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MALARIA IN PREGNANCY: MORBIDITIES AND MANAGEMENT

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ABSTRACT

Malaria infection during pregnancy remains an important public health concern especially in the tropics with substantial risk for the mother, her fetus and the neonate. More than 25 million African women in malaria endemic areas get pregnant and are at risk of infection with Plasmodium falciparum. Several pregnancy complications including miscarriage, preterm labor, intrauterine growth restriction (IUGR) and intrauterine fetal death (IUFD) have been associated with malaria. In early pregnancy treatment options are very limited partly due to drug resistance and the uncertainty about the safety of some antimalarials in pregnancy. Quinine still remains safe in all trimesters. A package of interventions for the prevention and control of malaria in the African Subregion during pregnancy has been recommended by the World Health Organization (WHO). These include intermittent preventive treatment (IPT), use of insecticide treated nets (ITNs) and access to effective case management for malaria illness and anemia.

Keywords: malaria in pregnancy, treatment, insecticide treated nets, intermittent preventive therapy.

INTRODUCTION

Malaria infection during pregnancy remains an important public health concern especially in the tropics with substantial risk for the mother, her fetus and the neonate[1]. It's estimated in 2010 that 216 million episodes of malaria occurred worldwide with resultant 655,000 deaths[2]. Up to 91% of malaria burden in that year occurred in Africa.

Malaria costs Africa an estimated 12 billion US Dollars in lost production annually[3]. At least 3,000 people die from malaria every day. Malaria also accounts for 40% of public health expenditure, 50% of outpatient visits and 30-50% of hospital admissions in areas where transmission is high[4,5].

Pregnant women and their infants are highly vulnerable to malaria. More than 25 million African women in malaria endemic areas get pregnant and are at risk of infection with Plasmodium falciparum[3,6]. Among pregnant women, studies have shown that the highest prevalence of malaria infection occurs in the 2nd trimester, with infection rate at delivery and in the postnatal period approximating to levels in non-pregnant women[7].

Several pregnancy complications like miscarriage, preterm labor, intrauterine growth restriction (IUGR) and intrauterine fetal death (IUFD) have been associated with malaria

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infection. These complications are produced by maternal and fetal hyperpyrexia, severe maternal and fetal anemia as well as placental parasitization[8]. Areas with seasonal transmission are endemic for malaria infection; usually confer a protective semi-immunity against Plasmodium falciparum to adult women during the first 10-15 years of life[16]. Adult women living in areas of unstable non endemic transmission, have no significant level of immunity, are more likely to be symptomatic when infected and at greater risk of having severe disease and of death.

Pathophysiology

Malaria infection develops via two phases: one that involves the liver (exoerthrocytic phase) and one that involves the red cell (erythrocytic phase). When an infected mosquito pierces skin to take a blood meal, sporozoites in the mosquitos'saliva enter the blood stream and migrate to the liver where they infect hepatocytes, multiplying asexually and asymptomatically for a period of 8-30days.

After potential dormant period in the liver, these organisms differentiate to yield thousands merozoites, which following rupture of their host cells escape into the blood and infect red cells to begin the erythrocytic stage of the life cycle. The parasite escapes from the liver undetected by wrapping itself in the cell membrane of the host liver cell.

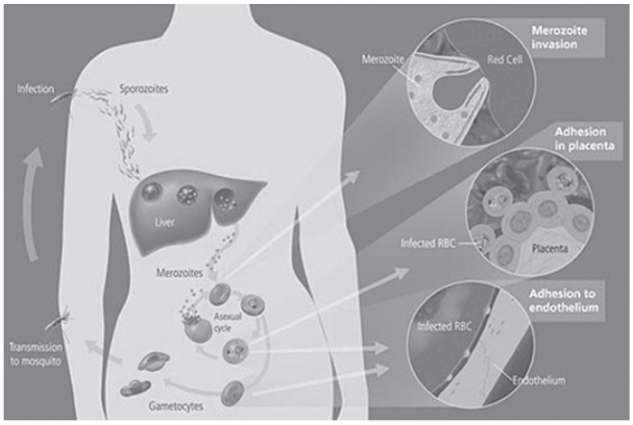
Within the red cell the parasites multiply further again asexually, periodically breaking out of their host cells to invade fresh red blood cells, thus the classical descriptions of waves of fever arise from these simultaneous waves of merozoites escaping and infecting red blood cells. Other merozoites develop in to immature gametes or gametocytes. When a fertilized mosquito bites and infected person, gametocytes are taken up with the blood and mature in the mosquito gut, fusing to form zygote which develops in to new sporozoites.

