Malaria in Pregnancy

Literature Review

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A mother with her baby in Ghana, sitting on a bed covered with an Insecticide Treated net. Between 2008 and 2010, a total of 294 million nets were distributed in sub-Saharan Africa.

Source: CDC

IMAGE SOURCE: Karen Kasmauski/Corbis

ABSTRACT

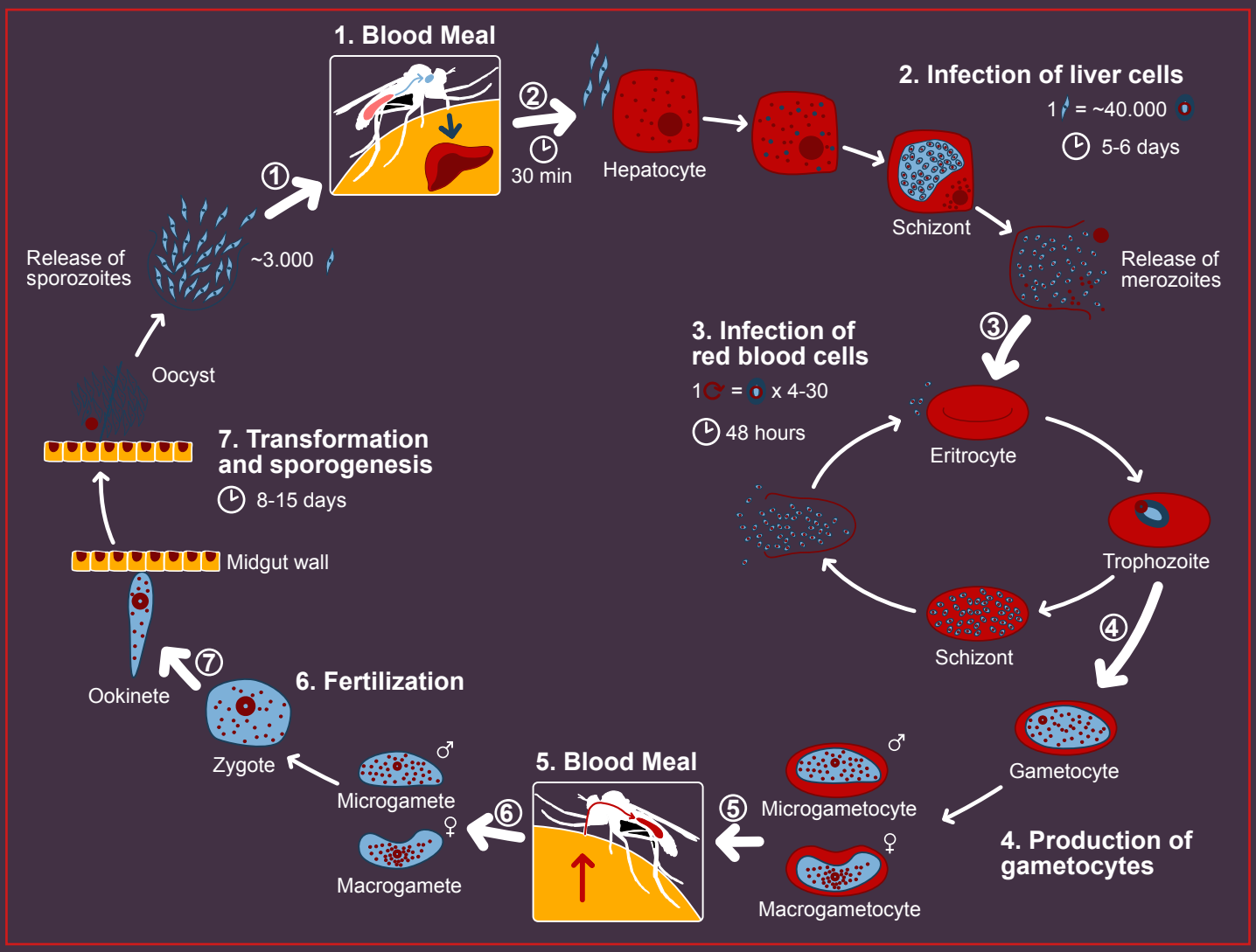
Malaria in Pregnancy (MiP) is one of the greatest causes of maternal morbidity and is hence one of the most serious contemporary public health issues. MiP have a variety of effects including low birth weight (LBW), spontaneous abortion, anemia, preterm delivery, stillbirth, congenital infection and ultimately, death. MiP is both hazardous and sensible as drugs normally used and successfully in curing Malaria might not be used in this case as these are generally contraindicated during pregnancy and might lead to teratogenicity and/or embryotoxicity. There exist 6 species of *Plasmodium* among which *Plasmodium falciparum* accounts for the highest number of deaths while *Plasmodium vivax* has a greater geographical coverage. There are two main tools recognized by the WHO that helps to fight malaria: Intermittent Preventive Treatment with Sulfadoxine-Pyrimethamine (IPTp-SP) and Insecticide-Treated Nets (ITNs). Due to the resistance of SP in some places, more research is been carried out on the other substituents such as Dihydroartemisinin-piperaquine (DP or DHA-PPQ), Chloroquine, Mefloquine and Intermittent Screening and Treatment in pregnancy (ISTp). Despite the development of resistance to Pyrethroid, the insecticide used to treat mosquito nets, the WHO still believes they are safe for usage.

