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Case Report

Malaria Falciparum in Pregnancy: A Case Series from an Endemic Area

Malaria Falciparum pada Kehamilan: Sebuah Studi Kasus Serial pada Area Endemis

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ABSTRACT

Malaria is a public health issue worldwide, especially in tropical areas such as Indonesia. Malaria in pregnant women leads to increased risks of anemia, low birth weight, and fetal death. In this study, we reported two cases of malaria in pregnancy in Sikka, East Nusa Tenggara, an endemic area, after several years with zero cases. The first case was malaria in the first trimester of pregnancy, while the second case was malaria with anemia and thrombocytopenia in the second trimester of pregnancy. Both patients were treated with supportive therapies and a combination of dihydroartemisinin-piperaquine (DHP) 1x3 tablets orally for three days, leading to a favourable outcome. Both cases showed that early diagnosis and combination therapy with the correct antimalarial agent is effective for malaria in pregnancy.

Keywords: *Endemic, infection, Plasmodium falciparum, tropical area*

ABSTRAK

Malaria merupakan masalah kesehatan masyarakat diseluruh dunia terutama pada daerah tropis seperti Indonesia. Malaria pada ibu hamil meningkatkan risiko anemia pada ibu, berat badan lahir rendah, dan kematian janin. Pada studi ini, kami melaporkan dua kasus malaria pada kehamilan di wilayah endemis, Sikka, Nusa Tenggara Timur setelah beberapa tahun nihil kasus. Kasus pertama merupakan kasus malaria pada kehamilan trimester pertama, sementara kasus kedua merupakan kasus malaria dengan anemia dan trombositopenia pada kehamilan trimester kedua. Kedua pasien mendapat terapi suportif serta kombinasi dihidroartemisin-piperakuin (DHP) 1x3 tablets per oral selama 3 hari, dan didapatkan luaran yang baik. Kedua kasus ini menunjukkan bahwa diagnosis dini secara tepat serta terapi kombinasi dengan terapi antimalaria yang tepat efektif untuk malaria dalam kehamilan.

Kata Kunci: Area tropis, endemik, infeksi, *Plasmodium falciparum*

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INTRODUCTION

Malaria is a public health problem worldwide, especially in tropical areas such as Indonesia. Malaria occurs due to infection from protozoan parasites of the genus *Plasmodium*. World Health Organization (WHO) reported that malaria mortality decreased by half from 30 in 2000 to 15 in 2013; the downward trend continued to 14 in 2019 and then increased to 15.1 in 2020 and finally decreased again in 2021 to 14.8. Globally, there were 2 billion malaria cases and 11.7 million deaths due to malaria recorded from 2000-2021. Southeast Asia contributed the most cases and deaths after Africa (1).

The pathogenesis of malaria infection is very complex, and there is still a poor understanding of the parasite's virulence on the severity of malaria. *P. falciparum* has the ability to mediate the attachment of infected erythrocytes to a number of ligands on endothelial cells. Some of infected erythrocytes attach within small blood vessels in the brain and other organs, allows the parasites to avoid passing through the spleen, where abnormal erythrocytes are abolished. Cytoadherence allows *P. falciparum* to mediate more severe manifestations of malaria falciparum through local inflammatory changes that cause organ dysfunction. In particular, malaria falciparum can progress to cerebral malaria, including coma, noncardiogenic pulmonary oedema, severe respiratory distress, and renal failure, severe anaemia, acidosis, hypoglycaemia, and other organ disfunction syndromes.

Malaria affects all individuals, including pregnant women. Pregnant women are susceptible to malaria infection due to changes in the immune system during pregnancy, both cellular and humoral immunity. *P. falciparum* is the most common cause of malaria in pregnant women. Malaria in pregnancy increases the risk of maternal anemia, low birth weight (LBW), and fetal death (2). Malaria parasites in pregnancy affect birth outcomes due to the parasite accumulation in the placental interfilial clefts (3,4). Malaria in pregnancy has a good prognosis when being detected and treated early.

