Malaria in Pregnancy

Angela Kasamba, PhD; Manon O. Enyaru, MD; Betty Dejene, MD

SUMMARY

Recently, malaria has been resurged around the globe from endemic areas where factors such as vector control cessation, insecticides vector resistance, and disease resistant drugs, environmental changes and political instability are causes for malaria to become an overwhelming infection especially in underdeveloped countries. It is important for health care providers to stay alert of the disease and its effects. During pregnancy catching Malaria infection is a significant public health problem the pregnant woman, her fetus, and the newborn child face which has substantial risks involved. Maternal illness and low birth weight associated with malaria is mostly due to *Plasmodium falciparum* infection which primarily occurs in Africa. It is estimated that each year approximately 50 million pregnant women are at risk of the adverse health impact of malaria that are living in malaria endemic areas. Approximately half of the pregnant women live in sub-Saharan Africa and there is an increment found in susceptibility of malaria in pregnant women as most of them reside in areas of intense *falciparum* transmission. Although some progress has been made in identifying the intermittent preventive treatment being one strategy and insecticide treated nets to be taken as another key strategy to control malaria in pregnancy in Africa but there is still long way to go to control malaria effectively in this high at risk group. From the biological mechanisms which explain the increased susceptibility during pregnancy to the most effective control measures we have still many gaps in knowledge that are needed to be addressed.

KEYWORDS

Malaria; Pregnancy; Birth deficiency; Tropical disease; Economic status

Chemoprophylaxis of malaria is imperative for all non-immune women visiting endemic malaria areas throughout pregnancy particularly in last third phase. Prophylaxis is also advised for all women residing in tropical countries where malaria occurs. Although wide range of effective drugs previously available for chemoprophylaxis has now become restricted, owing to the resistance of *P. falciparum* to antifolates (proguanil, pyrimethamine, trimethoprim). For preventing malaria in pregnant women the use of a combination of pyrimethamine with sulfadoxine (Fansidar) or with dapsone (Maloprim) is controversial, because of unproved pyrimethamine action and sulphonamides long term effects on the blood forming organs of the fetus (5-8). So the World Health Organization does not recommend Fansidar for malaria prophylaxis in pregnancy. However, the combination of pyrimethamine with dapsone (Maloprim) is partially considered by some and their views are divided over this combination. There are no side effects found regarding giving Maloprim dose to adults and this dosage has adequately been found to be good protection from *P. falciparum* malaria, even though the pharmacodynamics are not well matched, of the two active components.

In Britain expertise have an opinion that a woman should daily take folate or folinic acid (10 mg) however there is also no harm in taking Maloprim during pregnancy like the avoidance of the drug is not justified by the evidence. However, in France, United States and by the World Health Organisation Maloprim is not recommended. Furthermore, in areas with a high degree of resistance of *P. falciparum* the combinations of neither the pyrimethamine-sulfadoxine or pyrimethamine-dapsone are adequate for preventing malaria or guarantee full protection from infection with *P. vivax*.

**RISK FACTORS**

 Mothers are usually asymptomatic in high transmission settings but birth weight is often reduced in primigravida (1). Hypoglycaemia and pulmonary edema are commonly manifested as severe *falciparum* malaria during pregnancy. The binding of infected red cells to chondroitin-sulphate can be a source of recrudescence infection, which hinders in treatment of malaria in pregnancy, this binding also causes sequestration of parasites in the placenta. The parasites when multiplied with chondroitin-sulphate phenotype, elicits a specific
immune response explaining vulnerability after the first pregnancy. Women experiencing a single parasitaemic episode of either *P. falciparum* or *P. vivax* with the duration of pregnancy have high risk of anemia and low birth weight. Also a severe disease in the neonate occurs, and the clinician should be aware of this possibility.

The treatment options in areas of multidrug-resistant *P. falciparum* for malaria in pregnancy are limited (9). The deficiency of available drugs is also one of the adverse causes for multiple treatment failures and prolonged parasitisation of the feto-placental.