INTRODUCTION

Pregnant women continue to be the most-at-risk group for malaria infection after children (WHO, 2019). Yearly, about one hundred and twenty-five million women are pregnant in malaria-endemic regions (Dellicour et al., 2010). In Sub-Saharan Africa for example, 11 million pregnant women living in 38 countries got infected with malaria, representing 29% of all pregnancies in this region. Malaria which is already a dangerous disease is even more hazardous during pregnancy as drugs normally used in the treatment of the disease could be contraindicated in the case of pregnancy, leading to teratogenicity and/or embryotoxicity. Primaquine for example which is very successful in the treatment of *P. vivax* can not be used during pregnancy as there is a risk for fetal hemolysis and subsequently leading to liver hypnozoite parasite forms remaining and causing relapses in the mother (Fried & Duffy, 2017).

OVERVIEW OF MALARIA

There exist six species of *Plasmodium* capable of infecting humans. These include: *Plasmodium falciparum*, *Plasmodium vivax*, *Plasmodium ovale wallickeri*, *Plasmodium ovale curtisi*, *Plasmodium malariae*, and *Plasmodium knowlesi* (Milner, 2018). Most infections are caused by *P. falciparum* or *P. vivax* but infections involving more than one species can equally occur (Ahmadal-Agroudi, 2017). *P. falciparum* is responsible for the highest number of deaths due to malaria, especially in Sub-Saharan African while *P. vivax* causes milder infections but has a greater geographical coverage (Meibalan, 2017). Malaria is transmitted to humans by the vector, the female *Anopheles* mosquito through a bite which transfers the *Plasmodium* sporozoites from its salivary glands to the host's blood stream. A new cycle begins with a bite which introduces a *Plasmodium* into the bloodstream. The sporozoites travel through the bloodstream to the liver within 30 minutes where it becomes mature tissue schizonts after invading hepatocytes (lasts 7-30 days). Each infected hepatocyte can produce up to 30,000 merozoites. When the merozoites are finally released from the hepatocytes, they each infect a red blood cell (RBC). The RBC serves as host for the parasite to calmly mature into a trophozoite, a schizont then into a form of asexual replication which ultimately returns into the merozoite form. It takes between 48 and 72 hours, depending on the species of *Plasmodium* for about 25-30 merozoites to be released causing the first symptoms including fever. Some *Plasmodium* inside the RBC have the potential to convert to a sexual form called gametocyte. In case the host is bit again by a female *Anopheles* mosquito, the gametocyte is ingested by the mosquito and the cycle continues. Within the gut, the gametocytes develop into either male or female gametocytes. Fertilization takes place between a male and a female gametocyte, yielding a diploid zygote which later. Develops into an ookinete, invades the gut and becomes an oocyst. Haploid sporozoites are produced after the oocyst has undergone meiosis and then migrates to the salivary gland of the mosquito (Alvarez, Al-Khan & Apuzzio, 2005). In very rare cases, malaria could be acquired congenitally or by exposure to infected blood products (Lagerberg, 2008).



