

Prevention of Malaria in pregnancy: Sulfadoxine-Pyrimethamine intermittent preventive treatment, resistance, and update on potential preventive strategy

ABSTRACT

Malaria in pregnancy is a major international public health concern in tropical and subtropical regions because pregnancy is a unique period vulnerable to malaria infection. In the Sub Saharan Africa region, the subclinical infection usually occurs during pregnancy and which lead to the maternal anaemia, intrauterine growth retardation of foetus, low birth weight and infantile deaths. The WHO recommended to provide with Sulfadoxine and Pyrimethamine (SP) as intermittent preventive treatment (IPTp) for pregnant women living in moderate to high malaria transmission regions. The increasing number of resistant parasites to SP is a threatening matter for public health prophylaxis intervention. Therefore, in the context of threatening SP resistance, there is a need to consider the alternative strategies to IPTp-SP. This review discussed the epidemiology, pathophysiology, clinical features of malaria in pregnancy, current preventive regimen with SP, and threat of SP resistance and outlined the potential preventive treatment strategy with Dihydroartemisinin-Piperaquine (DP).

Keywords: *Malaria in pregnancy, Sulfadoxine-Pyrimethamine resistance, Dihydroartemisinin-Piperaquine, IPTp-SP, IPTp-DP, Plasmodium falciparum.*

1. INTRODUCTION

Malaria is an international public health concern in tropical and subtropical regions. This devastating disease is caused by *Plasmodium* species parasites and mainly transmitted through the bite of female *Anopheles* mosquitos [1]. Among the *Plasmodium* species, *P. falciparum* and *P. vivax* contribute to the higher percentages of cases [2], meanwhile, *Plasmodium falciparum* infection leads to severe or complicated malaria. In addition, *P. vivax* was found to cause severe infection in recent years [3].

Malaria in pregnancy is a particular concern because pregnancy is a unique period vulnerable for contracting malaria infection. Sub-Saharan African countries are considered as high and stable transmission regions, and subclinical infection usually occurs during pregnancy [4]. Since it does not reveal clinical signs and symptoms, both patients and clinicians are unaware of malaria infection, which can lead to complications for both mother and foetus. In endemic areas, malaria in pregnancy can cause severe maternal anaemia, maternal mortality; moreover, it can also affect the foetus and neonate expressed as intrauterine growth retardation, low birth weight and infantile deaths.

2. EPIDEMIOLOGY AND RISK OF MALARIA IN PREGNANCY

Millions of pregnant women and their foetus are under threat of complications of malaria in the endemic areas. Approximately 125 million pregnancies occur in areas of *P. falciparum* and *P. vivax* transmissions annually, including 30 million from Africa [5]. As a result of placental malaria, 10,000 maternal and 100,000 – 250,000 new-born deaths occur annually [6].

Pregnant women have higher chances of contracting malaria infection as they were found to be twice more attractive to *Anopheles arabiensis* mosquitos than non-pregnant women in a study conducted in Sudan [7, 8]. Primigravidae usually suffer from more frequent and severe malaria since they do not have the protective immunity against the placental malaria parasite [9]. Human Immunodeficiency

Virus (HIV) infected pregnant women have a higher risk of malaria infection and morbidity [10] as they suffer more frequent attacks of malaria, higher parasite density and placental parasitaemia, more maternal anaemia and more adverse foetal outcomes compared to the HIV negative pregnant women [11].

3. PATHOPHYSIOLOGY OF PLACENTA MALARIA

Placental malaria is the one of the major features of malaria during pregnancy and mainly caused by *P. falciparum* infection [12]. In malaria endemic areas, the women had early exposure during their childhood and they developed anti-disease immunity during adulthood. This immunity confer the prevention of clinical disease and life threatening illness, however, it is not protective against malaria infection in the placenta [13].

Placental malaria is the sequestration of infected red blood cells (RBCs) in the intervillous spaces within the placenta, which can cause infiltration of inflammatory cells and lead to the release of pro-inflammatory cytokines [14]. It is usually diagnosed after delivery of the child by histological evidence of infected RBCs or malaria pigment deposition in the placenta [12]. During pregnancy, the malaria parasite produces a new set of antigen on the infected RBC membrane, Variant Surface Antigen 2-Chondroitin Sulphate A (VAR2CSA), which mainly binds to the Chondroitin Sulphate A (CSA) receptor in the placenta [15]. The risks of developing maternal and foetal complications are highest in primigravidae due to the absence of the antibodies against the placenta specific antigen of the malaria parasites. During subsequent pregnancies, anti-Chondroitin Sulphate A (anti-CSA) antibodies were gradually produced by B lymphocytes in the body and the risk of malaria infection become less in multigravidae [16].

