagues[154] reported that a single dose of chlorproguanil (1.2 mg/kg) in combination with dapsone (2.4 mg/kg) was more effective and better tolerated than chloroquine.

The combination of dapsone with pyrimethamine was well tolerated by both the mother and the foetus during pregnancy, with good efficacy against malaria infection.[155-158]

Atovaquone-proguanil

Atovaquone, usually used to treat *Pneumocystis carinii* infections, has not been studied for tolerance during pregnancy. McGready and colleagues[152] reported low plasma concentrations during pregnancy (almost two thirds less than in non-pregnant women) of atovaquone and proguanil, which are used in combination for the treatment of malaria. Use of this combination is still limited because of rapid selection of mutants resistant to atovaquone due to mutations of the cytochrome-b gene of *P. falciparum*.[159-161]

Malaria prevention during pregnancy

Since 1980, African countries in which malaria transmission is stable have opted for chemoprophylaxis of malaria during

pregnancy with chloroquine.[118] The first cases of resistance of *P. falciparum* to chloroquine were reported in Africa in 1980, and cases emerged in Asia during the 1980s. Given the reduced efficacy of chloroquine, many studies have been conducted to find an alternative for preventing malaria during pregnancy. SP has proved to be promising, as shown in many trials after the work of Schultz and colleagues in Malawi.[129] WHO recommends three strategies to prevent malaria in pregnant women living in endemic areas:[126] i) four antenatal care visits, during which at least two doses of SP spaced at least 1 month apart are administered in the second trimester of pregnancy; ii) use of insecticide-treated nets to reduce the number of infective bites; and iii) immediate, adequate treatment of malaria. IPTp involves administering curative doses of SP to asymptomatic women (two doses for women with negative HIV status and three doses for women infected with HIV), with at least 1 month between consecutive doses. Because of the risk of embryotoxicity with SP, it should be administered from week 16 of amenorrhoea or week 14 of pregnancy.[126] This schedule was updated by WHO in 2012 with the recommendation that IPTp be given at every antenatal clinic visit if the visits are at least 1 month apart.[130]

IPTp with SP and use of mosquito nets impregnated with long-lasting insecticide significantly reduce the burden of malaria during pregnancy, and the interventions are cost-effective.[162-168] IPTp with SP (25 mg sulfadoxine and 1.25 mg pyrimethamine per kg body weight) reduces the adverse effects of malaria on maternal and fetal health during pregnancy[129,169-172] and can last up to 60 days in areas where *P. falciparum* strains are fully susceptible.[173,174] IPTp clears the placenta of possible parasites (therapeutic effect) and prevent further infection (prophylactic effect).[175]

Currently, the main obstacle to this strategy is the emergence and increasing frequency of resistance of *P. falciparum* to SP, already observed in many sub-Saharan African countries.[176-183] The emergence of resistance is due to accumulation of point mutations in the genes encoding dihydrofolate reductase (DHFR) and dihydropteroate synthase (DHPS), two key enzymes in the metabolic chain of *P. falciparum*. Pyrimethamine and sulfadoxine inhibit DHFR and DHPS, respectively. The number of mutations is correlated with the level of resistance of *P. falciparum*, as shown *in vitro*. The triple mutant N51I/C59R/SN108 in the *DHFR* gene and the double A437G/K540E mutant in the *DHPS* gene alone or in combination are associated with treatment failure with SP.[184] Therefore, changes in the level of resistance should be monitored by analysing these resistance markers,[185] with urgent research for alternatives for malaria prophylaxis during pregnancy. A study in Uganda showed that IPTp with dihydroartemisinin-piperaquine resulted in a lower burden of malaria than did treatment with sulfadoxine-pyrimethamine.[186] The study suggested administration of dihydroartemisinin–piperaquine every 4 weeks from as early as 16 weeks of gestation, which is in the line with the WHO recommendation.[130]

Will vaccination against malaria in pregnancy become possible? An ideal vaccine should simulate all the protective responses that occur in natural infections. A good current candidate is the VAR2CSA antigen, the structure of which differs from that of other PfEMP1 antigens. Identification of a distinct PfEMP1 variant, VAR2CSA as the dominant surface antigen and a clinically important target for a protective immune response to malaria in pregnancy has raised hope.[187]

The *VAR2CSA* gene displays significant polymorphism, as demonstrated by the number of possible unique antigens that have been produced; however, it is better conserved than other *VAR* genes, and VAR2CSA retains 75-83% of its amino acids between isolated strains.

