

RECENT TRENDS IN MANAGEMENT OF MALARIA IN PREGNANCY

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ABSTRACT

Malaria remains a significant causal factor in both maternal and fetal morbidity and mortality in this environment though it is essentially preventable. There are increasing incidence rates worldwide, including those areas of the world where, hitherto, malaria infection was rare.

More women than before now present with clinical malaria in pregnancy with both obstetric and non-obstetric complications, including severe anaemia, IUGR, miscarriage etc. Recent rapid diagnostic tests are available, more sensitive and specific than microscopy but their applications are limited in scope.

Antimalarial Combination Therapy (ACT), Intermittent Preventive Treatment (IPT), Insecticide Treated Nets (ITNs), good and adequate antenatal (ANC), intrapartum and postpartum care will ensure optimal health and reduction in the incidence rate of malaria infection in pregnancy.

KEYWORDS: RECENT TRENDS, MALARIA IN PREGNANCY, ROLL BACK MALARIA, ANTI-MALARIA COMBINATION THERAPY (ACT), INSECTICIDE TREATED NETS (ITNs).

INTRODUCTION

Malaria continues to be a scourge in tropical and subtropical regions of the world (1,2). Currently, it is endemic in about 100 countries, affecting 40% of world's population. The worldwide prevalence of the disease is estimated to be between 300 – 500 million clinical cases annually. Annual mortality due to malaria is estimated to be between 0.5 – 2.5 million people. More than 90% of world's malaria occurs in Sub-Saharan Africa. Malaria has been eliminated or effectively suppressed in several parts of the world

in past decades but is now undergoing resurgence (3). It is returning to areas from which it had been eradicated as well as spreading into new areas such as central Asia and Eastern Europe. Despite global economic development, people are dying from malaria now than 30 yrs ago.

EPIDEMIOLOGY AND CLINICAL FEATURES

Malaria in pregnancy remain a notable cause of maternal and perinatal morbidity and mortality, often associated with maternal illness, maternal anaemia, low

birthweight, preterm delivery and perinatal loss especially in the primigravidae (1-4). In semi-immuned pregnant women, malaria infection may be asymptomatic, pregnant women are at risk of clinical disease compared to non-pregnant women at all levels of endemicity (5). There is also destruction of both parasitized and unparasitized blood cells leading to a greater level of anaemia than can be explained on the basis of the RBCS parasitization alone (2,4).

It has been suggested that HIV positive pregnant women have malaria like non-immunes (5) and as such holoendemic regions like Africa, face the risk of the deleterious effects of malaria in previously semi-immuned pregnant women.

Primigravidity is a known risk factor in malaria in pregnancy. It not only becomes more prevalent in primigravidae but also more intense (4-7). The use of antimalarials in HIV/AIDS patients is thought to alter the glutathione levels and may exacerbate the oxidation-reduction imbalance attendant on HIV infection.⁶ There is increasing incidence in traveller's malaria noted in USA, Eastern Europe etc – this may be more related to the effect of globalisation, spread of chloroquine resistant strains of plasmodium species. Also the transmission rate and the degree of severity is worse in *P. falciparum* malaria than others hence worse severity is noted in African pregnant women.

The peak prevalence of parasitaemia will be altered by prior anti-malarial ingestion. In a study from Madan, Papua New Guinea, the peak prevalence in primigravidae studied reached 55% to compared to 86% in another study from Kenya (4,8,9). Studies have also suggested that the highest prevalence of infection occurs in the 2nd trimester with infection rates at delivery and in the postnatal period

approximating to levels in non-pregnant women possibly due to immunity boosting during the course of pregnancy (7).

Severe forms of the disease as reported by several authors (10-12) with hypersplenism (TSS) was prevalent then but it appears the prevalence of such severe form of malaria is rarer today especially in those semi-immuned patients who are routinely on malaria prophylaxis throughout the pregnancy (5,12,13) and linear growths have been reported in such primigravidae. Malaria is associated with miscarriages, preterm labour, Intrauterine growth retardation(IUGR) and even Intrauterine fetal death(IUFD). These effects are produced by maternal and fetal hyperpyrexia, severe maternal and fetal anaemia as well as placental parasitization. It was previously thought that malaria parasites do not cross the placenta into the fetal circulation. However recent studies have confirmed that congenital malaria is common in areas of high endemicity and is related to the immunological status of the mother (1-4,15,16).