This study reported two cases of malaria in pregnancy in Sikka, East Nusa Tenggara, an endemic area, after several years with zero cases. The first case was malaria in the first trimester of pregnancy in a 22-year-old woman G1P0A0 gestational age 5 weeks, and the second case was malaria in the second trimester of pregnancy in an 18-year-old woman G1P0A0 gestational age 27-28 weeks with anemia and thrombocytopenia. Both patients were treated with supportive therapies and a combination of Dihydroartemisinin-Piperaquine (DHP) 1x3 tablets orally for three days, leading to a good outcome. Both cases showed that following a correct diagnosis, combination therapy of Dihydroartemisinin-Piperaquine is effective for malaria in pregnancy.

CASE REPORT

Case 1

A 22-year-old G1P0A0 woman with a gestational age of 5 weeks and 6 days was taken to the Emergency Department (ED) of District General Hospital TC. Hillers Maumere Sikka, referred from the primary health care with a diagnosis of pregnancy with malaria. Two days earlier, the patient had intermittent headache, nausea without vomiting, and fever. Fever with chills and sweating started a day before the patient was taken to the hospital. The patient was pregnant with a gestational age of 5 weeks and 6 days. The patient had been married for a year. The patient had her first menstruation at the age of 13 years with a 28-day cycle, lasting 4-5 days, with 3-4x changes of pads. There were no obstetric complaints from the patient. The patient lives in Sikka, an endemic area and there was no history of prior contact with malaria patients. Prior to referral, based on these complaints, the patient underwent a complete blood test and Rapid Diagnosis Test (RDT) at the primary care. RDT was positive and the blood test showed no abnormalities.

The findings of physical examination at ED revealed a general state of moderate pain, compos mentis consciousness, blood pressure 100/70 mmHg, pulse rate 101x/min, respiratory rate 20x/min, and temperature of 37.9°C. On obstretic examination, the abdomen was found to be convex, and the uterus was not palpable on palpation examination. A repeated blood test at ED revealed a haemoglobin level 12.6g/dL, haematocrit 37.2%, leucocytes: 8,870/µl, thrombocytes 202,000/mL, Serum Glutamic Oxaloacetic Transaminase (SGOT) 22u/L, Serum Glutamic Pyruvic Transaminase (SGPT) 31µ/L, serum creatinine 0.65. On re-examination of parasite counts, *P. falciparum* count was 63/402 field of view asexual parasites without sexual phase parasites (Figure 1). Based on anamnesis and physical examination, the patient was diagnosed with G1P0000, 22 year old, 5 weeks 5 days gestation, with malaria falciparum.

During hospitalisation, the patient was given intravenous therapy of NaCl 0.9% 1500cc/24 hours, intravenous injection of ondansetron 3x4 mg, paracetamol 3x500 mg tablets orally if fever occurred, and a DHP 1x3 tablets orally for 3 days. After 3 days of treatment, the patient underwent evaluation of a complete blood test and parasite count. The blood test revealed a haemoglobin level 10.7g/dL, haematocrit 31.3%, leucocytes 8,050/µl, thrombocytes 181,000/mL and in the parasite count examination, *P. falciparum* was no longer found. The patient was then discharged from the hospital with Paracetamol 500 mg for take home medication.

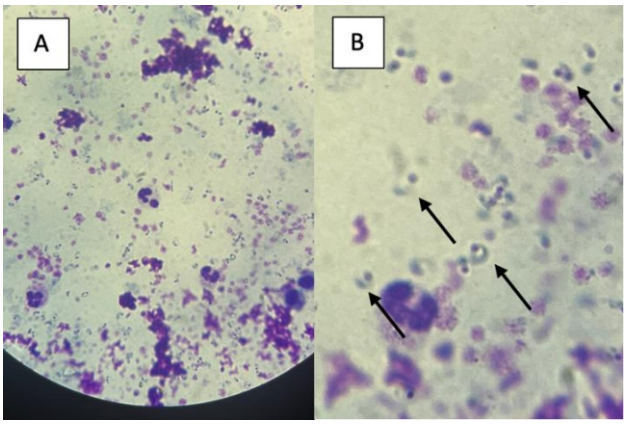

Figure 1. Microscopic re-examination of patient 1 blood smear, before antimalaria treatment