What is the risk of vertical transmission of malaria infection to the baby?

Vertical transmission to the fetus can occur particularly when there is infection at the time of birth and the placenta and cord are blood film positive for malaria (Appendix 2).

All neonates whose mothers developed malaria in pregnancy should be screened for malaria with standard microscopy of thick and thin blood films at birth and weekly blood films for 28 day

Malaria transmission Life cycle



Effect of Pregnancy on Malaria

Pregnant women are more susceptible to malaria infection when compared to non-pregnant women. They are more likely to become infected with Plasmodium falciparum malaria with more tendency towards increased severity of the disease[9,10,11]. This is partly due to transient depression of cell mediated immunity that occurs during pregnancy[12].

Because of enhanced pancreatic B cell function in pregnancy, pregnant women are also prone to hyperglycemia and are at risk of symptomatic hypoglycaemia when infected with plasmodium falciparum, as a result of maternal

hyperinsulinemia, parasite glucose requirements, maternal glucose requirement during febrile illness and decreased oral intake related to anorexia and emesis[13].Chondroitin sulphate A (CSA) is a ligand that is found on the placental syncytiotrophoblast. This ligand is not readily accessible on cells elsewhere in the body. Parasitized red blood cells (RBCs) found in the placentae of primigravidae manifest a remarkable preference to binding chondroitin sulphate A (CSA). This could explain the susceptibility of primigravidae to clinical malaria[24,25]. Studies have shown that anti adhesion immunoglobulin G antibodies against chondroitin sulphate A binding parasites are associated with protection of maternal malaria that is developed in subsequent pregnancies[16].

Effect of Maternal Malarial Infection On Pregnancy

The effect of malaria in pregnant woman varies with several factors such as the woman gravidity, level of immunity, trimester of pregnancy and the presence or absence of comorbidity[14]. Low parity, especially primigravidae and younger age are more susceptible to malaria infection[15]"Pregnancy-associated malaria is characterized by placental malaria and the sequestration of malarial parasites"[20]. Accumulation of plasmodium infected erythrocytes in the intervillous space, in the placenta, causing histologic changes including leukocyte-induced damage to the trophoblastic basement membrane is referred to as placental malaria[21]. This infection can occur in the absence of clinical symptoms[22]. Placental malaria and maternal anemia can precipitate preterm delivery leading to IUGR[23]. Malaria in pregnant women is an important cause of stillbirths, and low birth weight, acute respiratorydistress syndrome ARDS may develop in adults and in up to 25% of pregnant women.

Management

Table 1: *Schedule of Treatment of Acute Malaria*

Drug	Dosage	Route	Trimester	Complication
Chloroquine			All trimester	
Quinine	20 mg/kg loading dose in 5% dextrose over four hours and then 10 mg/kg over four hours.	Intravenous	All trimesters	
Quinine+Clindamycin	450mg,QDSx7days	Oral	All trimesters	
ACT:artemesin-combination-therapy			Second/third trimester	
Artesunate	2.4 mg/kg at 0, 12, 24 hrs, then Oral 2 mg/kg	Intravenous	only	
Riamet	three day course of (artemether (20mg) / lumefantrine (120mg)	Oral		
Malarone	atovaquone-proguanil (malarone).	Oral		
Primaquine	15 mg and 30 mg respectively, daily for 14 days54	Oral	Avoid in a ll trimesters	

Admit pregnant women with uncomplicated malaria to hospital and pregnant women with severe andcomplicated malaria to an intensive care unit.Intravenous artesunate are the treatment of choice for severe falciparum malaria. Use intravenousquinine if artesunate is not available.Use quinine and clindamycin to treat uncomplicated P. falciparum(or mixed, such as P.falciparumandP. vivax).Use chloroquine to treat P. vivax, P. ovale or P. malariae. Primaquine should not be used in pregnancy

Acute Malarial Infection

Malaria during pregnancy has adverse effects to both mother and the fetus. In early pregnancy

treatment options are very limited partly due to drug resistance and the un certainty about the safety of some antimalarials in pregnancy[51]. Nevertheless, pregnant women with malaria must be treated promptly with effective antimalarials to clear the parasites. When treating pregnant women with malaria infection, clinicians have to make treatment decisions based on the epidemiological resistance pattern, the severity of the infection and the available data regarding the safety of the anti-malarials. A Cochrane review highlighted the lack of qualitative data particularly with regard to drug safety in pregnancy; several innovations have since shown the improved risk benefit ratio[52].