The role of Chondrotic sulphate A (CSA).

Women living in endemic areas who were resistant to malaria between their pregnancy tended to lose this protection when they became pregnant.

This observation has often been interpreted as a consequence of the immunosuppression that is necessary to protect the fetus from being rejected by the mother's immune system. However, in malaria – endemic areas this increased susceptibility to malaria is disproportionately higher in primigravidae, a fact that is not easily explained by the fetus – related immunosuppression explanation.

The parasitized RBCs found in the placentae of primigravidae show a remarkable preference to binding to Chondroitin sulphate A (CSA), which is a ligand that is present on the placental syncytiotrophoblast but is not

readily accessible on cells elsewhere in the body. The high frequency of parasite found in the placenta that bind CSA can explain the susceptibility of primigravidae to clinical malaria and points to the importance to protection of immunization that is specific for parasite variants (14,15).

According to this hypothesis, any parasites that have adhesion specificity for CSA are eliminated from a non-pregnant individual, owing to a lack of a suitable adhesion receptor on the host cells, and presumably before they have induced appreciable levels to the CSA – specific plasmodium falciparum gene variants. In contrast, because CSA¹ becomes available in the developing placenta of primigravidae, parasites that are able to bind CSA and are present in the blood can suddenly multiply unhindered. With successive pregnancies, it can be assured that the levels of antibodies that are directed against the gene radiant molecules that can bind CSA increase, and are therefore able to limit the multiplications of CSA binding parasites; protection against pregnancy-associated malaria can be gradually acquired in this way (15).

The concept of Roll Back Malaria (RBM) Initiative is the only global initiative for the control of malaria. RBM is a global partnership to fight malaria, relying on national programmes on malaria control, international agencies/organisations, private sector participants and NGOs coming together to control or eradicate malaria. It is to further strengthen the existing strategies and interventions in order to maximize the impact of contribution from major stakeholders. This RBM initiative is to span a 10 year period (2001-2010) and has the following important elements:

- Bringing reliable, sustainable malaria prevention and early treatment to affected population.
- Investing in research and development of effective and affordable tools.

- Evaluating achievements against clearly defined goals: and.

- Building human and institutional resources (17).

The six critical elements of RBM which work together to help break the cycle of malaria transmission, cure patients and support developments are as follows:

- Evidence-based decisions using surveillance, appropriate response and building community awareness.

- Rapid diagnosis and treatment supporting home care, direct access to effective medications and wide availability of health services.

- Multiple prevention using insecticide-treated, net, environmental management to control mosquitoes and making pregnancy safer.

- Focused research to develop new medicines, vaccines and safe insecticides.

- Well coordinated action for strengthening existing health services, policies and providing technical support and

- Harmonized action to build a dynamic global movement.

DIAGNOSIS OF MALARIA

Prompt and accurate diagnosis is the key to effective disease management, one of the main interventions of the global malaria control strategy (19,20). Recent efforts have yielded more tools to diagnose reliably and accurately malaria other than the old reliable though cumbersome microscopic examination of blood.

Microscopy can still be considered as the 'gold standard' so long as highly qualified professionals are involved, quality of equipments and staining reagents are maintained and the type of blood smears (thick and thin films) are considered amongst others (19).

Rapid tests offer a complete package with all accessories needed, and their performance should be reliable, easy and safe to use even for junior staff and in

rural settings where microscopic examination of blood and all that it entails is cumbersome.

Rapid Diagnostic Tests (RDTs) are used to detect serum antigens of the plasmodia species using fixed antibodies onto strips of paper. The 2 main types are:

-Those that detect parasite enzyme lactose dehydrogenase (PLDH) from all four plasmodium species that affect humans. These can distinguish between *P. falciparum* from other species, but cannot distinguish between *P. vivax*, *P. ovale* and *P. malariae*.

