

MALARIA IN PREGNANCY: MORBIDITIES AND MANAGEMENT

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ABSTRACT

Malaria infection during pregnancy remains an important public health concern especially in the tropics with substantial risk for the mother, her fetus and the neonate. More than 25 million African women in malaria endemic areas get pregnant and are at risk of infection with *Plasmodium falciparum*. Several pregnancy complications including miscarriage, preterm labor, intrauterine growth restriction (IUGR) and intrauterine fetal death (IUFD) have been associated with malaria. In early pregnancy treatment options are very limited partly due to drug resistance and the uncertainty about the safety of some antimalarials in pregnancy. Quinine still remains safe in all trimesters. A package of interventions for the prevention and control of malaria in the African Subregion during pregnancy has been recommended by the World Health Organization (WHO). These include intermittent preventive treatment (IPT), use of insecticide treated nets (ITNs) and access to effective case management for malaria illness and anemia.

Keywords: malaria in pregnancy, treatment, insecticide treated nets, intermittent preventive therapy.

INTRODUCTION

Malaria infection during pregnancy remains an important public health concern especially in the tropics with substantial risk for the mother, her fetus and the neonate¹. It's estimated in 2010 that 216 million episodes of malaria occurred worldwide with resultant 655,000 deaths². Up to 91% of malaria burden in that year occurred in Africa.

Malaria costs Africa an estimated 12 billion US Dollars in lost production annually³. At least 3,000 people die from malaria every day. Malaria also accounts for 40% of public health expenditure, 50% of outpatient visits and 30-50% of hospital admissions in areas where transmission is high^{4,5}.

Pregnant women and their infants are highly vulnerable to malaria. More than 25 million

African women in malaria endemic areas get pregnant and are at risk of infection with *Plasmodium falciparum*^{3,6}. Among pregnant women, studies have shown that the highest prevalence of malaria infection occurs in the 2nd trimester, with infection rate at delivery and in the postnatal period approximating to levels in non-pregnant women⁷.

Several pregnancy complications like miscarriage, preterm labor, intrauterine growth restriction (IUGR) and intrauterine fetal death (IUFD) have been associated with malaria

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infection. These complications are produced by maternal and fetal hyperpyrexia, severe maternal and fetal anemia as well as placental parasitization⁸. Areas with seasonal transmission are endemic for malaria infection; usually confer a protective semi-immunity against *Plasmodium falciparum* to adult women during the first 10-15 years of life¹⁶. Adult women living in areas of unstable non endemic transmission, have no significant level of immunity, are more likely to be symptomatic when infected and at greater risk of having severe disease and of death.

Pathophysiology

Malaria infection develops via two phases: one that involves the liver (exoerythrocytic phase) and one that involves the red cell (erythrocytic phase). When an infected mosquito pierces skin to take a blood meal, sporozoites in the mosquito's saliva enter the blood stream and migrate to the liver where they infect hepatocytes, multiplying asexually and asymptotically for a period of 8-30 days.

After potential dormant period in the liver, these organisms differentiate to yield thousands merozoites, which following rupture of their host cells escape into the blood and infect red cells to begin the erythrocytic stage of the life cycle. The parasite escapes from the liver undetected by wrapping itself in the cell membrane of the host liver cell.

Within the red cell the parasites multiply further again asexually, periodically breaking out of their host cells to invade fresh red blood cells, thus the classical descriptions of waves of fever arise from these simultaneous waves of merozoites escaping and infecting red blood cells. Other merozoites develop in to immature

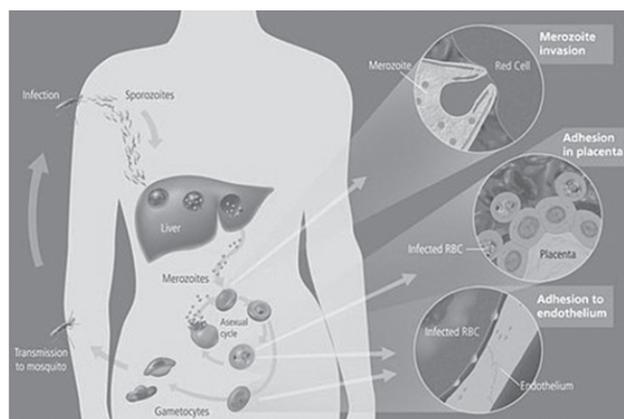
gametes or gametocytes. When a fertilized mosquito bites and infected person, gametocytes are taken up with the blood and mature in the mosquito gut, fusing to form zygote which develops in to new sporozoites.

