

Antimalarials During Pregnancy: A Review Article.

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Abstract

Plasmodium falciparum malaria in pregnancy poses substantial risk to pregnant women and their neonates. The WHO recommended that pregnant women with demonstrable malaria illness should be treated with effective and safe antimalarial drugs. Safety to the pregnant woman and her unborn child might be hampered by the spread of multi-drug resistant falciparum malaria and limited literature concern their usage during pregnancy. Chloroquine is generally considered safe in all trimesters of pregnancy; sulfadoxine- pyrimethamine appears safe in the second and third trimesters of pregnancy. Quinine is the drug of choice for severe malaria and has been reported to be safe even in the first trimester of pregnancy. Few reports are available concerning artemisinin usage during pregnancy although the World Health Organization recommended their usage during pregnancy. While Tetracyclines and primaquine are absolutely contraindicated during pregnancy, halofantrine, amodiaquine, mefloquine are of questionable safety during pregnancy. The first trimester of pregnancy (the period of organogenesis) is the critical period; only chloroquine and quinine were reported recently to have safety profile in this period. However, due to chloroquine resistance, quinine remains the drug of choice.

Key words: pregnancy, antimalarial, malaria

Introduction

Around 50 million pregnancies occur in malaria endemic areas every year, of which approximately half will occur in sub-Saharan Africa [1]. Pregnant women are more attractive to the main malaria vector [2] and are more susceptible to malaria than their non- pregnant counter- parts [3-4]. Malaria in pregnant women is associated with significant mortality and morbidity for both the mother and the fetus [4-7]. Treatment of all clinical episodes is the most available means to limit the impact of malaria on pregnancy and it has been recommended that pregnant women with demonstrable malaria illness should receive prompt treatment with effective and safe antimalarial drug [8, 9]. Case management is one of the packages of interventions for women to combat malaria during pregnancy as the current guidelines from the WHO Expert Committee on malaria suggest [10]. The treatment of malaria during pregnancy is confronted with the spread of multi-drug-resistant *P. falciparum* and the adverse effects of the drugs during pregnancy [11].

Chloroquine

Chloroquine, which is perhaps the most widely used antimalarial, is generally considered safe in all trimesters of pregnancy [12]. However, there are reports of increased spontaneous miscarriages particularly in cases of systemic lupus erythromatosis treated with high doses of chloroquine over a long period [13]. The current concept is not its safety but the wide spread of chloroquine resistant strains all over the world [11] and Sudan is not an exception [14].

Sulphonamides

Sulphonamides are also generally considered safe during the second and third trimesters of pregnancy; however, their usage in the first trimester was associated with increased birth defects [15, 16]. When given weekly as prophylaxis for a long period of time, SP has been associated with toxic reactions such as "Steven Johnson Syndrome", but there is no evidence that this was any greater in pregnant women [17]. Sulfadoxine-pyrimethamine is now the most common

antimalarial used for prophylaxis during the second and third trimesters of pregnancy, with excellent safety profile [18]

Quinine

Although quinine is the drug of choice for severe falciparum malaria [19], the American Food and Drug Administration (FDA) still categorizes it as a group x drug. This means that strong evidence against its usage during pregnancy had been noted. In the past, quinine had been reported to be associated with teratogenic effects and damage to the fetal optic and auditory nerves when taken at very high (abortifacient) doses [20-23]. These were retrospective reports and the exact numbers of patients were not known. Nevertheless, these reports may be behind the actual lag in the literature of quinine safety during pregnancy. This situation continued as it was and in 1968 quinine was reported as a labour-inducing agent [24]. Later on, when foetal monitoring was used for pregnant women with severe falciparum malaria, the uterine contractions were attributed to the high temperature rather than quinine. On the contrary, quinine had been found to have an inhibitory effect on uterine contractions through its antipyretic effect [25]. Recently hyperthermia had been reported among the human teratogens [26]. Quinine should be considered safe in pregnancy when taken at normal therapeutic doses [27, 28, & 29]. However, hypoglycaemia was one of the serious problems limiting quinine usage during pregnancy, but this problem could be avoided if quinine is used twice per day rather than the usual thrice a day regimen without affecting its efficacy [25, 30].