-Those detecting histidine rich protein II (HRPII). This antigen is only produced by *P. falciparum*.

There are a number of disadvantages to the currently available RDTs. HRPII tests detecting only *P. falciparum* infection are not suitable for use in areas where other species are prevalent since none of the current RDTs can differentiate between *P. vivax*, *P. ovale* and *P. malariae* and none are quantitative which decrease their effectiveness for evaluating prognosis or the efficiency of antimalaria drugs.

HRPII may persist for up to two weeks after successful treatments, so tests based on this antigen cannot be used to measure response to therapy (18). The choice of diagnostic test depends on the level of malaria endemicity, the prevalence of drug resistance and on the availability of appropriately trained staff, equipment and financial resources.

All existing RDTs are more expensive than microscopy therefore the widespread use of RDTs in Africa is not justified at present. However, the rapid spread of drug resistance and the anticipated widespread introduction of malaria control measures may mean that in the future, this cost benefit analyses will favour the increasing use of RDTs in Africa (18). Importantly, pregnancy does not appear to interfere with the sensitivity or specificity pattern of the RDTs. Also, the histological and or cytological

examination of placental tissue, polymerase chain reaction (PCR), tests as well as DNA-in-situ hybridization tests on plasmodium antigens are also useful but mainly of research interests.

TREATMENT OF MALARIA IN PREGNANCY-RECENT TRENDS

Treatment of malaria in pregnancy differs from the treatment of the same woman outside pregnancy in several respects:-

-Frequency and severity of infections are more in pregnancy particularly among primigravidae.

-Anaemia is commoner in pregnancy associated with malaria infection as the 'physiological anaemia' of pregnancy is worsened by the destruction of red blood cells (RBCs) occasioned by parasitaemia.

-Placental parasitization limits and reduces nutrients to the fetus, amongst others, thereby predisposing to IUGR or fetal death (IUD).

-Severe malaria in pregnancy increases the risk of abortions, preterm delivery e.t.c.

-Neonatal morbidity and mortality are increased in congenital malaria.

-Proper and judicious antimalarial use both for cure and prophylaxis in tandem with haematinics have been shown to be beneficial to both mother and fetus and can improve growth in teenage mothers as well increase fetal birthweight and outcome.

-Antimalarials useful outside pregnancy may become toxic to the fetus in pregnancy e.g Halfan, Metakelfin etc.

The pregnant women with malaria infection must be treated both medically and obstetrically, taking care of both maternal and fetal interests.

The principles of management of malaria in pregnancy

will include:

-Rapid and efficient diagnosis of malaria in pregnancy

-Adequate treatment of acute episodes of malaria in pregnancy.

-Prevention of complications such as severe uncomplicated malaria, cerebral malaria, anaemia, prematurity, congenital malaria as well as other maternal and fetal complications.

-Proper and continuous evaluation of the fetus during pregnancy

-Mandatory haematinics throughout pregnancy.

-Preventive measures in vector control including Insecticide-Treated-Nets(ITN), Insecticide Treated Materials (ITM) etc.

It is reasonable to expect confirmation of malaria infection in pregnancy, but majority of cases will present in rural areas (where microscopic diagnosis of malaria infection is limited) and also because they often present late and acutely ill, presumptive treatment with adequate doses is recommended between the result of the tests (2-7).

The choice of a suitable drug is predicated upon many factors, including gestational age of fetus, severity of the disease (whether complicated or not), the resistance of the infecting malaria parasites to the antimalaria drugs, cost of medications and the safety profile of the drug in both mother and the fetus. Ideally, effective care should clear both peripheral and placental parasites (5,6,18,21).

Intermittent Preventive Treatment (IPT) involves providing all pregnant women with at least two preventive doses of an effective antimalarial drug during routine antenatal clinic visits. This approach has been shown to be safe, inexpensive and effective (12-15). A study in Malawi, evaluating IPT showed a decline in placental infection (32% to 23%) and in the number of low birth weight babies(23% to 10%). It also found that 75% of all

pregnant women took advantage of IPT when offered (21).