What is the risk of vertical transmission of malaria infection to the baby?

Vertical transmission to the fetus can occur particularly when there is infection at the time of birth and the placenta and cord are blood film positive for malaria (Appendix 2).

All neonates whose mothers developed malaria in pregnancy should be screened for malaria with standard microscopy of thick and thin blood films at birth and weekly blood films for 28 day

Malaria transmission Life cycle



Effect of Pregnancy on Malaria

Pregnant women are more susceptible to malaria infection when compared to non-pregnant women. They are more likely to become infected with *Plasmodium falciparum* malaria with more tendency towards increased severity of the disease^{9,10,11}. This is partly due to transient depression of cell mediated immunity that occurs during pregnancy¹².

Because of enhanced pancreatic B cell function in pregnancy, pregnant women are also prone to hyperglycemia and are at risk of symptomatic hypoglycaemia when infected with *plasmodium falciparum*, as a result of maternal

hyperinsulinemia, parasite glucose requirements, maternal glucose requirement during febrile illness and decreased oral intake related to anorexia and emesis¹³. Chondroitin sulphate A (CSA) is a ligand that is found on the placental syncytiotrophoblast. This ligand is not readily accessible on cells elsewhere in the body. Parasitized red blood cells (RBCs) found in the placentae of primigravidae manifest a remarkable preference to binding chondroitin sulphate A (CSA). This could explain the susceptibility of primigravidae to clinical malaria^{24,25}. Studies have shown that anti adhesion immunoglobulin G antibodies against chondroitin sulphate A binding parasites are associated with protection of maternal malaria that is developed in subsequent pregnancies¹⁶.

Effect of Maternal Malarial Infection On Pregnancy

The effect of malaria in pregnant woman varies with several factors such as the woman gravidity, level of immunity, trimester of pregnancy and the presence or absence of comorbidity¹⁴. Low parity, especially primigravidae and younger age are more susceptible to malaria infection¹⁵. "Pregnancy-associated malaria is characterized by placental malaria and the sequestration of malarial parasites"²⁰. Accumulation of plasmodium infected erythrocytes in the intervillous space, in the placenta, causing histologic changes including leukocyte-induced damage to the trophoblastic basement membrane is referred to as placental malaria²¹. This infection can occur in the absence of clinical symptoms²². Placental malaria and maternal anemia can precipitate preterm delivery leading to IUGR²³. Malaria in pregnant women is an important cause of stillbirths, and low birth weight, acute

respiratory distress syndrome ARDS may develop in adults and in up to 25% of pregnant women.

Management

Table 1: Schedule of Treatment of Acute Malaria

Drug	Dosage	Route	Trimester	Complication
Chloroquine			All trimester	
Quinine	20 mg/kg loading dose in 5% dextrose over four hours and then 10 mg/kg over four hours.	Intravenous	All trimesters	
Quinine+Clindamycin	450mg,QDSx7days	Oral	All trimesters	
ACT:artemesin-combination-therapy	2.4 mg/kg at 0, 12, 24 hrs, then Oral	Intravenous	Second/third trimester only	
Artesunate	2 mg/kg three day course of	Oral		
Riamet	(artemether (20mg) / lumefantrine (120mg) atovaquone-proguanil (malarone).	Oral		
Malarone				
Primaquine	15 mg and 30 mg respectively, daily for 14 days ⁵⁴	Oral	Avoid in all trimesters	

Admit pregnant women with uncomplicated malaria to hospital and pregnant women with severe and complicated malaria to an intensive care unit. Intravenous artesunate are the treatment of choice for severe falciparum malaria. Use intravenous quinine if artesunate is not available. Use quinine and clindamycin to treat uncomplicated P. falciparum (or mixed, such as P. falciparum and P. vivax). Use chloroquine to treat P. vivax, P. ovale or P. malariae. Primaquine should not be used in pregnancy

Acute Malarial Infection

Malaria during pregnancy has adverse effects to both mother and the fetus. In early pregnancy

treatment options are very limited partly due to drug resistance and the uncertainty about the safety of some antimalarials in pregnancy⁵¹. Nevertheless, pregnant women with malaria must be treated promptly with effective antimalarials to clear the parasites. When treating pregnant women with malaria infection, clinicians have to make treatment decisions based on the epidemiological resistance pattern, the severity of the infection and the available data regarding the safety of the anti-malarials. A Cochrane review highlighted the lack of qualitative data particularly with regard to drug safety in pregnancy; several innovations have since shown the improved risk benefit ratio⁵².

