Malaria in Pregnancy

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SUMMARY

Malaria remains one of the highest contributors to the precarious maternal mortality figures in sub-Saharan Africa. At least 6 million women worldwide are at risk of malaria infection in pregnancy. Malaria contributes to at least 10,000 maternal deaths and to at least 200,000 newborn deaths annually. Malaria is a contributor or aetiologic factor in pregnancy complications including anaemia, spontaneous abortion, prematurity and stillbirths. Pregnancy results in increased incidence and severity of malaria. Cerebral malaria, acute renal failure and severe anaemia, rare complications in adults living in malaria endemic areas, may complicate malaria in pregnancy. Research implicate reduced maternal immunity from increased steroid levels in pregnancy, increased attractiveness of pregnant women to mosquito bites and increased adherence of parasitized erythrocytes to Chondroitin sulphate A expressed in the placentae. This is worse in the first and second pregnancies. With infection with the Human Immunodeficiency Virus [HIV], the effects of malaria in pregnancy are even worse.

Over the decades, there have been concerted worldwide collaborative efforts, spearheaded by the World Health Organization [WHO] and including governments and allied agencies to tackle the scourge of malaria in pregnancy. The main thrusts of such efforts have been: to increase the use of insecticide treated mosquito bed nets [ITN]; intermittent preventive treatment of malaria [IPT]; and adequate case treatment of acute malaria attacks in pregnancy. While for IPT, Sulfadoxine-Pyrimethamine [SP] combination has been proven to be of benefit in preventing acute and latent malaria in pregnancy and its associated complications, the WHO has introduced the use of Artemisinin-Combination Therapy [ACT] for the first-line treatment of uncomplicated malaria in pregnancy, the need to confirm malaria before treatment and the enforcement of completion of therapy once started. The Roll Back Malaria [RBM] campaign was launched as a strategy to curtail the incidence and scourge of malaria especially in the vulnerable groups including pregnant women. The Millennium Development Goals [MDGs] offer a new hope if adequately pursued to achieving eradication of malaria and its complications in pregnancy. There is need to support research into effectiveness and utilization of established and newer control measures.

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INTRODUCTION

'The scourge never ends'. This may be an apt description for one of the world's most prevalent infectious diseases-malaria. Malaria potentially affects about 50% of the world's population majority of who live in sub-Saharan Africa. Pregnant women and the under fives form the bulk of its worst victims in endemic areas[1-4]. Almost 30 million women are threatened by malaria in pregnancy annually with about 10,000 maternal mortalities attributed to the disease each year and about 200,000 newborn deaths annually[4,5]. It is obvious that malaria in pregnancy causes tremendous strain on already weakened health systems in endemic countries. The emergence of the Human Immunodeficiency virus scourge has introduced a worsened dimension to an already precarious condition. These all combine to make malaria infection a major public health problem in the tropics and subtropics.

The Association between Malaria And Pregnancy

Malaria on Pregnancy

Malaria has been shown in many studies to worsen certain pregnancy outcomes. These include an increased incidence of anaemia and spontaneous abortions. Others include intrauterine growth restriction [IUGR], stillbirths, prematurity, low birth weight, fetal distress and congenital malaria. The biological basis for these adverse outcomes has been extensively studied. Erythrocytes infected with Plasmodium falciparum accumulate in the placental bed. This is through adhesion of the infected erythrocytes to molecules of Chondroitin A present in the placenta6. A prevalence of placental parasitaemia of between 10 and 45% in malaria endemic areas has been reported with significant Plasmodium falciparum dominance1,[7,8] while our study in 2007 revealed a mean number of malaria parasites of 4250 parasites/µl as against 626 parasites/µl in peripheral blood1. Intraplacental parasitemia has also been shown to increase with gestational age8 with the highest risk of infection being in the second trimester[7] and often extending to the immediate postpartum period[9-11]. The effect of malaria in pregnancy is worse in the first and second pregnancies compared to higher parities[6,7]. Acute infection with high levels of placental parasitemia has been associated with preterm delivery[8,12] while

chronic placental parasitization is associated with intrauterine growth restriction, lower maternal hemoglobin and severe anaemia[13-15]. Despite the advance of medical knowledge on these effects, a recent study of pregnant women in our environment showed a poor knowledge of the fetal risks associated with malaria in pregnancy[16].