There are several maternal factors which are associated with the risk of malaria in pregnancy such as maternal age, parity and gestational age. It should be known that younger women particularly adolescents, are at higher risk of malaria infection than older women. Parity is dependent over it as it also affects the risk of malaria within primigravida which are higher than multigravida (10). However, most of the available data relating to malaria focuses on the last two (9) trimesters and during the second trimester the peak of malaria prevalence is highly expected to occur. In the first trimester of pregnancy malaria burden are scarce but it should not be ignored because the rates of occurring are similar to the second trimester. However, it should be kept in mind that there is a difficulty in collecting information about malaria so pregnant women should begin attending the antenatal clinic immediately after the first trimester, and focus on formative age of gestational with accuracy because there is an ambiguity in an info regarding the formation of the risk which begins towards the end of the first trimester.

**EFFECTS OF MALARIA INFECTION**

During pregnancy the effect of malaria infection depends on the degree of acquired immunity, which further depends on transmission intensity.

**Maternal Effects**

Significant evidences relating the effects of interactions between malaria and HIV/AIDS in pregnant women are found in studies. The capability of pregnant women is ruined by HIV infection in controlling a *P. falciparum* infection. HIV positive mothers are more likely to develop clinical and placental malaria; more often have detectable malaria parasitemia; and have higher malaria parasite densities in peripheral blood. Compared to women with either malaria or HIV infection, co-infected pregnant women are at increased risk of anemia, preterm birth and intrauterine growth retardation. Consequently women with dual malaria and HIV infection give birth to children who are at high risk of low birth weight or death during infancy (11).

Malaria can cause maternal anemia where malaria transmission is unstable and in the areas where infections are asymptomatic they substantially increase the risk of anemia and both symptomatic and asymptomatic infections can cause anemia. In stable transmission settings severe anemia is more often observed in primigravida more than in multigravida. In such case pregnancy malaria infections increase the risk of anemia in the first two trimesters, though in the third trimester an increased risk for infections has also been reported in one study. Preventing malaria infection by intermittent preventive treatment reduces the risk of anemia (IPTp).

Malaria as a cause of miscarriage seems more common where malaria transmission is unstable and a clinical attack with fever is known to be source towards which the majority of infections evolve, which itself determines miscarriage. Indeed, fevers without malaria also increase the risk of miscarriage.

Malaria has been reported as an important cause of maternal death which is often reported as co-morbidity, e.g. with eclampsia, in conditions which has any association with maternal mortality. However, the substantial reduction was observed in Thailand after the implementation of early detection and treatment of malaria.

**Prenatal Effect**

Includes the risk of low birth weight (LBW) with an increase in malaria (9), which is particularly found in primigravida, and for first or second trimester this risk has a possibility to elevate for infections though in an-
other study the risk for higher concentration of infections were expected in late pregnancy such an effect is due to intrauterine growth retardation (IUGR) in high malaria transmission settings rather than pre-term delivery because most infections are asymptomatic.

Preterm deliveries, still births and neonatal deaths have been associated with malaria within unstable transmission settings. LBW also associates *P. vivax* with it and if a woman is detected with a single infection of *P. vivax* she must be treated in the first trimester to eliminate any significant effect on gestation or birth weight.

**New Born and Infant Effects**

It has been lately reported that in neonates the disease course deteriorates quickly as parasites are vertically transmitted from mother in neonate within 7 days of birth and often carry an asymptomatic course and severe disease occurs. The clinician should not be forgetful and must treat parenteral antimalarial drugs to every case of neonatal malaria. Fever, irritation, feeding problems, hepatosplenomegaly, as well as anemia along with jaundice are attributed to be the clinical feature for parasites. Every child born is required to be assessed through the peripheral blood slide to a positive malaria smear mother (*P. falciparum* or *P. vivax*) or a mother receiving treatment within a week of delivery as there might be a clinical indication about the presence of malaria parasites at birth and at 7 days after delivery or if clinically indicated. Since frequent features of neonatal malaria are severe anemia and hypoglycemia so every neonate needs to undergo a clinical observation to gain negativity in malaria. Feeding a neonate continuously is an important factor for positive outcomes (11).

