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Malaria in Pregnancy: A Holistic Review and Approach to Laboratory Findings, Management and Outcomes

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Abstract

Malaria is an infectious disease caused by protozoa of the genus *Plasmodium*, transmitted by the bite of female mosquitoes Anopheles. Malaria can infect various populations including pregnant women. The incidence of malaria in pregnancy is quite high especially in tropical - endemic regions such as Indonesia, Papua New Guinea, Nigeria, West Africa and Sudan. It happens because there is no enhanced control activities such as two prevention approaches advocated by the WHO, as well prevention intermittently with sulfadoxine- pyrimethamine (SP) and the treatment of malaria during pregnancy. There are several factors that influence the high prevalence of malaria such as mosquito vectors, malaria parasites, human hosts and environment. As a result of the presence of malarial parasites in the placenta appear serious adverse outcomes to the mother, fetus and newborn. Malaria can be diagnosed with microscopy, rapid diagnostic test (RDT), and polymerase chain reaction (PCR).The first-line treatments recommended by the WHO in the second and third trimester of pregnancy are artemisinin-based combination treatments (ACT).

Keywords: Malaria, pregnancy, laboratory findings, management, outcomes

Malaria dalam Kehamilan: Telaah Holistik, Pendekatan Laboratorum, Tata Laksana dan Luarannya

Abstrak

Penyakit malaria merupakan infeksi yang disebabkan oleh genus *Plasmodium*, yang ditularkan melalui gigitan nyamuk Anopheles betina. Malaria dapat menginfeksi berbagai populasi termasuk perempuan hamil. Insidens malaria dalam kehamilan cukup tinggi terutama di wilayah tropis - endemik seperti Indonesia, Papua Nugini, Nigeria, Afrika Barat, dan Sudan. Hal itu terjadi karena ketiadaan penanggulangan/pencegahan seperti yang dianjurkan WHO yaitu pemberian sulfadoxine- pyrimethamine (SP) intermiten dan pengobatan malaria dalam kehamilan. Ada banyak faktor yang berperan terhadap kejadian malaria yakni nyamuk sebagai vektor, parasit malaria, manusia sebagai pejamu dan lingkungan yang juga berperan terhadap kejadian malaria dalam kehamilan. Malaria dalam kehamilan berakibat serius trehadap ibu, janin dan neonatus. Diagnosis dapat ditegakkan secara mikroskopi, *rapid diagnostic test* (RDT), dan polymerase chain reaction (PCR). Pengobatan lini pertama yang direkomendasikan oleh WHO pada trimester ke dua dan ketiga kehamilan adalah kombinasi artemisinin (*artemisinin-based combination treatments* - ACT).

Kata kunci: Malaria, kehamilan, pemeriksaan laboratorium, tatalaksana, luaran

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Introduction

Malaria is an infection caused by protozoa of the genus Plasmodium. The species of plasmodium include *Plasmodium falciparum*, *Plasmodium vivax*, *Plasmodium ovale* and *Plasmodium malariae.*[1]According to World Health Organization (WHO), most of the cases in 2016 were in the African (90%), followed by South-East Asia (7%) and Eastern Mediterranean (2%).[2] Malaria is also a cause of mortality and morbidity in pregnant women globally.[1,3] It is estimated 125 million women each year are at risk of malaria in pregnancy.[4-5] The incidence of malaria in pregnancy is still high, especially in endemic tropical countries such as Indonesia (Papua 10%, Nusa Tenggara Timur 5%)[6], Papua New Guinea 18,5%, Nigeria (Igbo-Eze North 50.7%)[7], and West Africa 40.2%[8] , and Sudan (Blue nile state 58.9%)[9]. No enhanced control activities as recommended by the WHO, as well prevention intermittently with sulfadoxine-pyrimethamine (SP) and the treatment of malaria during pregnancy, it can be a potential cause the prevalence remain high.[9]

Malaria infections could occur in blood of mother or in the placenta.The presence of infected erythrocytes or malaria pigment (haemozoin) in the placenta intervillous referred to as placental malaria. The occurrence of placental malaria is influenced by many factors such as primipara, multipara, live in rural areas, young age ≤ 23.2 year, did not undergo the ante natal care (ANC), do not use the nets when sleeping, and the absence of clinical symptoms malaria.[10-12]

As a result of the presence of malarial parasites in the placenta serious adverse outcomes occurs to the mother, fetus and newborn such as maternal anemia, low birth weight (LBW) baby, intrauterine growth restriction, preterm birth (PTB), miscarriage, stillbirth, and congenital malaria.[6,7,13-15]This article will discuss about the laboratory findings, management and adverse outcomes of malaria in pregnancy. The data taken were from the year 2014 to 2017 research articles.