4. CLINICAL FEATURES AND COMPLICATIONS

Clinical features of malaria range from asymptomatic to severe life threatening disease and the clinical outcome is influenced by three factors; (1) parasite factors such as antigenic variation and drug resistance; (2) host factors such as genetic factors, immune response or the balance of inflammatory cytokines and (3) environmental factors, for example, nutrition and access to treatment [17]. Symptomatic clinical malaria is common in unstable transmission areas whereas asymptomatic infection is dominant especially in adults in high and stable transmission areas because of the acquired immunity [18].

Immunocompromised state of pregnancy and sequestration of infected RBCs in the placenta were hypothesized as the main contributing factors for the complications of malaria in pregnancy [19]. Maternal anaemia is the one of the commonest complications arising from many factors including haemolysis of infected RBCs and destruction of RBCs by the spleen and immune responses [20]. If the pregnant woman has a peripartum haemorrhage, the pre-existing anaemia due to malaria will worsen the situation and can increase maternal mortality. Moreover, all forms of malaria have risks of abortion [1, 21].

Malaria infection causes maternal anaemia, derangement of tumour necrosis factor (TNF)-alpha and interleukin (IL)-10 productions, all of which can reduce placental growth, perfusion and finally jeopardize foetal outcomes [13, 14, 22].

5. PREVENTION OF MALARIA IN PREGNANCY

Malaria in pregnancy is preventable with effective strategies, which in turn, significantly reduce maternal and foetal complications. Historically, chloroquine was used as a weekly chemoprophylaxis in pregnancy however, widespread resistance caused lack of efficacy in the African region [23, 24]. The WHO now recommends using Sulfadoxine and Pyrimethamine as IPTp in Africa. Together with chemoprophylaxis, long-lasting insecticide treated nets (LLINs) are recommended to use in stable malaria transmission areas [25]. Additionally, vector control measures such as indoor residual spraying (IRS) are implementing as part of the malaria control program [25].

In unstable malaria transmission regions, the WHO advocates the provision of Long-lasting insecticidal net (LLIN), indoor residual spraying (IRS) and active case management. Intermittent preventive treatment with SP is not recommended in the Asia-Pacific region except in Papua New Guinea. Intermittent screening and treatment in pregnancy (ISTp) with Dihydroartemisinin-Piperaquine (DP) strategy has potential to prevent the complications in South-East Asia region [26].

6. INTERMITTENT PREVENTIVE TREATMENT IN PREGNANCY WITH SULFADOXINE-PYRIMETHAMINE (IPTp-SP)

Since malaria in pregnancy is preventable, the WHO recommended of providing IPTp-SP in all the endemic areas of Africa in 2012 [27]. Sulfadoxine and Pyrimethamine are antifolate combination drugs, Pyrimethamine inhibits dihydrofolate reductase (DHFR) and sulfadoxine inhibits the dihydropteroate synthase (DHPS) enzymes of the malaria parasites [28]. When Sulfadoxine and Pyrimethamine are used together, the antimalarial action is greater than in single drug therapy and their synergistic effect reduces the required dosage of individual drugs to treat the malaria infection [29]. Currently, 36 high-burdened countries have implemented IPTp-SP as their national policy [25]. A meta-analysis of datasets from 25 African countries has shown the benefits of IPTp-SP, resulting in the reduction of the low birth rate by 25% and neonatal mortality by 16% [30].

During the 1970s, the cure rate of SP was 80-90 % in Asia [31]. At present, it has been highly variable depending on the parasite's resistance level. If the parasite is fully sensitive to SP, the protective period can last up to 60 days [32, 33].

Initially, the IPTp-SP was recommended to provide two doses after quickening, where quickening is the first foetal movement usually occurring around week 18 to week 20 of pregnancy. However, the three-dose regimen was found to be more effective than two doses in reducing maternal and foetal complications in a meta-analysis of 7 trials in Africa [34]. In 2013, the WHO amended the schedule of IPTp-SP to provide at least three doses, as early as possible in the second trimester, at least one month interval in between the dosage.

Compliance to the recommended regimen need to emphasize achieve the aim of IPTp-SP program. In 2015, only 31% of pregnant women received the recommended three or more IPTp-SP doses in the report from 20 countries [25]. Several studies have been conducted to identify the barriers, which hamper the uptake of IPTp-SP in Africa and revealed that irregular attendance of antenatal care (ANC), stock-out of drugs and late attendance to ANC are the commonest causes of non-compliance to the recommended schedule [35, 36]. Despite the large number of IPTp-SP non-compliance pregnant women, there were few studies showing the outcome of poor compliance. Moreover, the emergence of SP resistant mutants increases the minimum inhibitory concentration (MIC) of the drug and shortens the prophylactic period [37].