It's preferable to confirm the diagnosis of malaria by laboratory investigations, however, where there is strong clinical suspicion, severe disease or when it's impossible to obtain prompt laboratory diagnosis, presumptive treatment can be commenced with available and safe anti malarials⁵³.

Chloroquine and quinine are safe in all trimesters of pregnancy but resistance is not uncommon especially with chloroquine.

According to the United Kingdom (U.K.) treatment guidelines for severe or complicated malaria, regardless of the species of Plasmodium parasites, artesunate is administered intravenously at a dose of 2.4 mg/kg body weight at 0, 12 and 24 hours, then daily thereafter. Oral artesunate at a dose of 2 mg/kg once daily is substituted for the intravenous one when the patient is well enough to take orally with addition of clindamycin. When there is no oral artesunate, a three day course of Riamet® (artemether (20mg)/lumefantrine (120mg) or atovaquone-proguanil (malarone®) or a seven day course of

quinine and clindamycin at 450mg, three times a day for seven days is administered⁵⁴.

Many antimalarials are considered not safe in pregnancy. Quinine, chloroquine, proguanil, pyrimethamine and sulfadoxine-pyrimethamine are considered safe in first trimester of pregnancy⁵⁵. Among them, quinine remains the most effective and can be used in all trimesters of pregnancy⁵⁶. WHO has also recommended the use of artemisinin combination therapy (ACT) in the first trimester if it's the only treatment available^{55,57}. The other alternative treatment for severe or complicated malaria is the use of intravenous quinine 20 mg/kg loading dose (no loading dose for those who have taken quinine or mefloquine) in 5% dextrose over four hours and then 10 mg/kg intravenously over four hours. In addition, clindamycin at a dose of 450 mg is added intravenously every four hours. Quinine dose should not exceed 1.4 g. oral quinine is substituted for intravenous when the patient can tolerate at a dose of 600 mg three times a day for seven days⁵⁴. Where treatment with intravenous quinine extends beyond 48 hours or the patient has renal or hepatic dysfunction, quinine dosing should be reduced to 12 hourly⁵⁸. For uncomplicated malaria infection due to Plasmodium falciparum, oral quinine is administered at a dose of 600 mg eight hourly and oral clindamycin 450 mg eight hourly for seven days. Those that cannot tolerate oral quinine, Riamet or atovaquone –proguanil combination can be used for uncomplicated malaria⁵⁴. In a situation where pregnant women present with complicated malaria, quinine 10 mg /kg can be administered intravenously in 5% dextrose over four hours every eight hours plus intravenous clindamycin 450 mg every eight hours. When the patient can tolerate oral medications with no vomiting, oral quinine can

be switched at a dose of 600 mg three times a day to complete five to seven days. Oral clindamycin can also be switched at 450 mg three times a day for seven days if the need arise⁵⁴. Non falciparum malaria (*P. ovale*, *P. vivax* and *P. malariae*) are treated with oral chloroquine (base) drug at a dose of 600 mg followed by 300 mg 68 hours later. Then, 300 mg on day two and day three based on the U.K. treatment guidelines⁵⁴. Resistant *P. vivax* is treated like uncomplicated *P. falciparum*⁵⁴. *P. ovale* and *P. vivax* are treated with oral primaquine at a dose of 15 mg and 30 mg respectively, daily for 14 days⁵⁴.