SOURCE: WIKIPEDIA COMMONS

Illustration of the life cycle of the malaria parasite *Plasmodium sp.*

MALARIA IN PREGNANCY

Prevention And Prophylaxis

In Sub-Saharan Africa, a region of moderate-to-high transmission of *P. falciparum* a high proportion of the population is asymptomatic, and this therefore includes pregnant women. Studies have shown that even asymptomatic or pauci-symptomatic infections with *P. falciparum* or *P. vivax* is associated with a decrease in birth weight (Desai et al., 2007) and with maternal and fetal morbidity especially due to the accumulation of infected erythrocytes in the mother's blood in the placenta (Rogerson et al., 2007). For this reason, preventive treatment using antimalarial drugs from the start of the second trimester of the pregnancy as well as the correct use of mosquito nets is highly recommended. The prevention of the disease is more complicated in pregnant women given a lot of contraindications associated with this state. In addition, there's a constant need for treatment improvement as parasite drug resistance which is already a general public health issue affect expecting mothers even more. There exist two main tools used to prevent pregnant women and the unborn children against malaria: Intermittent Preventive Treatment with Sulfadoxine-Pyrimethamine (IPTp-SP) and Insecticide-Treated Nets (ITNs) (Rogerson et al., 2017).

Since October 2012, WHO recommends IPTp-SP in all areas with moderate to high malaria transmission in Africa.

Source: WHO

Intermittent Preventive Treatment in pregnancy (IPTp)

IPTp is a full therapeutic course of antimalarial drugs given to pregnant women at routine antenatal care visits as a preventive measure against the disease ("Intermittent preventive treatment in pregnancy (IPTp)", 2020).

Sulfadoxine-Pyrimethamine (SP) is the first drug developed for IPTp and is to-date the only IPTp treatment fully endorsed by the WHO. The WHO recommends a minimum of four antenatal care (ANC) visits during pregnancy. It recommends that IPTp-SP is administered for all pregnant women in Sub-Saharan Africa at each ANC visit until the time of delivery provided there is at least a month apart between the intakes. IPTp-SP should preferably be administered as Directly Observed Therapy (DOT) of 3 tablets of Sulfadoxine/Pyrimethamine with each tablet containing 500 mg/25 mg SP summing up to a required dosage of 1500 mg/75 mg SP. The SP treatment can be given on an empty stomach or with food (WHO, 2013). In areas where the IPTp-SP was well administered, a decrease in the rates of maternal anemia and low birth weight was recorded. Despite the use of IPTp-SP being the most successful tool used in the fight against malaria during pregnancy in Africa, there are still some precautions which must be taken in order to administer the treatment. IPTp-SP can only be administered to women from the start of the second trimester up to close to the time of delivery. Even though more research needs to be carried out, studies have determined that the usage of IPTp-SP during the first trimester could be teratogenic leading to spontaneous abortion and congenital anomalies. Also, the administration of IPTp-SP within less than a month could lead to fatal cutaneous reactions. SP can also not be administered while the pregnant woman is on cotrimoxazole therefore pregnant women who are equally HIV patients and are receiving a cotrimoxazole treatment should not be prescribed IPTp-SP. Folic acid which is highly recommended for pregnant women in order to prevent or reduce the rate of congenital anomalies can interfere with the antimalarial treatment. This only happens if the intake of folic acid is as high as 5 mg/day. It is therefore recommended that pregnant women in Sub-Saharan Africa take a standard folic acid dose of 0.4 mg/day as at this does, there is no negative interaction with the antimalarial treatment (Peters et al., 2007).

Chloroquine was the first treatment used to prevent malaria in pregnancy and was administered as weekly chemoprophylaxis (Rogerson et al., 2017).

There is a constant need to find substitutes to presently existing and working medications as these substitutes might succeed where the prevailing ones are not conclusive. Dihydroartemisinin-piperaquine (DP or DHA-PPQ) has been highly considered as an alternative to SP for IPTp due to the increasing resistance to SP (Jagannathan et al., 2018). A study was conducted in Uganda, suffering from a widespread SP resistance where the participants, all HIV-uninfected pregnant adolescents and women were randomly assigned a treatment with SP, a three-dose DP treatment, or a monthly DP treatment. In this study, it was found out that the prevalence of placental malaria was higher in the IPTp-SP group (50%), followed by the three-dose IPTp-DP group (34.1%) while the monthly IPTp-DP group had the lowest (27.1%). The incidence of symptomatic malaria and the prevalence of parasitemia also followed the same ranking as above. The conclusion of the study was therefore that the monthly IPTp-DP treatment was superior to the three-dose IPTp-DP treatment and then to the IPTp-SP treatment in lowering the burden of malaria in pregnancy (Kakuru et al., 2016). There were however minimal differences between both treatments in risks of adverse birth outcomes such as low birth weight (LBW) and preterm birth (Jagannathan et al., 2018).