Laboratory Findings

The crucial issue in the management of malaria is consideration of the possibility of this diagnosis. Malaria should be suspected in anyone with a fever or a history of fever who has returned from or previously visited a malaria endemic area. There are no specific symptoms of malaria: most patients complain of fever, headache and general malaise, gastrointestinal disturbances, jaundice. Malaria infection during pregnancy is often asymptomatic.[16] The effects of malaria infection in the first trimester are largely unknown.[17] Because of the low parasitemia found in all age groups pregnant women may be the reason why they do not show malaria symptoms even though they are infected. This suggests that pregnant women can become carriers of malarial parasites without showing any symptoms of infection.[18] Malarial parasites in pregnancy can be found with microscopy, rapid diagnostic test (RDT), and polymerase chain reaction (PCR).

Microscopy examination was made using thick and thin smears on the same slide and stained with 5 % Giemsa for 30 minutes.[19] A smear was declared negative if examination of 100 high power fields did not reveal asexual parasites or gametocytes. For positive smears, parasite density was calculated by counting the number of asexual parasites per 200 leukocytes (or per 500, if the count is <10 asexual parasites/200 leukocytes), assuming a leukocyte count of 8,000/µl. When a thick smear was positive, the corresponding thin blood smear was read to determine the parasite species.[20]

Malaria rapid diagnostic tests (RDTs) assist in the diagnosis of malaria by detecting evidence of malaria parasites in human blood.

The test principle underlying malaria RDTs is the detection of parasite antigens, most commonly histidine-rich protein 2 (HRP2), parasite lactate dehydrogenase (pLDH), and/or parasite aldolase through lateral flow immunochromatography. Whereas HRP2 is specific to *Plasmodium falciparum*, pLDH and parasite aldolase are common to all *Plasmodium* species.[21]

RDT-HRP2 tests have a higher sensitivity compared with RDT-pLDH.[22] Based on this study, the HRP2 assay showed superior sensitivity but inferior specificity compared with the pLDH assay. The difference in sensitivity between the tests was due mostly to better detection with HRP2 at low parasite densities. Non-falciparum infections contributed to false negative results for both RDTs. In particular, in two-thirds of cases in which the HRP2 test was negative although microscopy detected parasites, the infection was caused by non-falciparum species. The higher specificity and positive predictive value of the pLDH assay was due to the fact that pLDH antigenemia closely mirrors parasitemia, while HRP2 commonly persists in the bloodstream weeks after successful treatment of malaria.[23]

When RDT-HRP2 performed on peripheral blood samples for pregnancy malaria diagnoses, the sensitivity was more than 90% when it compared with peripheral blood smears, and 80–95% when it compared with placental BSwith specificity between 61%- 94%. The sensitivity of RDT-HRP2 using peripheral blood samples was much lower when compared with PCR detection of parasite nucleic acids in peripheral or placental blood.[22]

Other alternatives for malaria diagnosis are DNA/RNA-based detection techniques, of which the PCR is the most widely used.[24] PCR methods to detect malaria infection were described more than two decades ago, and generally more sensitive for detecting parasite DNA than thick blood smears for detecting parasites. Whether applied to peripheral blood or placental blood samples, PCR methods yield positivity rates 20% or more above those of blood smears microscopy. Infections identified by PCR, or RDT when microscopy fails to detect parasites on blood smears are defined as submicroscopic infections. PCR methods have been applied to detect submicroscopic pregnancy malaria. Although these tools are more sensitive for parasite detection compared with microscopy, the test format and the time to obtain results are not suitable for use in a primary care setting.[22]

Management

Therapy

According to the WHO, seven days of quinine (10 mg) plus clindamycin (5 mg) twice a day is the preferred regimen to treat malaria in the first trimester of pregnancy.[25] If clindamycin is unavailable or unaffordable, quinine monotherapy should be given.[26] Although this regimen thought to be safe during pregnancy, we should be aware of the side effects. Clindamycin does pass through the placenta and may be accumulated in the fetal liver.[27] The use of quinine is limited by its disadvantages, including a long treatment course and an increased risk of hypoglycaemia.[28]

The first-line treatments now recommended by the WHO for malaria in the second and third trimester of pregnancy are artemisinin-based combination treatments (ACT); these are combinations of fast acting artemisinin-based compounds that combined with a drug from a different class. Artemisinin derivatives include dihydroartemisinin, artesunate and artemether.[29] They are eliminated rapidly and well tolerated; none of the studies reported serious adverse event attributed to the use of artemisinin.[30] Four ACTs are currently recommended:

artesunate–mefloquine, dihydroartemisinin-piperaquine, artesunate–amodiaquine, and artemether–lumefantrine.[31] The benefits of ACTs are their high efficacy, fast action, and the reduced likelihood of resistance developing.[32]