Oral chloroquine at a dose of 300 mg can be administered weekly to prevent relapse until delivery; following delivery, treatment should be postponed until three months after, following G6PD testing⁵⁴. Although exchange blood transfusion has not been proven beneficial in a randomized controlled trial, it has been an option in the treatment of severe malaria since 1974⁵⁹. For severe malaria with parasite density of more than 10%, Centre for Disease Control and Prevention (CDC) recommends exchange blood transfusion. This is assumed to have beneficial effects by removing infected red cells, improving the rheological properties of blood and reducing toxic factors such as parasite-derived toxins, harmful metabolites and cytokines⁵⁹. The fever developed following malaria infections has been associated with premature labour^{60,61} and fetal distress⁶². Treatment with antipyretics like paracetamol at standard dose is found to be effective⁵⁴. Other associated complications like mild to moderate anemia in pregnancy following malaria infection can be treated with ferrous sulphate and folic acid⁵⁴

Prophylaxis

Despite aneed, no effective vaccine currently exists, although efforts to develop one are ongoing. Several medications are available to prevent malaria in pregnancy and to prevent malaria in travellers to malaria –endemic countries.

The 'ABCD' of malaria prevention is a useful formula to remember the components are

- Awareness of risk
- Bite prevention
- Chemoprophylaxis
- Diagnosis and treatment which must be prompt

Intermittent Preventive Therapy

The use of IPT with sulfadoxine and pyrimethamine (SP) for the control of malaria in pregnancy in areas of moderate to high transmission was adopted by the WHO Expert Committee on Malaria in 1998²⁶. Hitherto, the prevention of malaria in pregnancy relied on weekly chloroquine prophylaxis, though chloroquine was effective^{27,28}. Poor compliance was the problem even before the emergence and widespread of drug resistance²⁹.

The purpose of IPT is to reduce the risk of low birth weight (LBW) and maternal anemia by clearing asymptomatic placental and peripheral parasitemia and providing pregnant women with protection against malaria infection between antenatal consultations³⁰. It was recommended by the WHO, the administration of two to three courses of SP (three tablets each contained 500 mg of sulfadoxine and 25 mg of pyrimethamine) after fetal quickening with each course administered not less than one month apart and all before the last four weeks of pregnancy³¹. This IPTp is adopted as a national policy in 37 countries, 33 of which are in Sub-Saharan Africa³².

Data from recent observational studies in Malawi, the first country where IPT-SP was implemented in 1993, revealed reduced effectiveness of SP for IPT³³. There is also a growing concern about the decreasing effectiveness of the two dose regimen of SP for IPT in other countries with high level of resistance to SP especially in Southern and Eastern African region where the prevalence of HIV is highest in the world³⁴. It's similarly observed that the HIV positive women require more doses of SP for IPTp to have effective protection against malaria in pregnancy than women who are HIV negative³⁵.

According to the recent recommendation by the Evidence Review Group (ERG) of the Global Malaria Programme¹, they suggest that, inspite of the increased prevalence in Plasmodium falciparum of molecular markers associated with resistance to SP (based on quintuple mutant dhps/dhfr haplotypes prevalence), in Sub-Saharan Africa, IPT-SP remains effective at preventing peripheral parasitaemia, maternal anemia and clinical malaria during pregnancy and is associated with reduced neonatal mortality³⁶⁻⁴⁰.

The evidence review group (ERG) of the Global Malaria Programme also commented on the number of IPTp doses that need to be administered during pregnancy to achieve the maximal beneficial effect of IPTp¹. An unpublished meta-analysis by Kayentao and colleagues which comprised seven controlled trials conducted in five Sub-Saharan African countries from 1994 to 2008, revealed three more doses of IPTp with SP was superior to the standard two dose regimen, regardless of the HIV status and gravidity of the pregnant woman in preventing low birth weight¹. The study also showed that women who received a median of

four doses of IPTp when compared with those on the two doses regimen also had a lower risk of moderate to severe maternal anemia, maternal malaria at delivery and placental malaria¹.

Other recommendations by the Evidence Review group include the administration of the last dose of IPTp with SP even after 36 weeks of gestation without safety concerns and the administration of IPTp as directly observed therapy¹. Administration of SP to patient on cotrimoxazole prophylaxis is contraindicated. Also the concomitant administration of SP with at least 5 mg of folic acid to pregnant women is contraindicated because folic acid reduces the efficacy of the antimalarial. However, SP can be administered even in an empty stomach¹.