Another very promising alternative to SP for IPTp is Mefloquine (MQ). In a study, a total of 4,749 HIV-uninfected pregnant women in Benin, Gabon, Mozambique and Tanzania were assigned an IPTp treatment with SP, single dose MQ (15 mg/kg), or split-dose MQ, all accompanied with the use of Insecticide-Treated Nets (ITNs). Women receiving IPTp-MQ had reduced risks of parasitemia (3.2% compared to 4.6% in IPTp-SP), anemia at delivery (40.5% compared to 44.1% in IPTp-SP), reduced incidence of clinical malaria (130/1,103.2 malaria episodes person/year (PYAR) compared to 96/551.8 episodes PYAR in IPTp-SP) and all-cause outpatient attendances (1,480/1,110.1 outpatients visits PYAR compared to 850/557.8 in IPTp-SP) . IPTp-MQ treatments had poorer tolerability levels than IPTp-SP. This included dizziness and vomiting with about 30% in both after the first dose and these numbers were almost halved after the second dose. There were however no differences in terms of LBW, prevalence of placental infection and adverse pregnancy outcomes between groups (González, 2014).

Fig. 3: Workers producing Choloquine Phosphate in a factory in Nantong City, Jiangsu Province, China.

Azithromycin has been associated in several studies in combination to other proven anti-malarial drugs such as Chloroquine, SP and DHA-PQ where it has proven to have a great positive impact on LBW (Rogerson et al., 2017).

In the scramble to find more efficient, tolerable, low-cost effective alternative treatments to prevent Malaria in Pregnancy (MiP), Intermittent Screening and Treatment in pregnancy (ISTp) has proven to be a good candidate. This treatment uses Rapid Diagnostic Tests (RDTs) for screening of pregnant women for malaria during ANC visits combined with an effective therapy for the women found to be RDT-positive. The effect of ISTp has been studied in combination to amodiaquine-artesunate (AQAS), dihydroartemisinin-piperaquine (DHA-PPQ) and artemetherlumefantrine (AL) in East and West African countries such as: Ghana, Gambia, Mali, Burkina Faso, Malawi, Kenya (WHO,

2015) and Asian countries like India and Indonesia. Based on the research conducted in West, the WHO concluded that ISTp used with either SP or AL as treatment was a good alternative in preventing third trimester maternal anemia, LBW and placental malaria. In East Africa, despite the high SP resistance, the WHO still concluded that ISTp-DHA-PPQ was not superior to IPTp-SP and given that IPTp-SP still retains much of its effectiveness in these areas, it was still retained as the main treatment (WHO, 2015).

Insecticide-Treated Nets (ITNs) / Long-Lasting Insecticidal Nets (LLINs)

The regular and timely use of ITNs, primarily LLINs, is one of the two main ways to prevent malaria during pregnancies. Since the year 2000, the WHO in partnership with Roll Back Malaria (RBM) had for objective to halt and begin to reverse the incidence of Malaria by 2015. This led to an international financing to fight malaria to increase by about twentyfold between 2000 and 2015 to provide the main control intervention: ITNs, Indoor Residual Spraying (IRS) and the use of artemisinin-based combination therapy (ACT) (Bhatt et al., 2015). In fact, LLINs especially are believed to have played a determining role in halving deaths by malarial infection as well as decreasing the disease incidence by over a third since the year 2000 (Ranson et al., 2016). A Cochrane review concluded that the use of ITNs reduces peripheral, placental parasitemia and decreases the risk of fetal loss in the women in their first to fourth pregnancies while leading to an increase in maternal hemoglobin concentrations and LBW. This review equally concluded that there was no need for further trials in Sub-Saharan Africa and that more efforts should instead be invested towards improving the coverage of pregnant women in ITNs and carrying further research instead in the associated use of ITNs and other treatments such as IPTp and the extension of this research in other regions such as Asia and Latin America (Gamble et al., 2006).