Pregnancy on Malaria

Pregnancy increases the frequency and severity of most infectious diseases but its effect on malaria seems worse[6,7]. Several theories have been put forward to explain this increased risk including changes to the cellular immune responses that otherwise should offer protection, and increased attractiveness of the pregnant woman to mosquitoes. The former is believed to result from the increased level of circulating maternal steroids in pregnancy[17]. This was the subject of the extensive research by Bouyou-Akotet et al in which they surmised that a sustained increase in cortisol level underlies the increased susceptibility of pregnant women to malaria[18]. Lindsay et al found that pregnant women attracted twice the number of anopheles mosquito compared to their non pregnant counterparts[19]. This they believed may be connected to certain physiological and behavioural changes that occur in pregnancy including increased volume of exhaled air and release of volatile substances from their skin surfaces due to increased skin temperature associated with pregnancy[19]. These substances may be detected by the mosquitoes hence leading to increased attractiveness of the pregnant woman to mosquito[19,20]. The susceptibility to malaria including its complications like anaemia is worse in the first and second pregnancies especially in young gravidaes[6,7,21].[Tables I & II] Though many of the infections may be asymptomatic in women in endemic countries, this does not preclude placental parasitization and its deleterious effects[7,17,21]. Up to 20% of pregnant women in endemic areas have asymptomatic parasitemia and a recent study showed that about 40% of these will present with clinical malaria within a four week period[17,21,22]. Cerebral malaria, acute renal failure and severe hemolysis, complications of malaria that are rare in adults in endemic areas, may be seen in pregnancy[17]. Our recent cross-sectional survey in Benin City showed that about 64-87% of pregnant women reported symptoms suggestive of malaria infection though a majority of these never had any confirmatory tests done[16,21]. With advancing parities, the immunologic protection against malaria in pregnancy increases.

Malaria in Pregnancy and HIV

The emergence of the Human Immunodeficiency Virus (HIV) scourge has further compounded the woes resulting from malaria in pregnancy. HIV infection impairs a pregnant woman's ability to control Plasmodium falciparum infection. HIV has been shown to increase the risk of placental malaria [RR-1.66], high density malaria parasitemia and febrile illness[23]. HIV in association with malaria increases the degree to which malaria is associated with maternal severe anaemia and low birth weight beyond the effect that will be expected of HIV alone. The protective effect of parity on the complications associated with malaria in pregnancy is blunted by HIV[23].

Malaria and Preeclampsia

Various studies have reported the association between malaria and preeclampsia. Basically, both diseases have been considered as diseases of the placenta[24]. Reduced placental perfusion has been a recognized feature of both pre-eclampsia and malaria[25]. Both conditions are commoner in young primigravidae and are associated with increased incidence of intrauterine growth restriction and maternal mortality[24]. Women with pre-eclampsia have been shown to have a three-fold increased risk of malaria parasitemia. Also, a five- fold increase of maternal death from eclampsia has been reported during the rainy season when malaria is more prevalent[26]. Nevertheless, the question as to whether the relationship is causal or casual is the object of further research[24].

Natural Immunity against Malaria in Pregnancy

Due to persistent exposure to mosquito bites, adults living in endemic areas develop natural immunity against malaria fever. This immunity which is mediated through hormonal and immunologic mechanisms is especially useful in pregnancy[6]. Antibodies directed against the surface of infected erythrocytes in the placenta protects against malaria complications. However, the production of these antibodies against infected placental erythrocytes is gravidity dependent hence this mechanism of protection is often absent in the first and sometimes second pregnancies[6].

Control of Malaria in Pregnancy

Over the decades, there have been worldwide concerted efforts, spearheaded by the World Health Organization (WHO) and including Governments of malaria endemic countries and allied donor agencies to tackle the scourge of malaria in pregnancy. One of these collaborative efforts was the Roll Back Malaria (RBM) initiative. The main thrusts of the campaign were hinged on three strategies: the use of insecticide treated nets (ITN); intermittent preventive treatment of malaria (IPT); and adequate case treatment of acute malaria in pregnancy. These strategies have been individually studied and found to confer immense benefits if adequately implemented.

Insecticide Treated Nets [ITN] have long been in use. These are mosquito nets that have been treated with Pyrethroids substances known to be deleterious to mosquitoes, the insects that spread the causative organisms that cause malaria[27]. ITNs have been shown to be safe and devoid of toxity when used according to instructions[27]. The nets are expected to be retreated every 6 months with pyrethroid. The Long Lasting Nets [LLN], which are factory treated with longer lasting insecticides whose potency last over 3 years, have been introduced but are not yet in wide spread circulation. Dedicated use of the ITNs has been shown by a recent Cochrane review to reduce placental malaria (RR 0.79), Intrauterine Growth Restriction (RR 0.77) and still births and spontaneous abortions (RR 0.67) and the protection cuts across all gravidae[2,28]. Despite these indisputable benefits of the use of ITNs, our study in Benin City showed that there is poor knowledge amongst parturients of the ability of ITNs to prevent malaria[16]. Also following expiration of the insecticide activity of the ITNs, most of the nets are not taken for retreatment

due to ignorance and cost.

