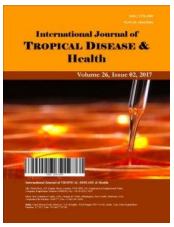

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A Review of Malaria Prevention in Pregnancy: Sulfadoxine-pyrimethamine Intermittent Preventive Treatment, Resistance and Update on Potential Preventive Strategy

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Authors' contributions

This work was carried out in collaboration between all authors. Authors MNNH and AEA managed literature searches. Authors MNNH and AEA wrote the initial draft of the manuscript. Authors WWM and HL managed literature search and advised for initial draft of the manuscript. Author MNNH wrote final draft of the manuscript. All authors read and approved the final manuscript.

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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 leads to the maternal anaemia, intrauterine growth retardation of the foetus, low birth weight and infantile deaths. The WHO recommended the use of sulfadoxine and pyrimethamine (SP) as intermittent preventive treatment (IPTp) for pregnant women living in moderate to high malaria transmission regions. The increasing number of SP-resistant parasites is a threatening matter for public health prophylaxis intervention. Therefore, in the context of threatening SP resistance, there is a need to consider the

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alternative strategies to IPTp-SP. This review discussed the epidemiology, pathophysiology, clinical features of malaria in pregnancy, a current preventive regimen with SP, and the 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* mosquitoes [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 the high and stable transmission regions, and subclinical infections usually occurs during pregnancy [4]. Since it does not reveal clinical signs and symptoms, both patients and clinicians remain unaware of malaria infection, which can lead to complications for both mother and the 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 *P. falciparum* and *P. vivax* transmission regions 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].

In a study conducted in Sudan, it was found that pregnant women have higher chances of contracting malaria infection as they are twice more attractive to *Anopheles arabiensis* mosquitos than non-pregnant women [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 compared to the HIV negative pregnant women [10] as they suffer more frequent attacks of malaria, higher parasite density and placental parasitaemia. Therefore they experience more maternal anaemia and more adverse foetal outcomes [11].

3. PATHOPHYSIOLOGY OF PLACENTA MALARIA

Placental malaria is one of the major features of malaria during pregnancy and mainly caused by *P. falciparum* infection [12]. In malaria endemic areas, generally the women experience early exposure during their childhood and develop anti-disease immunity during adulthood. This immunity confers 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 child delivery 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, namely, 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 are 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 are hypothesised as the main contributing factors for the complications of malaria in pregnancy. Schantz-Dunn and Nour [19] Maternal anaemia is one of the most frequent 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 jeopardise foetal outcomes [13,14, 22]. Additionally, in sub-microscopic malaria, the parasites remain undetectable with microscopy and can only identified with Polymerase Chain Reaction (PCR). This type of malaria can also jeopardise the pregnancy outcome and significantly associated with maternal anaemia [23].

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 weekly chemoprophylaxis in pregnancy. However, widespread resistance caused lack of efficacy in the African region [24,25]. The WHO recommended the use of sulfadoxine and pyrimethamine as IPTp in Africa. Together with chemoprophylaxis, long-lasting insecticide treated nets (LLINs) are recommended for the use in stable malaria transmission areas [26]. Additionally, vector control measures such as indoor residual spraying (IRS) are being implemented as a part of the malaria control program [26].

In unstable malaria transmission regions, the WHO advocates the provision of the 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 shown potential to prevent the compilations in South-East Asia region [27].

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

Since malaria in pregnancy is preventable, the WHO recommends providing IPTp-SP in all the endemic areas of Africa [28]. Sulfadoxine and pyrimethamine are used as antifolate combination drugs. Pyrimethamine inhibits dihydrofolate reductase (DHFR) whereas, sulfadoxine inhibits the dihydropteroate synthase (DHPS) enzymes of the malaria parasites [29]. 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 [30]. Currently, 36 high-burdened countries have implemented IPTp-SP as their national policy [26]. A meta-analysis of datasets from 25 African countries has shown the benefits of IPTp-SP, resulting in the reduction of the low birth weight by 25% and neonatal mortality by 16% [31]. Moreover, a study in Ghana revealed that IPTp-SP users had significantly lower sub-microscopic malaria infection during pregnancy compared to IPTp-SP nonusers [23].

During the 1970s, the cure rate of SP was 80-90% in Asia [32]. At present, it is 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 [33,34].

In 2004, the WHO initiated the recommendation of providing IPTp-SP two doses after quickening,

where quickening is the first foetal movement usually occurring around week 18 to week 20 of pregnancy [18]. 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 [35]. 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.

In compliance with the recommended regimen to achieve the aim of IPTp-SP program more emphasis is required. In 2015, only 31% of pregnant women received the recommended three or more IPTp-SP doses in the report from 20 countries [26]. 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 most frequent causes of non-compliance to the recommended schedule [36,37]. Despite the huge number of IPTp-SP non-compliance pregnant women, there were few studies done 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 [38].

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 [11,39]. Therefore, the WHO recommends 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 [40]. 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) [41].

6.2 Sulfadoxine and Pyrimethamine Resistance

Resistance to sulfadoxine and pyrimethamine has been recorded in South East Asia since 1981 [42]. The SP resistant strains seem to have originated in South East Asia, South America and they were gradually introduced to Africa [43,44]. The accumulation of sequential mutations in the *Plasmodium falciparum* gene confers the resistance to SP, which may lead to treatment failure. The level of SP resistance is directly related to the accumulation of mutations in dihydrofolate reductase (*dhfr*) and dihydropteroate synthase (*dhps*) genes. The higher the mutations, the higher the resistance will be [45]. In West Africa, the double (*dhps* A437, K540) and triple mutations (*dhfr* N51, C59, S108) are very common [46]. 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 [46].

The increasing number of resistant parasites is a threatening matter for public health prophylaxis intervention, and health officers 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 a high prevalence of placental malaria [47]. Similarly, IPTp-SP was found to be not protective against adverse outcomes such as placental malaria and maternal anaemia in Tanzania [48]. 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 piperaquine (320 mg), IPTp-DP, is a potential regimen to prevent malaria in pregnancy. A randomised controlled trial in Kenya has shown that IPTp-DP lowered the prevalence of malaria infection at the time of delivery compared to the IPTp-SP regimen [49]. 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 [50].

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 [51]. The meta-analysis of 11 randomised controlled trials on the DP (standard three-day regimen) revealed that monthly DP was effective and had the potential to be used as an intermittent preventive treatment for malaria infection [52]. The phase 3 clinical trial had been 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 [53]. The outcome of the more extensive evaluation trails might be beneficial to evaluate the safety and efficacy of DP to provide as IPTp.

8. CONCLUSION

Currently, IPTp-SP is the only recommended regimen in the stable malaria transmission areas and still show 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 be continued 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 treatments with dihydroartemisinin and piperaquine, IPTp-DP have a potential to prevent malaria in pregnancy. The outcome of the more extensive clinical trials might contribute to evaluate the safety and efficacy of DP to provide as IPTp.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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