The combination of artesunate-mefloquine is currently one of the most effective treatments against malaria in pregnancy.[33] Typical dosage are 100 mg artesunate and 220 mg mefloquine every 8 hours for 3 days.[34] Mefloquine has many characteristics such as long half-life, single dose administration, a well-characterized pharmacokinetic profile in pregnant women, and infrequent mefloquine resistance. It often gives rise to side effects such as asthenia, loss of appetite, dizziness, nausea, and vomiting.[33,35]

New infections can be prevented by long-acting artemisin such as dihydroartemisin-piperaquine especially for areas with high malaria transmission.[36] The fixed dose combination formulated in tablets containing dihydroartemisinin (40 mg) and piperaquine (320 mg) is commercially available in many countries in Asia, and also more recently in Africa. The fixed combination given once daily for 3 days was effective and well tolerated. The most common adverse effects are gastrointestinal (nausea, vomiting, abdominal pain, and diarrhea), but they are usually mild and self limiting.[37]

Artesunate-amodiaquine has the lowest side effects on the frequency of pulse and blood tension.[38] Some studies have shown that amodiaquine or combinations of amodiaquine with artesunate were better at clearing parasitaemia compared with chloroquine given alone. The total recommended treatment is 50 mg of artesunate and 153 mg of amodiaquine once a day for 3 days.[39]

Artemether-lumefantrine is a fixed-dose antimalarial drug combination in pregnancy containing 40 mg artemether and 240 mg lumefantrine per tablet as a 6-dose regimen given twice a day for 3 days. The first two doses should, ideally, be given 8 hours apart.[40] It is tolerated very well in the majority of cases, but it has the highest grade of reinfection because lumefantrine possesses short effect that it can be eliminated rapidly.[41]

Prevention

The prevention of malaria is important to reduce adverse outcomes of malaria in pregnancy. Centers for Disease Control and Prevention (CDC) recommends pregnant women who do travel to malaria countries to: I) begin a prophylactic antimalarial medication such as mefloquine (228 mg) or chloroquine (310 mg) before travelling begin i.e. two weeks before travel, during travelling once a week, on the same day of the week and continue post-travel for 4 weeks,II) [42] wear long-sleeved shirts and long pants to prevent mosquito bites, III) remain outdoors during peak time, IV) use insect repellent with N,N-Diethyl-m-toluamide (DEET) or Picaridin, and V) sleep in a well-screened or air-conditioned room or under a mosquito net treated with permethrin.[43] While the inhabitants of endemic areas, WHO recommends interventions such as intermittent preventive treatment in pregnancy (IPTp) and insecticides-treated nets (ITNs) to prevent and control malaria during pregnancy.[44]

Intermittent preventive treatment in pregnancy is the administration of antimalarial medications at predefined intervals with the intent to protect a pregnant woman against malaria.[45] It is advised not to be given to pregnant women in the first trimester because they are teratogenic and may cause fetal death.[46] Intermittent preventive treatment in pregnancy administration of SP, sulphadoxine (500 mg) and pyrimethamine (25 mg) starting as early as possible in the second trimester until the

time of delivery, with doses given at least 1 month apart, so that women receive at least three doses of SP during pregnancy.[47]

The usage of treated nets offer a form of personal protection and have repeatedly been shown to reduce severe diseases and death due to malaria for both the pregnant women and children in endemic regions.[48] The insecticides used for treating the nets kill mosquitoes and other insects. This insecticide also has repellent properties that reduce the number of mosquitoes that enter the house and attempt to feed thereby offering protection not only for the person under the net but also for those in the same room with the net owner.[49] In addition, other similar protection such as indoor insecticide residual sprays (IRS) and mosquito coils (MC) can also be used.[50]

Several studies have also mentioned some alternatives that can prevent malaria in pregnancy such as the consumption of azithromycin-chloroquine (250 mg azithromycin, 155 mg chloroquine) in combination doses, or supplementation with 25 mg zinc and 2500 IU vitamin A everyday.[51-53] However, there has not been much research to discuss this.

Outcomes

Malaria infections during pregnancy are often asymptomatic.[16] The effects of malaria infection in the first trimester are mostly unknown.[17] Low parasitemia found in all pregnant women age group may be the reason why malaria infection did not show any symptoms. This suggests that pregnant women can become carriers of malarial parasites without showing any symptoms of infection.[18]

Women primigravida uniquely vulnerable because they do not have a specific malaria immunity during pregnancy in the form of antibodies and memory B cells against a specific parasite variant surface antigens VAR2CSA. This protective antibody responses develop during subsequent pregnancies, providing protection against placental malaria. Live in rural area increase heterogeneous malaria transmission in Papua New Guinean.[11] Other data showed higher risk of placental malaria in women who experienced 0-1 episodes of malaria symptoms and <50% of the samples LAMP +; and women who have ≥ 2 episodes of malaria symptoms or ≥ 50% of the samples LAMP + compared to pregnant women without exposure to malaria.[12]