Commonly used drugs for the treatment of uncomplicated malaria in pregnancy is Chloroquine (CQ) in areas where the parasites are still sensitive, for example, most of West Africa, and Sulphadoxine- pyrimethamine (S-P) in areas of chloroquine resistance but where parasites still retain sensitivity to S-P. Other drugs used, though not commonly, in pregnancy include Amodiaquine Mefloquine, Quinine, Artemeter etc.

Antimalarial combination therapy (ACT) is now recommended by the WHO to treat or prevent drug resistance. Combination therapy enhances the activity and effectiveness of the drugs in synergism; also limits drug resistance. Usually both drugs have independent modes of actions. Commonly used ACTs include CQ/SP and Amodiaquine(AQ)- SP, but less common ACTs include AL-SP(Mefloquine-SP combination), AQ-AS, Proguanil-Dapsone(PG-DP)(LAPDAP) etc. There is increasing worry about the toxic effects of some of these drugs during pregnancy. For example, whereas CQ and Amodiaquine are very safe during all trimesters of pregnancy, SP, Mefloquine, Artemisin / Artemeter / Artesunate, either alone or in combination should be avoided in the first trimester of pregnancy. Lumefantrine and LAPDAP are still considered unsafe in pregnancy and more research efforts are currently directed towards its possible use in pregnant women (5).

In treating complicated or severe malaria in pregnancy, parenteral quinine or artemisin are the commonly used agents. Intravenous quinine is usually of as a loading dose of 20mg/ kg body weight over 4 – 6 hrs and followed 4–6 hrs later by 10mg/kg body weight; this is usually given until oral medication can be tolerated. The full treatment covers 5 – 7 days. When used as part of the ACT, e.g with

SP or artesunate, this treatment can be shortened to 3 days (5).

In complicated malaria in pregnancy, anemia and preterm contractions are common complications. Anaemia can be treated with oral double dose haematinics (ferrous-folic acid combination) or blood transfusion of packed cells. In severe anaemia (Hb <4gm%) or anaemic heart failure, exchange blood transfusion under diuretic cover may prove more beneficial than administration of straight whole blood transfusion alone. Injectable or oral forms of salbutamol will reduce the uterine contractions; this should be continued for a few more days after the feverish episodes have subsided.

OBSTETRIC MANAGEMENT OF PREGNANT WOMEN WITH MALARIA INFECTION.

Obstetric management is an integral part of the complete management of the malarious pregnant woman. It consists of antepartum, intrapartum and postpartum care.

ANTEPARTUM CARE OF PREGNANT WOMEN WITH MALARIA.

Essentially, during the antepartum or prenatal period, the antenatal clinic forms the template upon which the institutional treatment is based. As part of the routine antenatal care, history of malaria (in terms of frequency, severity and treatment history) is obtained; blood tests including full blood count and malaria parasites are routinely requested for. Harrison et al in their study from Zaria, Nigeria (12-14) had advocated for routine administration of oral Chloroquine tablets in curative doses at the booking clinic as well as prophylactic (IPT) doses during the subsequent visits. Other authors (2,5,23) agreed that S-P combination can be an effective substitute in areas where Chloroquine resistance is widespread. There is

usually a concomitant use of haematinics throughout pregnancy.

Insecticide treated Nets (ITNs) are valuable tools in controlling the malaria infection: this has proved very useful in Africa and elsewhere (23). ITNs decrease both the number of malaria cases and malaria death rates in pregnant women and their children. A study in an area of high malaria transmission in Kenya has shown that women protected by ITNs every night during their first four pregnancies produce 25% fewer underweight or premature babies. In addition, ITN use benefits the infant who sleeps under the net with the mother by decreasing the exposure to malaria infection (21). ITNs should be provided to pregnant women as early in pregnancy as possible, and their use should be encouraged for women throughout pregnancy and during the postpartum period. Health education programmes, social marketing and lobbying to reduce the prices of ITNs and re-treatments are helping to encourage the use of ITNs by pregnant women. There are prospects for long-lasting treated nets which are wash-resistant and based on the most recent technological development in the field of bio-active fibres and fabrics. These nets release insecticide over time and maintain their activity for at least 4years (21).

