Review Article

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Quick Response Code:

Management of malaria in pregnancy

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Pregnant women are especially susceptible to malaria infection. Without existing immunity, severe malaria can develop requiring emergency treatment, and pregnancy loss is common. In semi-immune women, consequences of malaria for the mother include anaemia while stillbirth, premature delivery and foetal growth restriction affect the developing foetus. Preventive measures include insecticide-treated nets and (in some African settings) intermittent preventive treatment. Prompt management of maternal infection is key, using parenteral artemisinins for severe malaria, and artemisinin combination treatments (ACTs) in the second and third trimesters of pregnancy. ACTs may soon also be recommended as an alternative to quinine as a treatment in the first trimester of pregnancy. Monitoring the safety of antimalarials and understanding their pharmacokinetics is particularly important in pregnancy with the altered maternal physiology and the risks to the developing foetus. As increasing numbers of countries embrace malaria elimination as a goal, the special needs of the vulnerable group of pregnant women and their infants should not be overlooked.

Key words Artemisinin - diagnosis - malaria - plasmodium - pregnant - treatment

Introduction

The global malaria burden has declined in recent years, but over 40 percent of the world's population remains at risk of infection, and over 400,000 people die every year[1]. In India, over 90 per cent of the population live in malaria transmission areas, with two-thirds of infections caused by *Plasmodium falciparum* and one-third by *P. vivax* and an estimate of 13 million cases and 24,000 deaths each year[1].

Pregnant women are particularly susceptible to malaria infection[2], and this susceptibility is attributed to immunological changes occurring in pregnancy, and to the unique predilection of a subset of *P. falciparum* parasites to sequester in the maternal blood spaces of the placenta[3]. This placental malaria infection helps the parasite avoid clearance by the immune system and especially filtration by the spleen. *P. falciparum* parasites express a protein on the red cell surface called VAR2CSA, which sticks to the placental receptor Chondroitin Sulphate A (CSA)[4]. Antibodies to VAR2CSA have been associated with protection from placental malaria and adverse birth outcomes[5] and a VAR2CSA-based vaccine is now in early clinical trials (NCT02647489 and NCT02658253, *https://www.clinicaltrials.gov*), with the aim of preventing malaria in pregnancy.

Placental sequestration is not a major feature of *P. vivax* infection[6], but the infection is common in pregnancy and has been associated with adverse

pregnancy outcomes including decreased birth weight and maternal anaemia[7]. However, a recent study found relatively low infection prevalence and modest associations with morbidity in five countries including India[8].

In high transmission areas, malaria in pregnancy is most common in first-time mothers and prevalence and densities of parasitaemia both decline over subsequent pregnancies. By contrast in low transmission areas, all pregnancies are equally at risk for *P. falciparum*, and probably *P. vivax* infection[9].

Consequences of malaria in pregnancy

The consequences vary with transmission intensity. When the transmission is high, maternal anaemia is common, and infant low birth weight due to foetal growth restriction and/or premature delivery is frequent[2]. In low transmission areas, when non-immune pregnant women become infected, malaria infection may become severe and life-threatening, requiring emergency treatment[2]. Maternal complications include acute lung injury, severe hypoglycaemia and coma while pregnancy loss due to miscarriage or stillbirth is also frequent. Malaria may be an under-recognized cause of maternal death[10].

Diagnosis

Microscopy

Microscopy of stained blood smears remains widely used to monitor the prevalence of malaria. For point-of-care testing, rapid diagnostic tests (RDT) are very effective for the diagnosis of symptomatic malaria infection, which tends to be accompanied by high parasitaemia. These are less effective as screening tools, being unable to reliably detect low-density infections which are common[11]. New, high-sensitivity RDTs will soon be evaluated in pregnant women.

Polymerase chain reaction (PCR)

Polymerase chain reaction is highly sensitive, with quantitative PCR able to detect very low-density malaria infection[12]. However, a specialized laboratory with trained staff is required, and assays are relatively time-consuming. Loop-mediated isothermal amplification (LAMP) has similar sensitivity to PCR but is more rapid and robust, and potentially applicable at the point of care[13,14]. Both are presently reserved for research settings.

We have a strong understanding of the relationship between infection detected by microscopy and adverse pregnancy outcomes[2], but the significance of sub-patent infection detected by PCR but not by microscopy and/or RDT is not yet clear. The sub-patent infection has been found to be associated with lower mean haemoglobin, and with low birth weight in primigravidae and premature delivery in multigravidae[15], but other studies have not found similar associations[16,17]. A pooled analysis (currently in preparation) should more clearly determine whether these low-density infections affect pregnancy outcomes.