Complication of malaria in pregnancy include anemia, low birth weight, IUGR, premature birth, abortus, stillbirth, and congenital malaria. Infection in first or second trimester raise the risk of LBW, wherein acute infection of malaria is associated with LBW, with an average birth weight 199 gram lower. Acute malaria infection with high parasitemia is associated with premature birth. Chronic infection also associated with premature birth, while chronic placental malaria infection with chronic massive intervillositis is associated with anemia and LBW in pregnancy, specifically moderate anemia (7.0-8.9 g/dL) and severe anemia (<7.0 g/dL). Pregnant women with malaria are 33% more likely to develop anemia. Low birth weight is also associated with peripheral malaria infection during labor. [9,11,43]

Infection of *P. falciparum* in early pregnancy can cause intra uterine growth restriction (IUGR) between 212-253 days of gestational age, and the gestational age becomes shorter. Birth weight and weight of the placenta also found reduced. Small placental volumes in early pregnancy may be used as IUGR predictor at birth. Small placental size is associated with disorder of trophoblast invasive, late complication, and premature birth due to exposure to the VAR2CSA protein. The process underlining VAR2CSA cause IUGR is not

fully understood. *Plasmodium falciparum* divide itself in erythrocyte, makes the infected erythrocytes are more prone to be discharged into the spleen. To prevent it, the parasite express *P. falciparum* erythrocyte membrane protein 1 (PfEMP1) in the surface of infected cells. PfEMP1 is a multiprotein and each of the parasite's genome encoded around 60 different variant of protein, which one of it is VAR2CSA. This protein binds to most of tumor cells, the bound cells show decreased migration, invasion, and growth. VAR2CSA also binds infected erythrocyte to syncytiotrophoblast expressed glycosaminoglycan and present in the intervillous section. The infected erythrocyte triggers the inflammation response that negatively affected the fetal growth. VAR2CSA also may affect trophoblast and cause permanent damage to proper uteroplacental circulation.[13]

Plasmodium falciparum detected during labor in peripheral blood flow and in the placental blood flow increase the risk of stillbirth, meanwhile *Plasmodium vivax* increase the risk of stillbirth if detected during labor but not when detected and treated during pregnancy. Association between *P. falciparum* infection during pregnancy and stillbirth is two times higher in low-medium endemic area compared to high-endemic area. Increased CLCX9 in peripheral blood flow during pregnancy linked with increased risk of born premature and abortus. Increased exosome or change of microparticles composition activated peripheral mononuclear cells has been speculated to cause proinflammation immune response which associated with born premature and abortus. Increased of IL-1β di placental blood circulation also associated with miscariage and born premature.[4,54]

Congenital malaria defined as presence of the malaria parasites in asexual form either in placental blood flow or in peripheral blood flow during the first week of life, caused by the transmission of the parasite through the placental before or during the labor. In Burundi, prevalence of congenital malaria shows 0% even though the survey was carried in meso-endemic area while in the wet, high transmission season. It is assumed that during the high transmission season, mothers acquired a high immunity level and their malaria specific antibody rise when the mothers exposed to the infection. None of the newborns born from microscopy or RDT positive mothers found to be qPCR-positive might can confirm that placenta play an effective role as a barrier. Two newborns born from mothers with high parasitemia found to be HRP-2 RDT positive, but negative with qPCR, suggest that the HRP-2 antigen can pass through the placenta, while the DNA isn't transmitted.[55]

Compared to Burundi, in Maumere, Indonesia, the prevalence of congenital malaria in selected subgroup of newborns with an increased risk of congenital malaria was 42,4%, while the prevalence in all newborns was 14,7%. The congenital infection of the parasite can occur at different time, either it is *in utero* or during labor. The mechanism might be done by direct penetration through the chorionic villi or might be through premature separation of the placenta. The infected infants are at 4,7 times higher risk to develop anemia. Congenital malaria mostly found in first or second child, similar to placental malaria.[56]

Infants born to mothers that has been exposed to malarial infection more than once, or experienced placental malaria before, have higher risk of impaired growth in the first year of life. Infants born to mothers infected with malaria in their first year of life may experience at least one episode of malaria (5%), acute respiratory infection (51%), or diarrhea (22%). The risk of malaria infection in infants increased three-folds in infants born to mothers with peripheral malaria infections, dan increase

more than ten-folds in infants born to mother with placental malaria.[57]

Conclusion

Malaria in pregnancy is common in everyday life, especially in endemic areas. Therefore, with prevention as early as possible, the definitive diagnosis and the best therapy should make pregnant women free from adverse outcomes such as maternal anemia, miscarriage, intrauterine growth restriction, low birth weight, preterm birth, stillbirth, and congenital malaria.

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