It's preferable to confirm the diagnosis of malaria by laboratory investigations, however, where there is strong clinical suspicion, severe disease or when it's impossible to obtain prompt laboratory diagnosis, presumptive treatment can be commenced with available and safe anti malarials[53].

Chloroquine and quinine are safe in all trimesters of pregnancy but resistance is not uncommon especially with chloroquine.

According to the United Kingdom (U.K.) treatment guidelines for severe or complicated malaria, regardless of the species of Plasmodium parasites, artesunate is administered intravenously at a dose of 2.4 mg/kg body weight at 0, 12 and 24 hours, then daily thereafter. Oral artesunate at a dose of 2 mg/kg once daily is substituted for the intravenous one when the patient is well enough to take orally with addition of clindamycin. When there is no oral artesunate, a three day course of Riamet ® (artemether (20mg)/lumefantrine (120mg) or atovaquone-proguanil (malarone ®) or a seven day course of quinine and clindamycin at 450mg, three times a day for seven days is administered[54].

Many antimalarials are considered not safe in pregnancy. Quinine, chloroquine, proquanil, pyrimethamine and sulfadoxine-pyrimethamine are considered safe in first trimester of pregnancy[55]. Among them, quinine remains the most effective and can be used in all trimesters of pregnancy[56]. WHO has also recommended the use of artemisinin combination therapy (ACT) in the first trimester if it's the only treatment available[55,57]. The other alternative treatment for severe or complicated malaria is the use of intravenous quinine 20 mg/kg loading dose (no loading dose for those who have taken quinine or mefloquine) in 5% dextrose over four hours and then 10 mg/kg intravenously over four hours. In addition, clindamycin at a dose of 450 mg is added intravenously every four hours. Quinine dose should not exceed 1.4 g. oral quinine is substituted for intravenous when the patient can tolerate at a dose of 600 mg three times a day for seven days[54]. Where treatment with intravenous quinine extends beyond 48 hours or the patient has renal or hepatic dysfunction, quinine dosing should be reduced to 12 hourly[58]. For uncomplicated malaria infection due to Plasmodium falciparum, oral quinine is administered at a dose of 600 mg eight hourly and oral clindamycin 450 mg eight hourly for seven days. Those that cannot tolerate oral quinine, Riamet or atovaquone –proquanil combination can be used for uncomplicated malaria[54]. In a situation where pregnant women present with complicated malaria, quinine 10 mg /kg can be administered intravenously in 5% dextrose over four hours every eight hours plus intravenous clindamycin 450 mg every eight hours. When the patient can tolerate oral medications with no vomiting, oral quinine can

be switched at a dose of 600 mg three times a day to complete five to seven days. Oral clindamycin can also be switched at 450 mg three times a day for seven days if the need arise[54]. Non falciparum malaria (P. ovale, P. vivax and P. malariae) are treated with oral chloroquine (base) drug at a dose of 600 mg followed by 300 mg 68 hours later. Then, 300 mg on day two and day three based on the U.K. treatment guidelines[54]. Resistant P. vivax is treated like uncomplicated P. falciparum[54]. P. ovale and P. vivax are treated with oral primaquine at a dose of 15 mg and 30 mg respectively, daily for 14 days[54].

Oral chloroquine at a dose of 300 mg can be administered weekly to prevent relapse until delivery; following delivery, treatment should be postponed until three months after, following G6PD testing[54]. Although exchange blood transfusion has not been proven beneficial in a randomized controlled trial, it has been an option in the treatment of severe malaria since 1974[59]. For severe malaria with parasite density of more than 10%, Centre for Disease Control and Prevention (CDC) recommends exchange blood transfusion. This is assumed to have beneficial effects by removing infected red cells, improving the rheological properties of blood and reducing toxic factors such as parasite-derived toxins, harmful metabolites and cytokines[59]. The fever developed following malaria infections has been associated with premature labour[60,61]and fetal distress[62]. Treatment with antipyretics like paracetamol at standard dose is found to be effective[54]. Other associated complications like mild to moderate anemia in pregnancy following malaria infection can be treated with ferrous sulphate and folic acid[54]

Prophylaxis

Despite aneed, no effective vaccine currently exists, although efforts to develop one are ongoing. Several medications are available to prevent malaria in pregnancy and to prevent malaria in travellers to malaria –endemic countries.