Placental histology

Histological examination of placental tissue at delivery is a sensitive tool for detection of active or past malaria infection. Past infection is detected as the malaria pigment, haemozoin, most commonly in fibrin deposits. Active infection can be accompanied by leucocytes infiltrates, principally monocytes, termed intervillositis, particularly in first-time mothers with little pregnancy-associated malaria immunity. In this group, it is strongly associated with low birth weight and maternal anaemia[18].

Management of malaria in pregnancy

Prevention

The World Health Organization (WHO) recommends[19] a three-pronged strategy for control of malaria in pregnancy in Africa including case management (prompt treatment with highly effective drug), use of insecticide-treated nets (ITNs) and intermittent preventive treatment (IPTp), the administration of a full treatment course of an effective antimalarial at regular antenatal visits, usually a month apart.

Intermittent preventive treatment in pregnancy (IPTp)

Currently, IPTp is only recommended in Africa, using sulphadoxine-pyrimethamine (SP). A meta-analysis revealed that three doses of IPTp were superior to two[20], and a multisite study showed that IPTp remains effective against low birth weight and anaemia, even when resistance to SP is high, which is common in Eastern and Southern Africa[21]. In the recent years, mefloquine and a combination of azithromycin and chloroquine have been evaluated for prevention of malaria in pregnancy. Mefloquine decreased parasite prevalence at delivery but was poorly tolerated[22], and the trial of azithromycin and chloroquine was stopped due to futility (*i.e.* inability to show a clear benefit over the comparator, SP); it, too, was poorly tolerated[23].

Recent studies[24,25] suggested that dihydroartemisinin-piperaquine (DHA-PQ) may be a suitable replacement for SP. It has also been studied in Indonesia as IPTp or intermittent screening and treatment (IST), and larger trials presently in progress should provide a definitive answer as to whether it is a suitable replacement for SP in Africa. We presently lack evidence regarding the benefit of IPTp in lower transmission countries (such as India). Challenges for SP IPTp include the lack of evidence regarding its effectiveness against *P. vivax*, and low levels of uptake[26].

An alternative to IPTp is IST. Using this approach, at each antenatal visit, an RDT is performed, and women testing positive receive an effective antimalarial, most commonly an artemisinin combination treatment (ACT). In part due to the low sensitivity of current RDTs, IST was not more effective than IPTp in preventing malaria and its complications in several studies in Africa[27], and it has not been endorsed by the Malaria Policy Advisory Committee (MPAC) to the WHO for wider use. A trial of IST has been recently concluded in India (personal communication) while high-sensitivity RDTs hold promise to overcome some of the weaknesses of the IST approach. A recent review summarized trials of IPTp and IST over the past five years[28].

Insecticide-treated nets (ITNs) and indoor residual spraying

Evidence primarily from trials in Africa shows that ITNs can prevent malaria and decrease low birth weight and other adverse pregnancy outcomes. There are limited data from Asia[29], where mosquito vectors and their biting behaviour are different[30], and where *P. vivax* is prevalent. Nevertheless, ITNs are a relatively cheap and probably effective tool for malaria prevention in pregnancy in India. Indoor residual spraying is used in parts of Africa and Asia, but there is little pregnancy specific data on its impact.

Severe malaria in pregnancy

When a pregnant woman presents with severe malaria, the priority is to save her life. The recommended treatment for severe malaria at any time in pregnancy is with parenteral artesunate[31]. The SEAQUAMAT trial showed it to be superior to parenteral quinine in Asian adults[32]. Once the woman recovers, treatment can be continued with appropriate oral medication. Pregnant women are particularly prone to hypoglycaemia, and blood sugar levels should be closely monitored.

Uncomplicated malaria in pregnancy

Falciparum malaria in the first trimester

Currently, quinine and clindamycin is the recommended treatment for women in the first trimester of pregnancy[31]. In many places, clindamycin is unavailable, and quinine monotherapy is prescribed. Side effects of the seven-day quinine regime, such as tinnitus or fullness in the ears, result in poor compliance, and the risk of recrudescence.

ACTs are a logical alternative to quinine, but establishing their safety in the first trimester has been challenging, especially because in animal studies, the drugs show embryo toxicity[33]. Pharmacovigilance, the monitoring of drug safety, is particularly important in pregnancy where both mother and developing foetus are at risk. A recent meta-analysis investigated the safety of ACTs in early pregnancy. Compared to quinine treatment, ACTs were not associated with increased risk of miscarriage, stillbirth or embryotoxicity[34]. This analysis has informed the decision of the WHO's MPAC to endorse the use of ACTs in the first trimester[35], although this is not yet recommended in the treatment guidelines[31].