Congenital malaria occurring in the neonatal period can contribute to infant morbidity and mortality. Active infection known to be Placenta malaria has been linked to neonatal and infant mortality. A recent study in The Gambia shows that infant’s growth is influenced by placenta during pregnancy, without any impact of LBW which results in more risks of deaths in infant and perinatal mortality by causing LBW. There is an approximation of 60%, regarding the reduction in neonatal mortality observed after the implementation of preventive measures taken for pregnant women, preventive measures include intermittent preventive treatment. With IPTp or insecticide-treated bed nets in malaria prevention in primi- and secundi-gravida, significantly 18% decreased risk of neonatal mortality.

There are long term effects of malaria in pregnancy because there are childhood, adolescence and adulthood effects found later. Moreover, malaria has a prolonged affect resulting in IUGR which further leads to LBW and then it may relate to diseases occurring in adulthood, like cancers or the metabolic syndrome.

**PATHOPHYSIOLOGY**

The immunological changes induced by pregnancy explains the increase in susceptibility, by hormonal factors, and by the higher attractiveness of pregnant women to mosquitoes put pregnant women at higher risk of contracting malaria than non-pregnant women. In pregnant women *P. falciparum*-infected erythrocytes bind to specific receptors and sequester in the placenta. Consequently in non-pregnant individuals they rarely bind to the other two commonly described receptors for example CD36 and the intracellular adhesion molecule (ICAM-1). The parasite antigens expressed in pregnancy on infected erythrocytes jointly recognized as variant surface antigen-pregnancy associated malaria (VSAPAM). In stable transmission settings they are not recognized by the immune system and vary from those expressed in non-pregnant individuals, explaining the higher risk in primigravidae. In the pathology of *falciparum* malaria, in pregnancy the surface antigen (VAR2CSA) binds chondroitin sulphate and VAR2CSA is encoded by the *var2csa* gene which belongs to the family of the erythrocyte membrane protein (PfEMP1) and is described in pregnant women with falciparum malaria. Anti-VAR2CSA specific IgGs are associated with a favorable pregnancy and cannot be found in men. Besides the response of antibody to VSAPAM, cytokine responses have been observed in pregnant women with malaria.

The attractiveness of pregnant women increases to mosquitoes is explained within the context of physiological and behavioral changes during pregnancy. The exhale breath and abdominal temperature enhance, which may render pregnant women are the physiological changes which make the women more easily detectable by mosquitoes. While on the other hand behavioral changes include the changes in which pregnant women urinate twice as frequently as non-pregnant women, due to which they have to leave their beds at night and as a result they are exposed to mosquito bites.
Malaria associated with placenta has been described for stable and unstable transmission settings as they include presence of parasites, inflammatory variations and hemozoin (pigment) deposition. There are four levels of placental changes which have been characterized, acute which includes presence of parasites and absence of malaria pigment, chronic in which both parasites and malaria pigment are present, past infection which has no parasite but pigment are present and no infection in which both parasites and malaria pigment are absent. Recently, in Tanzania a stable transmission and in Thailand an unstable transmission setting have been proposed as 2-parameter grading system, which distinguishes between inflammation and pigment deposition and correlates with pregnancy outcomes.

Moreover, the ambiguity is still there regarding the mechanism at the basis of malaria-related preterm delivery, however risks in fever, anemia, and high levels of TNF alpha or interleukin 10 have been identified as important factors.

There is an association between maternal anemia and LBW which occur due to IUGR, and elevated levels of cytokines. Although there is still no exposure to exact mechanism since it seems due to chronic infections that causes a reduction in fetal circulation and placental insufficiency. Falciparum infection relating to Placental endocrine changes is considered another possible mechanism leading to IUGR. Immature erythrocytes (reticulocytes) are infected by P. vivax which limits the parasite densities. Additionally during pregnancy it can relapse due to the activation of liver hypnozoites. Variant surface antigens at the basis of placenta sequestration are not expressed by vivax parasites so that this does not occur frequently. Nevertheless, the mechanisms are implicit at the basis of these observations.

**CLINICAL PRESENTATION**

**Diagnosis**

It is essential to conduct a cautionary diagnosis for malaria in pregnancy to prevent any sort deleterious effects to the mother and the fetus. The clinical signs of malaria are usually non specific in pregnant women, and stable transmission makes most infections as asymptomatic. Therefore, parasitological diagnosis confirms the suspected malaria cases either by microscopy or testing through rapid diagnostic. Nevertheless, other methods like PCR and placental histology are also helpful though the latter can be done post delivery so that during pregnancy it cannot be used for the management of infections.