Several studies have mentioned the potential alternatives to SP for IPTp⁴¹⁻⁴³ with mefloquine and azithromycin based combination being the leading candidates under study. A randomized clinical trial in Benin (n=1601) demonstrated mefloquine to be more superior to SP in preventing placental malaria (prevalence 1.7 vs 4.4% of women; p=0.005) and clinical malaria (incidence: 26 cases per 10,000 person-months vs 68 cases per 10,000 person-months; p=0.007)⁴⁴.

Insecticide Treated Nets

It was in 1897 that the transmission of malaria by the bites of Anopheles mosquitoes was discovered by Ronald Ross. Immediately after his discovery, he realized that due to the fact these mosquitoes bite at night, bed nets should be a useful protection against malaria infection⁴⁵. It was in the 1980s when insecticides began to be applied to bed nets, which greatly found to increase their effectiveness in reducing malaria infection even when the bed nets are torn⁴⁵. Fast acting synthetic insecticides, which are certified

safe by WHO like deltamethrin (k-othrine) at 0.025 grams/m² of netting, alphacypermethrin (fendona) at 0.02 grams/m², lampdacyhalothrin (icon) at 0.01 grams/m² and etofenprox (vectron) at 0.20 grams/m² have been available and they all add a chemical barrier to the net's imperfect physical barrier⁴⁵.

Studies have shown that the use of insecticide treated nets reduces anemia and the prevalence and density of malaria parasitemia in pregnancy especially in areas of intense and perennial malaria transmission⁴⁶⁻⁴⁸.

In a systematic review of randomized controlled trials on the benefits of insecticides treated nets for the prevention of malaria in pregnancy; the review showed that women of low gravidity randomized to insecticides treated nets (ITNs) delivered fewer LBW babies and were less likely to experience either miscarriage or abortion⁴⁹. Despite the reduction in malaria infections found in the studies, there was no demonstrable overall effect on mean hemoglobin and data on maternal anemia were inconsistent⁴⁹.

Another trial which was conducted in Thailand Myanmar border compared ITNs to untreated nets. The area is characterized by a highly seasonal *Plasmodium falciparum* and *Plasmodium vivax* malaria infection. The study showed a statistically significant reduction in anemia and fetal loss in all gravidae but no benefit on birth weight or gestational age⁵⁰.

Postnatal Care

Chemoprophylaxis for breastfeeding women Mefloquine (5mg/kg once a week) is the recommended drug of choice for prophylaxis in the second and third trimesters for chloroquine-resistant areas. With very few areas in the world free from chloroquine resistance, mefloquine is

essentially the only drug considered safe for prophylaxis in pregnant traveller. Vertical transmission to the fetus can occur particularly when there is infection at the time of birth and the placenta and cord are blood film positive for malaria.

All neonates whose mothers developed malaria in pregnancy should be screened for malaria with standard microscopy of thick and thin blood films at birth and weekly blood films for 28 days.

Pregnancy Counseling

Women planning pregnancy and travelling to a destination where there is a risk of contracting malaria should be advised there may be harmful consequences for the pregnancy. Prophylaxis is not 100% effective and malaria is associated with increased risk of miscarriage. Women should be advised not to travel or to choose an alternative destination. If it not possible to delay either the pregnancy or the travel plan, advice from a specialist with current experience of malaria should be sought (Box 2). Chloroquine and proguanil are not efficacious in chloroquine-resistant areas and cannot be recommended because of this.⁸⁵ There are very few chloroquine-sensitive areas remaining. To avoid completely any potential adverse drug effects from preconceptual and first-trimester exposure, it is advisable to wait for complete excretion of the drug, if it was taken for prophylaxis, before becoming pregnant (Table 3). Nevertheless, unplanned conception while taking malaria prophylaxis is not considered a reason to recommend termination of pregnancy, owing to the low risk of teratogenicity.

CONCLUSION

Malaria is a mosquito-borne infectious disease caused by the genus plasmodium, beginning with bite from an infected female anopheles. Several pregnancy complications like severe anaemia miscarriage, preterm labor, intrauterine growth restriction (IUGR) Reduction of birth weight and intrauterine fetal death (IUFD) have been associated with malaria infection. Disease transmission can be reduced by intermittent preventive treatment (IPT), access to effective case management for malaria illness and preventing mosquito bites- by distribution of mosquito nets (ITN) and insects' replants or with mosquito control measures such as spraying insecticides and draining standing water.

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