As more efforts are invested in the elimination of the mosquito vector to decrease the proliferation of malaria, there is a proportional selection pressure applied on the mosquitoes population causing them to develop resistance to the insecticides or products used in the treatment of LLINs. The spread and strength of this resistance is increasing dramatically, posing a threat to the universal control of malaria as we know it. The increase in the resistance of Pyrethroid is due to the continuous exposure of the *Anopheles* mosquitoes due to their use in agriculture as household products. Also, the number of LLINs in use in Africa can be quantified in terms of hundreds of millions which are all impregnated with Pyrethroid, and therefore a further increase in resistance cannot be surprising (Ranson et al., 2016).

Vaccine against MiP

Placenta malaria is a condition where infected malaria cells are accumulated in the maternal blood spaces of the placenta. Tits primary mediator is the VAR2CSA protein expressed on these infected erythrocytes and the antibody to the VAR2CSA protein is associated with improved pregnancy. A vaccine based on this knowledge of the VAR2CSA protein is on clinical trial. In case the clinical trial is successful, there is a possibility that the vaccine could be given to adolescent girls with a human papilloma virus vaccine (Rogerson et al., 2017).

CONCLUSION

Throughout this review, it has been established that pregnant women are highly vulnerable to malaria. In areas of moderate-to-high transmission for example, it is of paramount importance that all pregnant women should be placed under anti-malarial treatment as a means of prevention even without the presence of any symptoms as in these regions, a lot of patients could be asymptomatic. There is no more an inch of doubt about the. Vulnerability of pregnant women to malaria and, the effectiveness of Intermittent Preventive Treatment with Sulfadoxine-Pyrimethamine (IPTp-SP) and In-

secticide-Treated Nets (ITNs). However, the effectiveness of these treatments are evaluated based on low birth weight (LBW) which is determined by way too many factors. For future research therefore, it will be interesting to evaluate the sole effect of anti-malarial treatments when all the other factors affecting LBW are held constant or eliminated.

REFERENCES

Ahmadal-Agroudi, M., El-Mawla Megahed, L. A., Abdallah, E. M., & Morsy, T. A. (2017). A MINI OVERVIEW OF MALARIA IN PREGNANCY. Journal of the Egyptian Society of Parasitology, 47(1), 177–196.

Alvarez, J. R., Al-Khan, A., & Apuzzio, J. J. (2005). Malaria in pregnancy. Infectious diseases in obstetrics and gynecology, 13(4), 229–236. https://doi.org/10.1080/10647440500148339

Bhatt, S., Weiss, D. J., Cameron, E., Bisanzio, D., Mappin, B., Dalrymple, U., Battle, K., Moyes, C. L., Henry, A., Eckhoff, P. A., Wenger, E. A., Briët, O., Penny, M. A., Smith, T. A., Bennett, A., Yukich, J., Eisele, T. P., Griffin, J. T., Fergus, C. A., Lynch, M., … Gething, P. W. (2015). The effect of malaria control on Plasmodium falciparum in Africa between 2000 and 2015. Nature, 526(7572), 207–211. https://doi.org/10.1038/nature15535

Dellicour, S., Tatem, A. J., Guerra, C. A., Snow, R. W., & ter Kuile, F. O. (2010). Quantifying the number of pregnancies at risk of malaria in 2007: a demographic study. PLoS medicine, 7(1), e1000221. https://doi.org/10.1371/journal.pmed.1000221

Desai, M., ter Kuile, F. O., Nosten, F., McGready, R., Asamoa, K., Brabin, B., & Newman, R. D. (2007). Epidemiology and burden of malaria in pregnancy. The Lancet. Infectious diseases, 7(2), 93–104. https://doi.org/10.1016/S1473-3099(07)70021-X

Fried, M., & Duffy, P. E. (2017). Malaria during Pregnancy. Cold Spring Harbor perspectives in medicine, 7(6), a025551. https://doi.org/10.1101/cshperspect.a025551

Gamble, C., Ekwaru, J. P., & ter Kuile, F. O. (2006). Insecticide-treated nets for preventing malaria in pregnancy. The Cochrane database of systematic reviews, 2006(2), CD003755. https://doi.org/10.1002/14651858.CD003755.pub2

González, R., Mombo-Ngoma, G., Ouédraogo, S., Kakolwa, M. A., Abdulla, S., Accrombessi, M., Aponte, J. J., Akerey-Diop, D., Basra, A., Briand, V., Capan, M., Cot, M., Kabanywanyi, A. M., Kleine, C., Kremsner, P. G., Macete, E., Mackanga, J. R., Massougbodgi, A., Mayor, A., Nhacolo, A., … Menéndez, C. (2014). Intermittent preventive treatment of malaria in pregnancy with mefloquine in HIV-negative women: a multicentre randomized controlled trial. PLoS medicine, 11(9), e1001733. https://doi.org/10.1371/journal.pmed.1001733