The 'ABCD' of malaria prevention is a useful formula to remember the components are

- Awareness of risk
- Bite prevention
- Chemoprophylaxis
- Diagnosis and treatment which must be prompt

Intermittent Preventive Therapy

The use of IPT with sulfadoxine and pyrimethamine (SP) for the control of malaria in pregnancy in areas of moderate to high transmission was adopted by the WHO Expert Committee on Malaria in 1998[26]. Hitherto, the prevention of malaria in pregnancy relied on weekly chloroquine prophylaxis, though chloroquine was effective[27,28]. Poor compliance was the problem even before the emergence and widespread of drug resistance[29].

The purpose of IPT is to reduce the risk of low birth weight (LBW) and maternal anemia by clearing asymptomatic placental and peripheral parasitemia and providing pregnant women with protection against malaria infection between antenatal consultations[30]. It was recommended by the WHO, the administration of two to three courses of SP (three tablets each contained 500 mg of sulfadoxine and 25 mg of pyrimethamine) after fetal quickening with each course administered not less than one month apart and all before the last four weeks of pregnancy[31]. This IPTp is adopted as a national policy in 37 countries, 33 of which are in Sub-Saharan Africa[32].

Data from recent observational studies in Malawi, the first country where IPT-SP was implemented in 1993, revealed reduced effectiveness of SP for IPT[33]. There is also a growing concern about the decreasing effectiveness of the two dose regimen of SP for IPT in other countries with high level of resistance to SP especially in Southern and Eastern African region where the prevalence of HIV is highest in the world[34]. It's similarly observed that the HIV positive women require more doses of SP for IPTp to have effective protection against malaria in pregnancy than women who are HIV negative[35].

According to the recent recommendation by the Evidence Review Group (ERG) of the Global Malaria Programme[1], they suggest that, inspite of the increased prevalence in Plasmodium falciparum of molecular markers associated with resistance to SP (based on quintuple mutant dhps/dhfr haplotypes prevalence), in Sub-Saharan Africa, IPT-SP remains effective at preventing peripheral parasitaemia, maternal anemia and clinical malaria during pregnancy and is associated with reduced neonatal mortality[36-40].

The evidence review group (ERG) of the Global Malaria Programme also commented on the number of IPTp doses that need to be administered during pregnancy to achieve the maximal beneficial effect of IPTp[1]. An unpublished meta-analysis by Kayentao and colleagues which comprised seven controlled trials conducted in five Sub-Saharan African countries from 1994 to 2008, revealed three more doses of IPTp with SP was superior to the standard two dose regimen, regardless of the HIV status and gravidity of the pregnant woman in preventing low birth weight[1]. The study also showed that women who received a median of four doses of IPTp when compared with those on the two doses regimen also had a lower risk of moderate to severe maternal anemia, maternal malaria at delivery and placental malaria[1].

Other recommendations by the Evidence Review group include the administration of the last dose of IPTp with SP even after 36 weeks of gestation without safety concerns and the administration of IPTp as directly observed therapy[1]. Administration of SP to patient on cotrimoxazole prophylaxis is contraindicated. Also the concomitant administration of SP with at least 5 mg of folic acid to pregnant women is contraindicated because folic acid reduces the efficacy of the antimalarial. However, SP can be administered even in an empty stomach[1].

Several studies have mentioned the potential alternatives to SP for IPTp[41-43] with mefloquine and azithromycin based combination being the leading candidates under study. A randomized clinical trial in Benin (n=1601) demonstrated mefloquine to be more superior to SP in preventing placental malaria (prevalence 1.7 vs 4.4% of women; p=0.005) and clinical malaria (incidence: 26 cases per 10,000 person-months vs 68 cases per 10,000 person-months; p=0.007)[44].

Insecticide Treated Nets

It was in 1897 that the transmission of malaria by the bites of Anopheles mosquitoes was discovered by Ronald Ross. Immediately after his discovery, he realized that due to the fact these mosquitoes bite at night, bed nets should be a useful protection against malaria infection[45]. It was in the 1980s when insecticides began to be applied to bed nets, which greatly found to increase their effectiveness in reducing malaria infection even when the bed nets are torn[45]. Fast acting synthetic insecticides, which are certified

safe by WHO like deltamethrin (k-othrine) at 0.025 grams/m^2 of netting, alphacypermethrin (fendona) at 0.02 grams/m^2, lampdacyhalothrin (icon) at 0.01 grams/m^2 and etofenprox (vectron) at 0.20 grams/m^2have been available and they all add a chemical barrier to the net's imperfect physical barrier[45].