Note: (A) The pheripheral blood smear was taken from day 3 post-onset, stained with Giemsa, and observed at a 40X magnification. (B) *P. falciparum* ring forms/ asexual parasites forms (indicated by black arrows) were observed in intensity of 63/402 fields.

Case 2

An 18-year-old female G1P0A0 with a gestational age of 27-28 weeks was admitted to the Emergency Department (ED) of District General Hospital TC. Hillers Maumere Sikka with referal from the primary health care with a diagnosis of pregnancy with malaria falciparum and mild anemia. Two days earlier, at first, the patient felt weak and suffer from joint pain, then followed by headache and fever. The headache was felt as if it was bound and had worsened since it first appeared. The fever, accompanied by chills was felt intermittently. The patient claimed to be pregnant with a gestational age of 7 months. The patient was unmarried and experienced her first menstruation at the age of 12 years with a 28-day-cycle, for 7 days, with 3-4x change of pads. The patient reported that her pregnancy was fine with no obstetric complaints. The patient lives in Maumere, an endemic area and there was no history of prior contact with malaria patients. Prior to referral, based on these complaints, the patient underwent a complete blood test and parasite count at the primary care. Results showed that *Plasmodium* parasites were detected and haemoglobin (Hb) level was 8.2g/dL suggesting a mild anemia.

The physical examination at ED revealed a general state of moderate pain, compos mentis consciousness, blood pressure 90/60 mmHg, pulse rate 92x/min, respiratory rate 20x/min, and temperature of 38.1°C. The general physical examination revealed no significant abnormalities. The obstetric examination revealed a convex abdomen with a fundus uteri height of 16 cm and a foetal heart rate of 143x/min. Repeated blood test revealed a haemoglobin level 7.2g/dL, haematocrit 22%, leucocytes 7,810/µl, thrombocytes 51,000/mL, SGOT 8u/L, SGPT 14µl/L, serum creatinine 0.62. Parasite counts showed *P. falciparum* at 135/506 field of view asexual parasites without sexual phase parasites (Figure 2). Based on anamnesis and physical examination, the patient was diagnosed with G1P0000 18 year old, 27 – 28 weeks gestational age, with malaria falciparum, moderate anemia, and thrombocytopenia.

During hospitalisation, the patient was given intravenous therapy of NaCl 0,9% 500cc/24 hours, Ranitidine 2x50 mg intravenously, Paracetamol 3x500 mg tablets orally if fever occurred, and DHP 1x3 tablets orally for 3 days.

After 3 days of treatment, the patient underwent evaluation of a complete blood test and parasite count. The blood test revealed a haemoglobin level: 6.91 g/dL, haematocrit 20.5%, leucocytes 9,910/µl, thrombocytes 128,000/mL and in the parasite count evaluation, *P. falciparum* was found with the number of sexual parasites 2/500 field of view without the presence of asexual parasites (Figure 3). Patient was then given 2 PRC bags transfusion, followed by examination of parasite and complete blood counts. The blood test revealed haemoglobin 9.4g/dL, thrombocytes 230,000/mL and no detected *P. falciparum* parasites. The patient was then discharged from the hospital with take home medication Paracetamol 500mg, Ferrous Sulphate 300 mg, and Vitamin C 100mg.