One of the most widely used methods for diagnosing malaria is microscopy even in pregnancy. It has an advantages of determining the parasite density and species whereas its major disadvantage is its sensitivity that the need of a regular power supply cannot go below 10-15 parasites per unit therefore, it is highly possible that a substantial proportion of infected pregnant women would go undetected because of extremely low densities of parasites or sequestering of parasites in the placenta, hence both conditions contains deleterious effects on the health of mother’s and her offspring.

For detecting circulating malaria antigens rapid diagnostic tests (RDT) can also be used. Generally, the sensitivity of RDTs is lower than of microscopy for the diagnosis of malaria in pregnancy but the time needed is shorter than for microscopy and the minimal training is required for their use. Although RDT cannot estimate the parasite density but they can detect malaria antigens. It is estimated that the sensitivity of RDT on peripheral blood as a reference test through peripheral microscopy was 81% and the sensitivity using placental microscopy as the reference on placental blood was 81%.

Hence in stable malaria transmission settings, Microscopy is used for the diagnosis of MiP in Africa. Although PCR detects parasite DNA but it can also be used for the diagnosis of malaria infection but health facilities lack its availability.

**Severe Malaria**

It has been identified that women in last two trimesters of pregnancy are at a higher risk of developing severe malaria. Severe malaria is connected to pulmonary edema and hypoglycemia hence mortality is found in pregnant women and they are treated through artesunate or quinine varying between 9% and 12%.

**PREVENTION AND TREATMENT**

**Prevention**

Insecticide treated bed nets (ITN) are the most effective and widely used preventive measures of malaria in
pregnancy. Currently sulfadoxine-pyrimethamine (SP) is a recommendation for at least two times during the second and third trimester of pregnancy. The WHO and many sub-Saharan African countries have included SP in their malaria control program. Many trials have shown that SP given as IPTp is efficacious in stable transmission settings, for preventing the adverse consequences of malaria during pregnancy however, SP resistance represents a major threat (4, 8).

Another approach for malaria infections is systematic screening at regular intervals which may be more appropriate in low transmission settings of malaria and the low risk of infection between antenatal visits. It has already been mentioned to have protective efficacy than IPTp but more thorough evaluation measures are probably needed. Drug resistant malaria has only been the form of malaria control on the Thai-Burmese which has impacted significantly on maternal mortality rates.

In future, it is expected to have vaccines specifically designed to prevent MiP. VAR2CSA seems the most promising option in the early stages of development, however, several uncertainties are still found including the number of antigenic variants to be combined, the timing of the vaccine, e.g. during pregnancy, whether to target only first pregnancies or to make sure that the children are born to vaccinated mothers.

**Treatment**

Treating pregnant women with malaria after parasitological confirmation of the diagnosis reduces the unnessary exposure to anti-malarial of both the mother and the fetus. The recommendations, say that chloroquine, quinine, clindamycin and proguanil is certainly safe in the first trimester whereas for second trimester recommendations, ACTs are effective in the area or a 7-day combination of either artesunate and clindamycin, or quinine and clindamycin for uncomplicated malaria. Parental anti-malarial is recommended in case of severe malaria.

Nevertheless, if treatment is not delayed the artesunate and quinine (parenteral) reduces the risk of death and the treatment should be started immediately with the most readily available drug.

**CONCLUSIONS**

There are deleterious effects of MiP to both the mother and the child. The mechanisms to be implemented are still unknown in areas where transmission is low and unstable. Since peripheral microscopy does not detect the large proportion of infected women having parasites seizure in the placenta the diagnosis of MiP is hence challenging. The only way to prevent MiP is using currently available control methods, i.e. ITNs and IPTp, but for women with the highest risk such as adolescent primigravida the challenge is attaining a high coverage. The alternative to SP for the IPTp is still unclear and there is also a need of having more sensitive diagnostic methods as it would help improving early diagnosis during pregnancy resulting in appropriate management.