Intermittent preventive treatment in pregnancy (IPTp). World Health Organization. (2020). Retrieved 20 April 2020, from https://www.who.int/malaria/areas/preventive_therapies/pregnancy/en/

Jagannathan, P., Kakuru, A., Okiring, J., Muhindo, M. K., Natureeba, P., Nakalembe, M., Opira, B., Olwoch, P., Nankya, F., Ssewanyana, I., Tetteh, K., Drakeley, C., Beeson, J., Reiling, L., Clark, T. D., Rodriguez-Barraquer, I., Greenhouse, B., Wallender, E., Aweeka, F., Prahl, M., … Dorsey, G. (2018). Dihydroartemisinin-piperaquine for intermittent preventive treatment of malaria during pregnancy and risk of malaria in early childhood: A randomized controlled trial. PLoS medicine, 15(7), e1002606. https://doi.org/10.1371/journal.pmed.1002606

Kakuru, A., Jagannathan, P., Muhindo, M. K., Natureeba, P., Awori, P., Nakalembe, M., Opira, B., Olwoch, P., Ategeka, J., Nayebare, P., Clark, T. D., Feeney, M. E., Charlebois, E. D., Rizzuto, G., Muehlenbachs, A., Havlir, D. V., Kamya, M. R., & Dorsey, G. (2016). Dihydroartemisinin-Piperaquine for the Prevention of Malaria in Pregnancy. The New England journal of medicine, 374(10), 928–939. https://doi.org/10.1056/NEJMoa1509150

Lagerberg R. E. (2008). Malaria in pregnancy: a literature review. Journal of midwifery & women's health, 53(3), 209–215. https://doi.org/10.1016/j.jmwh.2008.02.012

Meibalan, E., & Marti, M. (2017). Biology of Malaria Transmission. Cold Spring Harbor perspectives in medicine, 7(3), a025452. https://doi.org/10.1101/cshperspect.a025452

Milner D. A., Jr (2018). Malaria Pathogenesis. Cold Spring Harbor perspectives in medicine, 8(1), a025569. https://doi.org/10.1101/cshperspect.a025569

Moore, B. R., Salman, S., & Davis, T. M. (2016). Treatment regimens for pregnant women with falciparum malaria. Expert review of anti-infective therapy, 14(8), 691–704. https://doi.org/10.1080/14787210.2016.1202758

Peters, P. J., Thigpen, M. C., Parise, M. E., & Newman, R. D. (2007). Safety and toxicity of sulfadoxine/pyrimethamine: implications for malaria prevention in pregnancy using intermittent preventive treatment. Drug safety, 30(6), 481–501. https://doi.org/10.2165/00002018-200730060-00003

Ranson, H., & Lissenden, N. (2016). Insecticide Resistance in African Anopheles Mosquitoes: A Worsening Situation that Needs Urgent Action to Maintain Malaria Control. Trends in parasitology, 32(3), 187–196. https://doi.org/10.1016/j.pt.2015.11.010

Rogerson, S. J., Hviid, L., Duffy, P. E., Leke, R. F., & Taylor, D. W. (2007). Malaria in pregnancy: pathogenesis and immunity. The Lancet. Infectious diseases, 7(2), 105–117. https://doi.org/10.1016/S1473-3099(07)70022-1

Rogerson, S. J., & Unger, H. W. (2017). Prevention and control of malaria in pregnancy - new threats,

new opportunities?. Expert review of anti-infective therapy, 15(4), 361–375. https://doi.org/10.1080/14787210.2017.1272411

WHO. (2013). WHO policy brief for the implementation of intermittent preventive treatment of malaria in pregnancy using sulfadoxine-pyrimethamine (IPTp-SP). WHO.

WHO. (2015). Retrieved from https://www.who.int/malaria/mpac/mpac-sept2015-erg-mip-report.pdf

WHO. (2019). WORLD MALARIA REPORT 2019. Retrieved from https://www.who.int/malaria/publications/world-malaria-report-2019/World-Malaria-Report-2019-briefing-kit-eng.pdf?ua=1

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