Intermittent Preventive Treatment [IPT] of malaria in pregnancy refers to the giving of at least 2 preventive treatment doses of an effective antimalarial drug during routine antenatal care to all pregnant women. Historically, weekly Chloroquine tablets or weekly Pyrimethamine tablets were given to prevent malaria in pregnancy but low compliance and then resistance led to the new concept of IPT[29-31]. The present concept involves the use of Sulfadoxine-Pyrimethamine [SP] combination. The SP combination has shown great promise in prophylaxis against malaria in pregnancy. Its prophylactic effect may last 2-3 months in areas with sensitive parasites[31,32]. In asymptomatic malaria infection, SP clears placental parasitization which has been proven to be the culprit in the causation of the various complications. Based on this, it is advocated that SP be given at least twice in pregnancy with the first dose being given early in the second trimester and the subsequent doses given at least 4 weeks apart. In patients with increased risks as in HIV positive patients, at least 3 doses of SP is advocated while in sicklers, daily doses of Paludrine is the preferred prophylaxis. The beneficial effect of SP is significant mainly in the first and second pregnancies[2]. SP could find further advantage as therapy for acute malaria fever. However, there is need to restrict SP to IPT to prevent resistance[2]. There have been concerns raised about the blunting of acquisition of pregnancy specific malaria immunity and newborn susceptibility to malaria following IPT[32]. This is undergoing further research. A recent Cochrane review showed that IPT led to a statistically significant reduction of placental malaria [RR-0.34] and severe anaemia [RR-0.62][7,33].

Adequate Case Treatment

This involves the use of effective chemotherapeutic agents to treat acute malaria attacks. In its most recent publication, the WHO introduced new guidelines for malaria treatment[34]. This involves the use of Artemisinin-based Combination Therapy [ACT] as first line treatment for uncomplicated malaria. It also emphasized the need to confirm diagnosis of malaria before treatment and the need to complete therapy once commenced to prevent resistance. Proper treatment of acute cases has been shown to prevent placental parasitization[35].

Other Control Measures

Age long tested measures need to be strengthened in the fight against malaria in pregnancy. Environmental sanitation, provision of better housing conditions and improved socio-economic stratus of the citizenry are all useful measures in this regard. Clearing of bushes, avoidance of stagnant water and female empowerment are among some specific measures to control malaria in pregnancy.

Strategies

Malaria in pregnancy still exerts its toll on pregnant women and their unborn babies today because of poor implementation of known key practices. Implementation of strategies has been the focus of numerous programmes. One of the major of these is the ROLL BACK MALARIA [RBM] initiative. This initiative was launched in 1998 by the WHO, UNICEF, UNDP and the World Bank. It aimed at bringing together various stakeholders including governments of endemic countries to forge a common front against malaria. The African summit on RBM was held in Abuja, Nigeria on the 25th of April, 2000. The major target was to reduce the burden of disease associated with malaria by 50% by 2010. Among strategies for delivery of the various interventions include an increase in the scope of antenatal care, avoidance of drug resistance to available chemotherapeutic agents and to increase utilization of antenatal care. In the course of these interventions, the massive distribution of ITNs to households was to be a major target. While a worthwhile venture, massive campaigns to promote the use is important as majority of women in a recent study conducted in Benin City are not aware of the potential benefit of the use of ITNs[16]. For effective utilization of the IPT of malaria, incorporation into the routine antenatal care holds the key to compliance[36]. The WHO reports that over 60% of pregnant women in sub-Saharan Africa have at least one antenatal care visit5. Therefore implementing the DIRECTLY OBSERVED TREATMENT [DOT] of SP will go a long way in achieving reduction in the dangerous effects of malaria in pregnancy. Recently, the WHO has, in collaboration with partners, developed rapid diagnostic test strips to diagnose malaria before instituting chemotherapy to avoid the emergence of resistance. The need to improve the system of drug supply and to assist governments in stamping out fake and substandard drugs is also being addressed as part of the key strategies of control of malaria in pregnancy.