Studies have shown that the use of insecticide treated nets reduces anemia and the prevalence and density of malaria parasitemia in pregnancy especially in areas of intense and perennial malaria transmission[46-48].

In a systematic review of randomized controlled trials on the benefits of insecticides treated nets for the prevention of malaria in pregnancy; the review showed that women of low gravidity randomized to insecticides treated nets (ITNs) delivered fewer LBW babies and were less likely to experience either miscarriage or abortion[49]. Despite the reduction in malaria infections found in the studies, there was no demonstrable overall effect on mean hemoglobin and data on maternal anemia were inconsistent[49].

Another trial which was conducted in Thailand Myanmar border compared ITNs to untreated nets. The area is characterized by a highly seasonal Plasmodium falciparum and Plasmodium vivax malaria infection. The study showed a statistically significant reduction in anemia and fetal loss in all gravidae but no benefit on birth weight or gestational age[50].

Postnatal Care

Chemoprophylaxis for breastfeeding women

Mefloquine (5mg/kg once a week) is the recommended drug of choice for prophylaxis in the second and thirdtrimesters for chloroquine-resistant areas. With very few areas in the world free from chloroquine resistance, mefloquine is essentially the only drug considered safe for prophylaxis in pregnant traveller Vertical transmission to the fetus can occur particularly when there is infection at the time of birth and the placenta and cord are blood film positive for malaria

All neonates whose mothers developed malaria in pregnancy should be screened for malaria withstandard microscopy of thick and thin blood films at birth and weekly blood films for 28 days**.**

Pregnancy Counseling

Women planning pregnancy and travelling to a destination where there is a risk of contracting malaria should be advised there may be harmful consequences for the pregnancy. Prophylaxis is not 100% effective and malaria is associated with increased risk of miscarriage. Women should be advised not to travel or to choose an alternative destination. If it not possible to delay either the pregnancy or the travel plan, advice from a specialist with current experience of malaria should be sought (Box 2). Chloroquine and proguanil are not efficacious in chloroquine-resistant areas and cannot be recommended because of this.85There are very few chloroquine-sensitive areas remaining. To avoid completely any potential adverse drug effects from preconceptual and first-trimester exposure, it is advisable to wait for complete excretion of the drug, if it was taken for prophylaxis, before becoming pregnant (Table 3). Nevertheless, unplanned conception while taking malaria prophylaxis is not considered a reason to recommend termination of pregnancy, owing to the low risk of teratogenicity

CONCLUSION

Malaria is a mosquito-borne infectious disease caused by the genus plasmodium, beginning with bite from an infected female anopheles. Several pregnancy complications like severe anaemia miscarriage, preterm labor, intrauterine growth restriction (IUGR) Reduction of birth weight and intrauterine fetal death (IUFD) have been associated with malaria infection. Disease transmission can be reduced byintermittent preventive treatment (IPT), access to effective case management for malaria illness and preventing mosquito bites- by distribution of mosquito nets (ITN) and insects' replants or with mosquito control measures such as spraying insecticides and draining standing water.

REFERENCES

1. World Health Organization (WHO),malaria policy advisory committee meeting, WHO Evidence Review Group: Intermittent Preventive Treatment of Malaria in Pregnancy (IPTp) with sulfadoxine – pyrimethamine (SP), Session 4; WHO Headquarters, Geneva. 2012
2. National Population Commission (NPC) [Nigeria], National Malaria Control Programme (NMCP) [Nigeria], and ICF International. 2012. Nigeria Malaria Indicator Survey 2010. Abuja, Nigeria: NPC, NMCP, and ICF International
3. WHO. Malaria and HIV interactions and their implications for Public Health Policy. Reports of a Technical Consultation, Geneva, 2004.
4. Malaria PK. Park's Textbook of Preventive and Social Medicine. Seventeen Ed. JabalPur: M/S BarnasidasRhanot; 2002. P. 192-201
5. KaboreAntoinne. Overview of malaria in West Africa. Vol No 5. Lagos Nigeria: WHO Newsletter; 2001.p. 23
6. WHO. A strategic framework for malaria prevention and control during pregnancy in the African region. Brazzaville: World Health Organization Regional Office for Africa, 2004
7. Akindele JA, Sowunmi A and Aborweyere EJ. Congenital malaria in a hyperendemic areas: a pre-liminary study> Annals Trop Paed 1993; 273-6
8. Jimoh AAG. Recent trends in management of malaria in pregnancy. Afr J ClnExperMicrobiol 2006; 7(2): 116-124
9. Snow RW, Craig MH, Hewton CRJC, Steketee RW. Thepublic health burden of *Plasmodium falciparum* malaria in Africa:Deriving the numbers. DCPP Working Paper No. 11. Bethesda,MD: Fogarty International Center, Disease Control PrioritiesProject, National Institutes of Health; 2003
10. Parise ME, Ayisi JG, Nahlen BL, Schultz LJ, Roberts JM,Misore A, et al. Efficacy of sulfadoxine-pyrimethamine for preventionof placental malaria in an area of Kenya with a highprevalence of malaria and human immunodeficiency virus infection.Am J Trop Med Hyg 1998;59:813–22.
11. World Health Organization. A strategic framework for malariaprevention and control during pregnancy in the African region.Brazzaville: WHO Regional Office for Africa, 2004. Available from:*www.cdc.gov/malaria/pdf/strategic_framework_mip_04.pdf* [AccessedFebruary 27, 2008].
12. Griffith KS, Lewis LS, Mali S, Parise ME. Treatment ofmalaria in the United States: A systematic review. JAMA 2007;297:2264 –77.
13. Bouyou-Akotet MK, Ionete-Collard DE, Mabika-ManfoumbiM, Kendjo E, Matsiegui PB, Mavoungoi E, et al. Prevalence