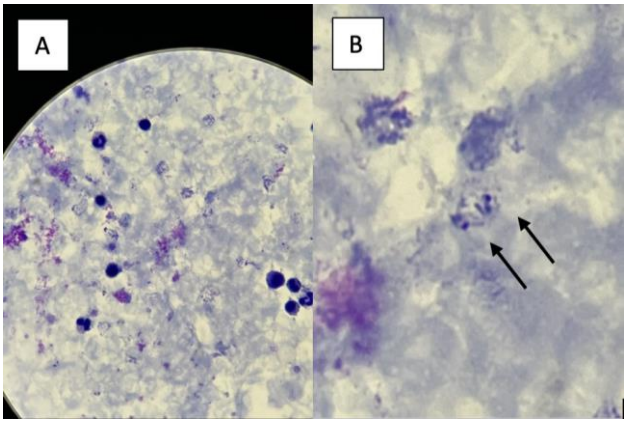

Figure 2. Microscopic re-examination of patient 2 blood smear, before antimalaria treatment

Note: (A) The pheripheral blood smear was taken from day 3 post-onset, stained with Giemsa, and observed at a 40X magnification. (B) *P. falciparum* asexual parasites forms (indicated by black arrows) were observed in intensity of 135/506 fields.

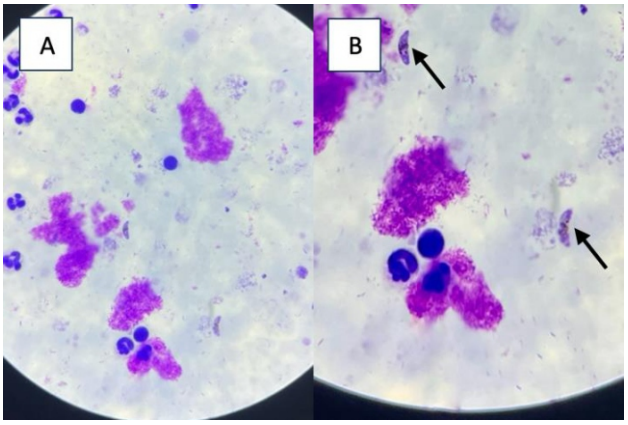

Figure 3. Microscopic re-examination of patient 2 blood smear, after 3 day antimalaria treatment

Note: (A) The pheripheral blood smear was taken after 3-day antimalaria treatment, stained with Giemsa, and observed at a 40X magnification. (B) *P. falciparum* sexual parasites forms or gametocyte (banana shaped) were observed in intensity of 2/500 fields.

DISCUSSION

Malaria has non-specific signs and symptoms. Malaria can be suspected clinically if fever is present. Clinical malaria diagnosis alone has low specificity and risks overtreatment. Exclusion of other causes of fever is necessary before diagnosing malaria. In endemic areas, malaria is suspected in any patient with a fever ≥37.5°C without any underlying cause. In areas with stable malaria transmission, malaria should be suspected in children with palmar erythema or with haemoglobin levels <8g/dL. All patients with suspected malaria should be confirmed with a Rapid Diagnosis Test (RDT) or parasitological test in all settings (2,5). Sikka district in East Nusa Tenggara is an endemic area for malaria. The case's complaints which indicate the suspicion of malaria, include weakness, headache, and fever. Therefore, RDT and parasite counts were performed at primary health care, which were positive for malaria falciparum.

Malaria in pregnancy is most commonly caused by *P. falciparum* (2). The malaria transmission cycle begins when anopheles mosquitoes containing malaria parasites bite humans, causing sporozoites from the mosquito's salivary glands to enter the blood and liver. The malaria parasite forms a schizont stage in the tissues within liver cells (exo erythrocytes). The merozoites exit through the ruptured infected liver cells and enter the erythrocytes to form the schizont stage in the erythrocytes (erythrocyte stage). In this phase, young to mature trophozoites form and exit after the erythrocyte cell ruptures. Most of the merozoites re-enter the erythrocyte, and a small percentage form male and female gametocytes ready to continue the life cycle in the mosquito's body through mosquito suction (sporogony stage) (6). Pregnant women are more susceptible to malaria infection and tend to show symptoms compared to non-pregnant women (7). Parasite levels in the blood of malaria patients are considered more prevalent in pregnant women (8). During pregnancy, adaptations occur in the maternal immune system to protect the mother and her future baby from pathogens while avoiding harmful immune responses against the allogeneic fetus. There is little evidence showed that the maternal immune system is generally suppressed during pregnancy and have higher risks for certain types of infections (9).