Regular antenatal attendance is of great importance as a single missed monthly clinic visit can result in a two-fold increase in malaria incidence (15). Increased awareness on the effects of malaria and anaemia on pregnancy during the booking period has been known to improve antenatal clinic attendance and compliance to treatment. The Roll back Malaria (RBM) Initiative and Safe Motherhood Programme place the antenatal treatment and control of malaria in pregnant women on a high pedestal in achieving improved maternal and fetal morbidity and mortality.

INTRAPARTUM MANAGEMENT OF MALARIA IN PREGNANCY

Active management of labour ensures constant monitoring of the parturient woman. In the event of intrapartum malaria or prelabour malaria, the elevated body temperature and associated dehydration can cause adverse conditions such as maternal and fetal tachycardia which may contribute to fetal morbidity and possible mortality.

Intrapartum management of parturient malarious women should include treatment of the acute malaria with suitable agents (according to the local sensitivity pattern) and avoiding the S-P combination because of its increased tendency to cause neonatal jaundice. In severe cases, Quinine and the Artemisin derivatives are suitable agents. Concomittant rehydration, analgesia and antipyretics are mandatory. Input and output chart intrapartum will closely monitor the renal effect in such women in labour. Presence of proteinuria or haemoglobinuria should make the exclusion of eclampsia or the blackwater fever complicating severe malaria imperative. However, these two can co-exist in an haemoglobin SS disease patient with often severe fatal outcome. Pseudo-toxaemia in pregnancy of such patients needs to be differentiated from the more pathologic severe pre-eclampsia or eclampsia.

Routine intrapartum haemoglobin check is mandatory as ongoing haemolysis or pre-existing maternal anemia can substantially affect maternal and fetal outcome (18). Blood transfusion may be necessary to mitigate against such undesirable outcomes.

POSTPARTUM MANAGEMENT OF MALARIA IN PREGNANCY.

Following delivery, the mother should complete her antimalarials and supportive treatment. The fetus should be properly examined and congenital malaria excluded.

The newborn's peripheral venous blood should be done to check for malaria parasites. Cord blood and placental smears should be taken for analysis. Experience by many authors (4-6) have shown that heavy maternal parasitaemia significantly increases placental parasitization and fetal parasitaemia with consequent fetal anaemia and possible fetal demise.

It is noteworthy that studies have also reported positive neonatal parasitaemia up to the first week in an otherwise negative parasitaemic neonatal at birth; this can be explained by the passage of the parasitized cells out from the hepatic stage usually after three days. It is therefore advocated that in suspicious babies, peripheral blood collection can be done up to the end of the first week since any parasitaemia after the first week may be due to a newly acquired postnatal infection (2,4). Treat the neonatal for malaria infection with suitable agents, which may include Chloroquine, Quinine, Artemisin etc. Avoid the use of S-P, LAPDAP in the neonatal period. Correction of neonatal anaemia and monitoring of the neonatal jaundice level may necessitate exchange blood transfusion (EBT) and physiotherapy.

The use of malaria vaccine in both the mother and the fetus postpartum is still inconclusive and controversial and many trials are underway to ascertain their safety profile and effectiveness.

CONCLUSION

Malaria in pregnancy remains a significant contributor to maternal and fetal morbidity and mortality. Adequate and effective diagnosis as well as judicious antimalarial treatment and supportive

services will help reduce the magnitude of maternal and fetal loss.

The concept of Roll Back Malaria incorporating the use of ITNs, intermittent use of antimalarials antenatally, adequate treatment of malarious attacks etc as well as adequate and effective antenatal, intrapartum and postpartum care of the mother and child should effectively reduce the scourge of the consequences of malaria in pregnancy.

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