ofPlasmodium falciparum infection in pregnant women in Gabon.Malar J 2003;2:18.

14. Coll O, Menendez C, Botet F, Dayal R, Xavier Carbonell-Estrany AT, Weisman LE, et al. Treatment and prevention ofmalaria in pregnancy and newborn. J Perinat Med 2008;36:15–29.
15. Mutabingwa TK, Bolla MC, Li JL, Domingo GJ, Li X, FriedM, et al. Maternal malaria and gravidity interact to modify infantsusceptibility to malaria. PLoS Med 2005;2:e407.
16. Dorman E SC. Malaria in pregnancy. CurrObstet Gynaecol2000;10:183–9.
17. Snow RW, Craig MH, Hewton CRJC, Steketee RW. Thepublic health burden of *Plasmodium falciparum*malaria in Africa:Deriving the numbers. DCPP Working Paper No. 11. Bethesda,MD: Fogarty International Center, Disease Control PrioritiesProject, National Institutes of Health; 2003.
18. Desai M, terKuile FO, Nosten F, McGready R, Asamoa K,Brabin B, et al. Epidemiology and burden of malaria in pregnancy.Lancet Infect Dis 2007;7:93–104.
19. Sirima SB, Sawadogo R, Moran AC, Konate A, Diarra A,Yameogo M, et al. Failure of a chloroquine chemoprophylaxisprogram to adequately prevent malaria during pregnancy inKoupéla District, Burkina Faso. Clin Infect Dis 2003;36:1374–82.
20. Lagerberg RE. Malaria in pregnancy: a literature review. J Midwifery Womens Health 2008; 53: 209-15
21. Uneke CJ. Impact of placental *Plasmodium falciparum*malariaon pregnancy and perinatal outcome in sub-Saharan Africa: I:Introduction to placental malaria. Yale J Biol Med 2007;80:39 –50.
22. Staalsoe T, Shulman CE, Dorman EK, Kawuondo K, MarshK, Hviid L. Intermittent preventive sulfadoxine-pyrimethaminetreatment of primigravidae reduces levels of plasma immunoglobulinG, which protects against pregnancy-associated *Plasmodiumfalciparum* malaria. Infect Immun 2004;72:5027–30.
23. Adegnika AA, Verweij JJ, Agnandji ST, Chai SK, BreitlingLP, Ramharter M, et al. Microscopic and sub-microscopic *Plasmodiumfalciparum* infection, but not inflammation caused byinfection, is associated with low birth weight. Am J Trop Med Hyg2006;75:798–803.
24. Harrison KA, Ibeziaka A. Maternal anemia and fetal birth weight. J ObstetGynecolBrithCwlth. 1973; 80: 798-804
25. Lars H. Clinical disease, immunity and protection against Plasmodium falciparum malaria in populations living in endemic areas. Expert Reviews Molecular Med 1998, 1-10
26. WHO. WHO Expert Committee on Malaria. Geneva: World HealthOrganization, 2000.
27. Cot M, Le Hesran JY, Miailhes P, Esveld M, Etya'ale D, Breart G.Increase of birth weight following chloroquine chemoprophylaxisduring the fi rst pregnancy: results of a randomized trial in Cameroon.*Am J Trop Med Hyg*1995; **53:** 581–85.
28. Cot M, Roisin A, Barro D, et al. Effect of chloroquine prophylaxisduring pregnancy on birth weight: results of a randomized trial. *Am J Trop Med Hyg*1992; **46:** 21–27.
29. Rukaria-Kaumbutho RM, Ojwang SB, Oyieke JB. Resistance tochloroquine therapy in pregnant women with malaria parasitemia.*Int J Gynaecol Obstet*1996; **53:** 235–41.
30. Gosling RD, Cairns ME, Chico RM and Chandramohan D. Intermittent preventive treatment against malaria: an update. Expert