6.1 HIV AND IPTP-SP

HIV infected pregnant women are not only more vulnerable to malaria infection but also to diminished response to antimalarial drugs [11, 38]. Therefore, the WHO recommended the provision of more than three doses of IPTp-SP in HIV positive pregnant women who are not taking co-trimoxazole prophylaxis for opportunistic infections [39]. Pregnant women on daily co-trimoxazole should avoid taking IPTp-SP since their redundant action and the synergistic effect might worsen adverse drug reactions (ADRs) [40].

6.2 SULFADOXINE AND PYRIMETHAMINE RESISTANCE

Resistance to Sulfadoxine and Pyrimethamine has been revealed in South East Asia since 1981 [41]. The SP resistant strains seem to have originated in South East Asia, South America and they were gradually introduced to Africa [42, 43]. The accumulation of sequential mutations in the *Plasmodium falciparum* gene confers the resistance to SP, which may lead to treatment failure. The level of resistance to SP is directly related to the accumulation of mutations in *dhfr* and *dhps* genes. The greater the mutations, the higher the resistance will be [44]. The double (*dhps* A437, K540) and triple mutations (*dhfr* N51, C59, S108) are commonly occurred in West Africa [45]. In addition, the presence of quintuple *dhfr* N51, C59, S108 – *dhps* A437, K540 mutations and sextuple mutant (*dhps* A581 mutation in addition) are threatening concern of SP resistance and the prevalence of quintuple mutation is highest in East Africa [45].

The increasing number of resistant parasites is a threatening matter for public health prophylaxis intervention, and health officials should monitor the progress of mutants in the African region.

7. POTENTIAL STRATEGY FOR PREVENTION OF MALARIA IN PREGNANCY

Some studies revealed the possibility of reducing the protective efficacy of SP in Africa. A study in Uganda mentioned that among the participant pregnant women who reported receiving at least two-doses of IPTp-SP had high prevalence of placenta malaria [46]. Similarly, IPTp-SP was found to be not protective against adverse outcomes such as placenta malaria and maternal anaemia in Tanzania [47]. Therefore, in the context of threatening SP resistance, there is a need to consider the alternative strategies to IPTp-SP. Clinical trials had been conducted to consider the most suitable regimen to overcome this forthcoming SP resistance threat in Africa.

7.1 DIHYDROARTEMISININ-PIPERAQUINE (DP)

Intermittent preventive treatment with Dihydroartemisinin (40 mg) and Piperazine (320 mg), IPTp-DP, is a potential regimen to prevent malaria in pregnancy. A randomized controlled trial in Kenya shown that IPTp-DP lowered the prevalence of malaria infection at the time of delivery compared to the IPTp-SP regimen [48]. The prevalence of placental malaria was significantly lower in 3-doses of IPTp-DP and monthly IPTp-DP groups compared to 3-doses of IPTp-SP group among the 300 HIV-negative pregnant women in Uganda [49].

Although the IPTp-DP was not superior to IPTp-SP in the prevention of low birthweight and preterm delivery, DP was found to be effective in preventing placental malaria. The combination of IPTp-DP with azithromycin might have a potential benefit in the prevention of malaria and other asymptomatic bacterial infection in pregnant women [50]. The meta-analysis of 11 randomized controlled trials on the DP (standard three-day regimen) revealed that monthly DP is effective and have potential to use as intermittent preventive treatment for malaria infection [51]. The phase 3 clinical trial is being conducted in the area of high SP resistance in Kenya, Malawi and Tanzania to evaluate the safety and efficacy of IPTp-DP vs IPTp-DP with azithromycin vs IPTp-SP [52]. The outcome of the larger evaluation trials might be beneficial for the policy makers to adopt the preventive strategy.

8. CONCLUSION

Currently, IPTp-SP is the only recommend regimen in stable malaria transmission areas and still having benefit on birth weight and maternal anaemia in the SP resistance regions. However, the increasing number of resistant parasites to SP is a threatening matter for public health prophylaxis intervention. Close monitoring and surveillance should continue on the SP resistance mutations of malaria parasites. Moreover, in the context of threatening SP resistance, there is a need to consider the alternative strategies to IPTp-SP. The intermittent preventive treatment with Dihydroartemisinin and Piperazine, IPTp-DP have a potential to prevent malaria in pregnancy. The safety and efficacy of IPTp_DP in the large clinical trials outcomes may also contribute to the adoption of new preventive strategies.

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