Second and third trimester

A recent large trial compared four different ACTs, namely artemether-lumefantrine, amodiaquine-artesunate, mefloquine-artesunate, or dihydroartemisinin piperaquine (DHA-PQ), for treatment of uncomplicated malaria in the 2nd and 3rd trimesters of pregnancy, in 3428 pregnant women[36]. All drugs were highly effective (95% or more), with artemether-lumefantrine being associated with the fewest adverse events while DHA-PQ was associated with the greatest post-exposure prophylaxis. This evidence strongly supports the use of ACTs as first-line treatment for malaria in the second and third trimester[31]. In Papua, Indonesia both *P. falciparum* and *P. vivax* were resistant to previous first-line drugs, and the introduction of DHA-PQ was associated with substantial declines in maternal malaria and anaemia, congenital malaria and low birth weight[37].

Vivax malaria

Chloroquine remains an effective treatment for vivax malaria in most of the world, although resistance that emerged in Papua New Guinea and Indonesia is spreading. ACTs (apart from artesunate-SP) are also highly effective for treatment of vivax malaria, and parenteral artesunate is highly effective in the severe vivax disease[31]. An increasing number of countries

recommend ACTs for treatment of all forms of uncomplicated malaria[38].

Primaquine is contraindicated in pregnancy due to the risk of severe haemolysis in glucose-6-phosphate dehydrogenase (G6PD) deficient individuals. Pregnant women may require suppressive treatment, usually with chloroquine, until delivery. Small amounts of primaquine enter breast milk, so G6PD testing of the infant is recommended in lactating women before they are prescribed primaquine[31].

Pharmacokinetics of antimalarials in pregnancy

Over the recent years, the pharmacokinetics of antimalarials have been investigated in pregnant women, with the aim of determining whether dose adjustment is required[34]. For artemether-lumefantrine, some evidence points towards a need to extend treatment duration[34] but at present, no dose adjustments have been recommended[31]. There is no clear evidence for dose adjustments for other drugs in pregnancy at this time.

Special groups: HIV-infected women

HIV infection increases the risk of malaria in pregnancy[39]. HIV infected women who are prescribed co-trimoxazole to decrease opportunistic infections should not receive IPTp (where otherwise recommended) because of the increased risk of severe skin reactions such as Stevens-Johnson syndrome. Mefloquine decreased parasite prevalence in HIV-infected women but appeared to increase the risk of mother-to-child transmission of HIV[40]. DHA-PQ is currently being evaluated as an alternative for IPTp. An additional consideration is the risk of drug interactions between antimalarials and antiretrovirals[41], which may require dose adjustment or even avoidance of certain drugs. To date, little is known about the impact of antiretroviral therapy or immune system reconstitution on the interactions between malaria and HIV.

Access

An optimal approach to control and prevention of malaria in pregnancy requires close cooperation between malaria control and reproductive health programmes. Training to improve knowledge of both health service staff and private sector suppliers of antimalarials regarding optimal case management in pregnancy may be required. Diagnostic tools for pregnancy malaria and drugs recommended for treatment of pregnant women need to be available at all levels of the health system.

Future directions

Malaria elimination

Countries across the Asia-Pacific including India have committed to malaria elimination by 2030[42]. There are implications for management of malaria in pregnant women, and for campaigns such as mass drug administration (MDA). Currently, DHA-PQ is the most widely used drug for MDA, but it does not yet have an established safety record in early pregnancy, and hence, women who are possibly in early stages of pregnancy should be excluded from such campaigns. Where pregnant women are excluded from MDA campaigns, a significant part of the remaining burden may be found in these women[43].

Pregnant women may be a useful sentinel population to monitor malaria changes[44]. The majority of women attend antenatal care at least once, so they are readily accessed, and parasite prevalence can be easily monitored. The analysis suggests these measures correlate well with a more established measure, the parasite prevalence in children under 5[45].

Conclusion

Pregnant women are uniquely susceptible to malaria. Optimal malaria prevention varies with the transmission; in higher transmission areas ITNs have demonstrated benefits. Whether preventive treatment approaches such as IPTp or IST will have a place outside Africa will depend on results of studies presently in progress. In lower transmission settings, women may lack malaria immunity and are at risk of developing severe, potentially fatal disease or losing their babies to miscarriage or stillbirth; they require immediate diagnosis and treatment. ACTs are recommended in most circumstances, although quinine remains the first choice in the first trimester of pregnancy. The approach to treatment should be tailored according to pregnancy trimester and clinical severity of malaria.

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