Rev Anti Infect 2010; 8(5): 589-606

31. World Health Organization. Malaria in Pregnancy Working Group. Minutes of the 8th Strategic Planning Meeting. World Health Organization, Geneva, Switzerland (2007).
32. World Health Organization. World Malaria Report 2009. World Health Organization, Geneva, Switzerland (2009).
33. Feng G, Simpson JA, Chaluluka E, Molyneux ME, Rogerson SJ. Decreasing burden of malaria in pregnancy in Malawian women and its relationship to use of intermittent preventive therapy or bed nets. *PLoS One*2010;**5**(8)**:**e12012.
34. UNAIDS/WHO. Global report: UNAIDS report on the global AIDS Epidemic 2010. *Joint United Nations Programme on HIV/AIDS* 2010;**UNAIDS/10.11E** (JC1958E).
35. Filler SJ, Kazembe P, Thigpen M, Macheso A, Parise ME, Newman RD, et al. Randomized trial of 2-dose versus monthly sulfadoxine-pyrimethamine intermittent preventive treatment for malaria in HIV-positive and HIV-negative pregnant women in Malawi. *J Infect Dis*2006;**194**(3)**:**286-93.
36. Kapito-Tembo A, Meshnick SR, van Hensbroek MB, Phiri K, Fitzgerald M, Mwapasa V. Marked reduction in prevalence of malaria parasitemia and anemia in HIV-infected pregnant women taking cotrimoxazole with or without sulfadoxine-pyrimethamine intermittent preventive therapy during pregnancy in Malawi. *J Infect Dis*2011;**203**(4)**:**464-72.
37. Wilson NO, Ceesay FK, Obed SA, Adjei AA, Gyasi RK, Rodney P, et al. Intermittent preventive treatment with sulfadoxine-pyrimethamine against malaria and anemia in pregnant women. *Am J Trop Med Hyg*2011;**85**(1)**:**12-21.
38. Mockenhaupt FP, Bedu-Addo G, Eggelte TA, , Holmberg V, , et al. Rapid increase in the prevalence of sulfadoxine-pyrimethamine resistance among Plasmodium falciparum isolated from pregnant women in Ghana. *J Infect Dis*2008;**198**(10)**:**1545-9.
39. Menéndez C, Bardají A, Sigauque B, Romagosa C, Sanz S, Serra-Casas E, et al. A randomized placebo-controlled trial of intermittent preventive treatment in pregnant women in the context of insecticide treated nets delivered through the antenatal clinic. *PLoS One*2008;**3**(4)**:**e1934.
40. , Bardají A, , Sanz S, Aponte JJ, Mabunda S, et al. Malaria prevention with IPTp during pregnancy reduces neonatal mortality. *PLoS One*2010;**5**(2)**:**e9438.
41. Chico RM, Pittrof R, Greenwood B, Chandramohan D. Azithromycin– chloroquine and the intermittent preventive treatment of malaria in pregnancy. *Malar J 2008;*7: 255
42. Newman RD, Parise ME, Slutsker L, Nahlen B, Steketee RW. Safety, efficacy and determinants of effectiveness of antimalarial drugs during pregnancy: implications for prevention programmes in *Plasmodium falciparum*-endemic sub- Saharan Africa. *Trop. Med. Int. Health* 8, 2003;488–506
43. Vallely A, Vallely L, Changalucha J, Greenwood B, Chandramohan D. Intermittent preventive treatment for malaria in pregnancy in Africa: what's new, what's needed? *Malar. J.2007;*6: 16
44. Briand V, Bottero J, Noël H, Masse V, Cordel H, Guerra J, *et al.* Intermittent treatment for the prevention of malaria during pregnancy in Benin: a randomized, open-label equivalence trialcomparingsulfadoxine–pyrimethamine with mefloquine. *J Infect Dis 2009;*200(6),