Malaria is divided into two types: malaria without complication and severe malaria. Malaria without complication has symptoms of a cold phase, a hot phase with fever, headache, and seizures. These complaints generally persist for 6-10 hours and appear every 2-3 days. Severe malaria is mostly caused by P. falciparum and has symptoms of organ failure, including cerebral malaria, haemolysis, pulmonary oedema, respiratory distress, severe thrombocytopenia, renal failure, and cardiovascular failure (10). In general, the symptoms of fever in malaria are divided into three phases. The first phase (cold) involves chills and shivering for 15-60 minutes. The second phase (hot) appears after 2-6 hours with a fever that can reach 41°C followed by headache, dry skin, nausea, and vomiting. The last fever phase decreases with sweat output for 2-4 hours. Fever is associated with the release of mature schizonts from ruptured erythrocytes and the formation of cytokines. Fever in malaria falciparum can occur every 48 hours, but it is often found that fever appears irregularly and does not show a clear periodicity. This classic febrile pattern is usually not seen early in the course of malaria. (10) *P. falciparum* infection in pregnancy is commonly associated with an increased risk of maternal anemia, low birth weight (LBW), and foetal death (2).

In this case, anemia and thrombocytopenia were found with a haemoglobin (Hb) level 7.2g/dL and thrombocytes: 51,000/mL. Malaria in pregnancy is associated with a significant risk of maternal anemia, especially in the late trimester (11). In this case series anemia was found on the older gestastional age. Anemia in malaria results from the destruction of *plasmodium*-infected erythrocytes and rupture of uninfected erythrocytes due to haemolysis which is caused by the increased osmotic pressure of the erythrocytes. Anemia is caused by the destruction of infected and uninfected erythrocytes, decreased haematopoiesis, and bleeding. According to research, haemoglobin levels in most patients will continue to decrease on the first and second day of treatment and rise slowly until day 28. The increase in haemoglobin levels is related to the state of parasitaemia and the rate of parasite elimination (12).

There are several hypotheses regarding thrombocytopenia in malaria infection. Thrombocytopenia is assumed to be related to peripheral platelet destruction, platelet accumulation in the spleen, and excessive platelet consumption (13). The increased rate of platelet destruction in malaria infection is suspected to be mediated by the increased immunoglobulin G (IgG) specific immune cells in the blood that bind to platelets and malaria antigens (14). Platelets are also assumed to be able to mediate the clumping of erythrocytes which were infected by P. falciparum. In addition, in malaria infection, the endothelium is activated, resulting in the loss of endothelium permeability function. This process results in the overconsumption of platelets and other proteins to repair endothelial permeability function, leading to thrombocytopenia (15). In our case, blood tests on day 3 of treatment showed no increase in haemoglobin (6.91 g/dL) and an increase in thrombocytes (128,000/mL). Transfusion of 2 bags of red blood cells was given to the patient, to increase the patient's haemoglobin level to 9.4 g/dL and thrombocyte level to 230,000/mL.

The correlation of parasite virulence to malaria severity remains poorly understood. P. falciparum is able to mediate the attachment of infected erythrocytes to a number of ligands on endothelial cells. As a result, some of erythrocytes that are infected with plasmodium parasites do not circulate; instead, they attach within small blood vessels in the brain and other organs. This phenomenon, referred to as cytoadherence, allows the parasites to avoid passing through the spleen, where the abnormal erythrocytes are abolished. Cytoadherence allows P. falciparum to mediate the more severe manifestations of malaria falciparum through local inflammatory changes that cause organ dysfunction. In particular, malaria falciparum can progress to cerebral malaria, including coma, noncardiogenic pulmonary oedema, severe respiratory distress, renal failure, severe anemia, acidosis, hypoglycaemia and other organ dysfunction syndromes. In our case there were no sign or symptops of organ dysfunction.