There is special concern of drug safety during early pregnancy, the period of organogenesis in human. While both artemisinins and sulphadoxine-pyrimethamine were reported to cause fetal resorption when given in the first trimester [15]. Recent reports of quinine use during early

pregnancy were free from any increase in the rate of miscarries or the rate of congenital malformations [27, 28].

Quinine failures were reported from Sudan among pregnant and non-pregnant populations [31, 32], in spite of similar response of pregnant and non-pregnant women [30].

Mefloquine

Mefloquine (MQ) is a quinolinemethanol compound that has been extensively used in Asia for the treatment of falciparum malaria either alone or in combination with other antimalarials. The safety of MQ has been evaluated through retrospective and prospective studies. An early study reported no increase in the rate of congenital malformations, when MQ had been used for prophylaxis during pregnancy [33]. However, in one prospective study MQ prophylaxis during pregnancy was more frequently associated with still birth than SP chemoprophylaxis, but this rate did not differ from that in the community [34]. Small-sized prospective study conducted in eastern Sudan reported no increase in the miscarriage or stillbirth rate, yet some cases of resistance to MQ were reported [35]. The rate of miscarriage was high when MQ was used for prophylaxis during early pregnancy [36]. Although, most data suggest that MQ is safe during pregnancy, data from a recent retrospective study in Thailand suggest a significant increase in risk of stillbirth among women treated with MQ [37]. This data highlight the need for continued vigilance in monitoring adverse events of women treated with MQ during pregnancy.

Proguanil

Proguanil is generally considered safe during pregnancy for the treatment or prophylaxis for falciparum malaria. Pregnant women who took it during the second and third trimesters showed no increase in the rate of miscarriage or congenital malformations [38-40].

Malarone

A fixed combination of atovaquone (250 mg) and proguanil (100 mg) and it is well and better tolerated in non- pregnant and pregnant populations [40, 41].

Amodiaquine

Several African countries have begun using amodiaquine-containing combinations as first-line antimalarial treatment, with the result that a substantial number of pregnant women are likely to be exposed to amodiaquine. However, little information is available on amodiaquine safety and efficacy during pregnancy. Amodiaquine delivered by mass drug administration or medicated salts gave very little information on amodiaquine safety. Therefore, there is an urgent need for studies on amodiaquine safety and tolerability during pregnancy since current data are not sufficient to recommend its use during pregnancy, particularly as an intermittent preventive treatment [42]. However, serious or life- threatening adverse effects (agranulocytosis, hepatotoxicity and aplastic anaemia) linked to the use of AQ had been reported during prophylaxis for long period [43].

Artemisinins

Artemisinins are relatively new drugs not related to quinolines and have been shown to be effective for multidrug-resistant *P. falciparum* strains [44]. Artemisinins are available in a variety of oral (artemisinin, artemether, artesunate and dihydroartemisinin), parental (artemether, artemether and artesunate) and rectal (artesunate and dihydroartemisinin) formulas. These compounds have received widespread attention in recent years for the treatment of severe falciparum malaria and multidrug-resistant falciparum malaria [45, 46]. Recent studies of pregnant women who received these compounds found no increase in the rate of miscarriage or congenital malformations and their babies had normal milestones [46-49], some of

these women received these compound in their first trimester of pregnancy and sometimes in combination with other antimalarials (MQ, SP). Recently a WHO consultancy has recommended the usage of these compounds during the second and third trimesters of pregnancy [50]

The fixed combination of oral artemether-lumefantrine (Coartem™), an artemisinin combination therapy is highly effective and well tolerated in non pregnant populations [51]. It is the second line treatment for uncomplicated *P. falciparum* malaria in Sudan. There is no any data about its safety during pregnancy until now.

Primaquine and doxycycline

Primaquine and doxycycline are generally contraindicated during pregnancy. Primaquine is used primarily for radical cure of *P. vivax* and *P. ovale*. It is contraindicated during pregnancy because of hemolytic event [52]. Tetracyclines can cross the placenta easily and lead to disturbance of skeletal growth, permanent discoloration of the teeth, cornea and lenses [53]. Doxycycline does not cause clinically significant staining of the teeth following use in childhood [54].

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