In 2010 already, it is obvious that there has been failure in achieving the set goals and targets. Despite the tagging of the years 2001-2010 as the United Nations decade to roll back malaria, implementation of the various policies has remained poor. Having missed this target, another opportunity exists with the Millennium Development Goals [MDGs]. The need to improve maternal health and combat malaria are two of the MDGs[37]. With the target days as 2015, this may be considered as another window of opportunity following previous missed opportunities. Malaria control programmes must be intergrated with other programmes aimed at combating maternal mortality[36]. Involvement of the communities in the programme will improve uptake. Research on issues of malaria should engender generous support and encouragement. Notable areas of research will include ways to improve uptake of established prophylactic measures and discovery of more efficient control measures. Ongoing research on vaccine against malaria needs also to be supported. Production of vaccines to prevent adherence of infected erythrocytes to Chondroitin sulphate A is a possible measure that could reduce the complications associated with malaria in pregnancy especially in young primigravidae[6]. As we take stock of measures so far put in place, the 50th anniversary of the Nigerian Medical Association [NMA] and coincidentally the 10th anniversary of the African RBM summit should be a time for sober reflection and a time for renewed commitment by governments at all levels to the fight the unending scourge of malaria in pregnancy.

Table 1: P. falciparum infection rates and densities assessed with microscopy among pregnant women attending two antenatal clinics in Edo State, Nigeria

	Parasitised		Parasite density		Non-parasitised		
Characteristic	**n**	**(%)**	**Mean count ± SD**	**Range**	**n**	**(%)**	**p value[a]**
Parasitaemia (overall) (n = 630)	125	19.8	2,920.35 ± 3,033.98	20011,000	505	80.2	
Parasitaemia by gravidity[b]							
Primigravidaeb (n = 115)	28	24.3	1,897.75 ± 1,295.31	3905,333	87	75.7	0.393*
Secundigravidae (n = 138)	27	19.6	1,691.66 ± 2,099.79	16811,000	111	80.4	
Multigravidae (n = 372)	69	18.5	1,805.48 ± 1,770.35	1959,828	303	81.5	
Parasitaemia by trimesterc							
First trimester (n = 17)	4	23.5	767.00 ± 281.44	5001,143	13	76.5	0.444**
Second trimester (n = 165)	38	23.0	1,831.61 ± 1,727.91	2008,213	127	77.0	
Third trimester (n = 389)	72	18.5	1,981.92 ± 2,099.94	16811,000	317	81.5	

[a]Chi-squared test, *χ^2 = 1.866, **χ^2 = 1.622. [b]p (ANOVA) = 0.649 (primigravidae vs secundigravidae vs multigravidae). cp (ANOVA) = 0.040 (first vs second vs third trimesters).

Table 2: Anaemia among pregnant women attending two antenatal clinics in Edo State, Nigeria

	Cases		Mean haemoglobin concentration		
	n	**(%)**	**g/dl ± SD**	**Range**	**p value[a]**
Non-anaemic	203	33.1	11.10 ± 0.28	11.0012.00	
Anaemiab	400	65.1	9.73 ± 0.85	7.2010.80	
Primigravidae	78	70.9	9.83 ± 0.67	7.8010.80	0.322*
Secundigravidae	83	61.9	9.81 ± 0.83	7.5010.80	
Multigravidae (n = 370)	239	64.6	9.71 ± 0.87	7.2010.80	
Severe anaemiac	11	1.8	6.63 ± 0.5	5.306.90	
Primigravidae (n = 110)	3	2.7	6.83 ± 0.12	6.706.90	0.575**
Secundigravidae (n = 134)	3	2.2	6.17 ± 0.81	5.306.90	
Multigravidae (n = 370)	5	1.4	6.59 ± 0.30	6.006.52	

[a]Chi-squared test, *χ^2 = 2.265, **χ^2 = 1.107. [b]Haemoglobin concentration <11g/dl; p (ANOVA) = 0.277 (primigravidae vs secundigravidae vs multigravidae). cHaemoglobin concentration <7g/dl; p (ANOVA) <0.0001 (primigravidae vs secundigravidae vs multigravidae).

Table 3: Sequelae of malaria parasitemia (4 weeks follow up)

Level of parasitemia at booking	**MP+**	**MP++**	**MP+++**
Number of asymptomatic patients at booking	26	13	9
Number/Percentage of patients who developed symptoms of malaria after 4 weeks	6(23%)	6(46%)	5(56%)

Pearson's χ^2 =1.860. P value =0.394

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