991–1001

45. Curtis C. Insecticide treated bednets to prevent malaria. SciDev Net 2005. www.scidev.net/en. Accessed May 25, 2013
46. Marchant T, Schellenberg JA, Edgar T, Nathan R, Abdulla S, Mukasa O, et al. Socially marketed insecticide-treated nets improve malaria and anemia in pregnancy in southern Tanzania. Trop Med Intern Health. 2002; 7(2): 149-58
47. Dolan G, terKuile FO, Jacoutot V, White NJ, Luxemburger C, Malankirii L, et al. Bednets for the prevention of malaria and anemia in pregnancy. Trans R Soc Trop Med Hyg, 87. 1993.p.620-6
48. D' Allesandro U, Langerock P,Bennet S, Francis N, Cham K, Greenwood BM. The impact of a national impregnated bed net programme on the outcome of pregnancy in primigravidae in the Gambia. Trans R Soc Trop Med Hyg, 90. 1996.p.487-92
49. Gamble C, Ekwaru PJ, Garner P, terKuile FO. Insecticide-Treated Nets for the Prevention of Malaria in Pregnancy: A Systematic Review of Randomised Controlled Trials. PLoS Med 2007; 4(3): e107. doi:10.1371/journal.pmed.0040107
50. Dolan G, terKuile FO, Jacoutot V, White NJ, Luxemburger C, et al. Bed nets for the prevention of malaria and anaemia in pregnancy. Trans R Soc Trop Med Hyg1993; 87: 620–626.
51. McGready R, Lee SJ, Wiladphaingern J, Ashley EA, Rijken MJ, Boel M, et al.Adverse effects of falciparum and vivax malaria and the safety of antimalarial treatment in early pregnancy: A population-based study. *Lancet Infect Dis* 2011 Dec 13; [e-pub ahead of print]. (http://dx.doi.org/10.1016/S1473-3099(11)70339-5)
52. Orton LC, Omari AA. Drugs for treating uncomplicated malaria in pregnant women. Cochrane Database Syst Rev. 2008 Oct 8;(4):CD004912.
53. Gerstl S, Dunkley S,Mukhtar A, De Smet M Baker S, and MaikereJ. **Assessment of two malaria rapid diagnostic tests in children under five years of age, with follow-up of false-positive pLDH test results, in a hyperendemic falciparum malaria area, Sierra Leone.** Malar J. 2010; 9: 28. Published online 2010 January 21. doi: 10.1186/1475-2875-9-28PMCID: PMC2835716. Accessed May 24, 2013
54. RCOG Green-Top Guideline. The diagnosis and Treatment of Malaria in Pregnancy. Royal College of Obstetricians and Gynaecologist. 2010.p. 2-29Available at: *www.rcog.org.uk › Guidance › Guidelines › Search for a guideline*. Accessed May 28, 2013
55. Kakkilaya BS. Treatment of uncomplicated P. falciparum malaria. Malariasite.com 2012-2015. Available at www.malariasite.com/malaria/treatment4.htm. Accessed June 1, 2013
56. Guidelines for the treatment of malaria. 2nd Edition. World Health Organization. Geneva, 2010. pp 19-21. Available athttp://whqlibdoc.who.int/publications/2010/9789241547925_eng.pdf
57. Malaria Drug Policy (2010). Directorate of National Vector Borne Disease Control Programe. New Delhi. 2010. Available athttp://nvbdcp.gov.in/Doc/drug-policy-2010.pdfAccessed Jun 2, 2013
58. McGready R, Stepniewska K, Lindegardh N, Ashley EA, La Y, Singhasivanon P, *et al*. The pharmacokinetics of artemether and lumefantrine in pregnant women with uncomplicated falciparum malaria. *Eur J*

*ClinPharmacol*2006;62:1021–31.

59. Treatment of Malaria (Guidelines for Clinicians). CDC. Available at www.cdc.gov/malaria/resources/pdf/clinical guidance.pdf. Accessed June 2, 2013
60. Deen JL, von Seidlein L, Pinder M, Walraven GE, GreenwoodBM. The safety of the combination artesunate andpyrimethamine-sulfadoxine given during pregnancy. *Trans RSoc Trop Med Hyg*2001;95:424–8.
61. Hill DR, Baird JK, Parise ME, Lewis LS, Ryan ET, Magill AJ. Primaquine: report from CDC expert meeting on malaria chemoprophylaxis I. *Am J Trop Med Hyg*2006;75:402–15.
62. Phillips-Howard PA, Wood D. The safety of antimalarial drugs in pregnancy. *Drug Saf*1996;14:131–45.