Thus, a limited number of antigens is possible, although the degree of antigenic variation among globally isolated parasite lines has not been determined.[188] Research on a VAR2CSA-based vaccine includes mapping CSA-binding sites and antibody epitopes, defining Duffy binding-like domains preferentially recognized by immune sera and assessing functional activity by antibodies raised against recombinant Duffy binding-like domains.[189,190] In 2014, the European Vaccine Initiative hosted a meeting to harmonize clinical development, immunoassays and standards to assess candidate vaccines against placental malaria. The panel concluded that early clinical trials should be conducted of VAR2CSA-based vaccine candidates in women in areas endemic for *P. falciparum* malaria before their first pregnancy.[191] Currently, a VAR2CSA-based vaccine candidate, PAMVAC, is being tested in Beninese women by an Europian Union funded multi-country consortium (PlacMalVac project, ClinicalTrials.gov Identifier: NCT02647489).[192]

Co-infections with malaria during pregnancy: an emerging challenge for control

Co-infection with HIV

Co-infection with HIV increases susceptibility to malaria in pregnant women. Malaria and HIV both cause substantial morbidity and mortality, particularly in sub-Saharan Africa, and it has been estimated that an additional 500 000 malaria infections occur each year in pregnant women due to decreased immunity after HIV infection.[193] Concurrent HIV infection and malaria during pregnancy is a very serious problem for both maternal and child health.[194] Pregnant women infected with HIV are more likely to have malaria episodes,[195,196] and the association has a synergistic effect, particularly on severe anaemia, to increase maternal mortality.[197,198] Several studies (reviewed in [193]) also show an increased prevalence of low birth weight (<2500 g), preterm delivery and intrauterine growth retardation in co-infected women. Co-infection with malaria is also associated with an increased HIV load, increasing the risk for mother-to-child transmission of HIV.[199,200]

Concurrent management of malaria and HIV infection in pregnancy in sub-Saharan Africa is challenging. Medications against the two infections must be administered with pcaution because of interactions and overlapping toxicity (reviewed in [201]). For example, co-administration of quinine and protease or non-nucleoside reverse transcriptase inhibitors can be cardiotoxic by inhibiting cytochrome P450 enzyme activity.[202]

HIV-positive women who are not taking co-trimoxazole prophylaxis for opportunistic infections can take a monthly dose of SP,[203] which is significantly more effective than the two-dose regimen in these women and does not depend on the degree of SP resistance.[170,203,204] Co-trimoxazole has been shown to decrease malaria morbidity in children and HIV-infected adults[205-207] because it shares the same drug targets as SP and is hence effective against protozoan infections.[208] The first report of the greater effectiveness of co-trimoxazole than IPTp with SP against malari in HIV-infected pregnant women was published in 2011.[209] In 2014, Denoeud-Ndam *et al*.[210] showed that co-trimoxazole alone provided adequate protection against malaria in HIV-infected pregnant women. In light of the increasing prevalence of antifolate-resistant parasites,[211] however, it is uncertain whether SP and co-trimoxazole will remain effective against malaria.

Infection with helminths with and without HIV

Emerging evidence during the past decade has implicated intestinal worm (helminth) infections as important causes of adverse pregnancy outcomes and impaired women's reproductive health (reviewed in [212]). Hookworms are important public health threats for women of reproductive age, and a recent study from Gabon reported a 66% prevalence of intestinal helminths in pregnant women.[213] In sub-Saharan Africa, hookworm infection is highly prevalent, with almost 99 million cases in women, 37.7 million among women of reproductive age and 6.9 million among pregnant women.[214,215]

The worldwide distribution of helminths, malaria and HIV overlap.[216] Co-infection with helminths and malaria parasites cause significant morbidity in the host, particularly in the presence of HIV infection. Malaria in pregnancy due to *P. falciparum* and helminthic infections in HIV-infected pregnant women are severe public health problems. The prevalence of both malaria and helminths in HIV-infected pregnant women in Ruhuha province in Rwanda was estimated to be 10.1%.[217] A study in Kenya found that mother-to-child transmission of HIV was significantly higher when the women were co-infected with one or more helminths (48%) than in women with no helminth infection (10%; P<0.01; adjusted odds ratio, 7.3; 95% confidence interval, 2.4-33.7).[218]

Conclusions

Malaria is the commonest tropical parasite-transmitted disease during pregnancy, and, although the problem has been studied widely, there are still major challenges. Malaria infection during pregnancy requires rapid diagnosis and appropriate treatment to avoid complications for the woman and her foetus. Safe, new, effective antimalarial agents are urgently needed, in view of the growing resistance of *P. falciparum* to IPTp, as prophylactic chemotherapy is the main tool for controlling malaria during pregnancy. Special attention should be paid to the management of co-infection with HIV and with helminths, and studies of drug interactions between antiretroviral and antimalarial agents when co-administered in pregnancy are essential.

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