Unlike other species, *P. falciparum* expresses the receptor *P. falciparum* Erythrocyte Membrane Protein-1 (PfEMP1) on infected erythrocytes (16). In pregnancy, the infected erythrocytes express a variant of the PfEMP1 receptor called VAR2CSA which plays a role in the adhesion process to syncytiotrophoblasts and especially to the placental intervilli space (3,4). In active infection, dense deposits of infected erythrocytes can be found in the placenta in the placental intervilli space, monocytes and macrophages. The accumulation of infected erythrocyte deposits in the placenta causes reduced placental blood flow, increasing the risk of abortion, stunted foetal growth, premature birth, stillbirth, or low birth weight (17). Pregnant women infected with *P. falciparum* should be treated immediately, even if asymptomatic. Such treatment aims to inhibit progressive and severe infection, reduce maternal anemia as well as prevent fetal complications by killing parasites in the placenta.

Up to now, no theory mentions the effectiveness, safety and pharmacokinetics of antimalarial drugs as therapy in pregnancy, especially in the first trimester. WHO

recommends the medication of 1x10 mg quinine together with 2x5 mg clindamycin for seven days for the first line of uncomplicated malaria therapy in the first trimester of pregnancy. If clindamycin is not available, quinine can be given as monotherapy. For treatment of malaria without complications in the second and third-trimester pregnancies, WHO recommends treatment with artemisinin with dihydroartemisinin derivatives, artesunate and artemether. The four recommended artemisinin are 100mg artesunate – 220mg mefloquine every 8 hours for 3 days, 40mg dihydroartemisinin – 320mg piperaquine (DHP) fixed dose for 3 days, 50mg artesunate – 153mg amodiaquine once daily for 3 days, and 40mg artemether – 240mg lumefantrine fixed dose for 3 days. In Asia, the DHP combination is widely used and is the first-line treatment for malaria without complications in pregnancy in Indonesia for all trimesters. In both cases, the effectiveness of the DHP combination after 3 days of treatment was shown by the absence of sexual parasites from the parasite count. Asexual parasites can persist for up to 28 days after antimalarial treatment. In the case of recurrent, parasite count examination after one week from the first dose of the DHP, neither sexual nor asexual parasites of P. falciparum were found.

Pregnant women who live in malaria-endemic areas should receive chemopreventive treatment, and pregnant women traveling to endemic areas should receive chemoprophylaxis to prevent malaria (2). Administration of chemopreventive and chemoprophylaxis can reduce parasitemia, prevent severe malaria complications, and improve pregnancy outcomes. The WHO recommends the earliest possible administration of Sulfadoxine-pyrimethamine (SP) in the second trimester every time the patient visits for ANC until birth and not before 13 weeks of gestation. Instead of giving this safe treatment to the patient during pregnancy, SP administration is considered to have the ability to reduce the incidence of anemia, reduce the risk of malaria infection of the placenta, reduce the risk of LBW, and reduce the incidence of premature birth (2). In Indonesia, chemoprophylaxis treatment for pregnant women who live in malaria-endemic areas is not routinely given.

In conclusion, malaria in pregnancy is a severe problem because it can increase maternal mortality and affect infant outcomes if not addressed quickly and appropriately. It is necessary to perform routine malaria screening and administering chemoprevention to pregnant woman in endemic areas and chemoprophylaxis to women traveling to endemic areas to prevent malaria infection. Despite not stated in WHO guideline and recommendations, in Indonesia, the use of 1x3 DHP tablets per oral for 3 days is effective for malaria in pregnancy during the 1st, 2nd, or 3rd trimesters.

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