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# Recurrent Vivax Malaria in Pregnancy: A Case Report

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**ABSTRACT**

Malaria in a pregnant woman is more complicated than in other populations since it can cause stillbirth, spontaneous abortion, anemia, low birth weight, and infant mortality. Therefore, this case report was written. A 26-years-old pregnant woman in the 2nd trimester came with a chief complaint of fever. The fever was typical malaria and had a history of vivax malaria a month before. According to the result of her rapid diagnostic test, microscopic examination, and complete blood count, she was diagnosed with recurrent vivax malaria with anemia and thrombocytopenia in pregnancy. Dihidroartemisin-Pipieraquin (DHP) without primaquine was given to eradicate parasites. Packed red cells transfusion, iron, and folic acid supplementation were administered to improve and prevent recurrent anemia. Weekly chloroquine prophylaxis to prevent relapse during pregnancy cannot be applied due to chloroquine-resistant in Indonesia, so complete doses of primaquine were planned to be given after breastfeeding time to prevent relapse in the next.

**Keywords;** vivax malaria, recurrent, relapse, pregnancy, anemia, low birth weight

## INTRODUCTION

Malaria infection in Indonesia, especially in the east region, has still become an enormous public health problem due to the climate condition that is co-distribution of Anopheles mosquito. The endemic area of malaria in Indonesia is Papua, West Papua, and NTT. The incidence rate of malaria in 2017 was 261,617 cases with 100 mortality cases (Kemenkes, 2018b). Based on a population-based study in Papua in 2004–2009, there were 294,000 vivax malaria cases with the mortality rate ranging from 0.012% to 0.063% (WHO, 2015b).

*Plasmodium vivax*has the widest geographical distribution of the four human malaria, with about 35% of the world's population being at risk. The parasitemia is typically low and it has a dormant phase in the liver where diagnostic tools are still unable to recognize it, making this species difficult to detect and treat (WHO, 2015b; WHO, 2018). The relapse cases of vivax malaria are high. Around 78% of Indonesian soldiers who were not provided with primaquine therapy returning to Java from Papua suffered a relapse. The average rate of relapses was 2.7 per person per year (WHO, 2015b).

Malaria in pregnant women is risky than in other populations, especially in the first and second pregnancies. It can cause stillbirth, spontaneous abortion, maternal anemia, placental parasitemia, low birth weight, and infant mortality. Malaria in pregnancy is the cause of 5–12% of low birth weight and 35% of preventable low birth weight. It plays role in 75,000-200,000 infant deaths every year (WHO, 2007; Rogerson*et al*., 2007). Besides, the management of therapy malaria in pregnancy is different from other populations.

This case report aims to explain about diagnosis, management, and complication of recurrent vivax malaria in pregnancy.

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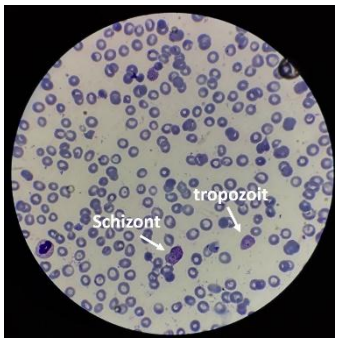
## CASE

A 26-year-old housewife with 20th week of pregnancy came to the emergency ward Dr. Soetomo General Hospital. The patient suffered from fever for 10 days before admission. Fever occurs every 2 to 3 days preceded by chills then followed by high fever and profuse sweating. Patients also complain of nausea, vomiting, and decreased appetite. The patient lived in Papua, an endemic area, for 1 year and went back home to Madura, a non-endemic area, 2 weeks before admission. The patient had a history of vivax malaria about 1 month before admission treated with quinine three times a day for 1 week, but but not taken regularly because of the side effects of nausea and vomiting.

The patient was currently in the 5th month of her second pregnancy. When in 1st trimester of this pregnancy she had been screening for malaria and the result was negative.

Physical examination showed blood pressure of 100/60 mmHg, pulse rate of 110 times per minute, respiratory rate or 22 times per minute, and axillary temperature of $38^0$celsius. The conjunctiva looked pale. The obstetric physical examination resulted fundal height at umbilical level, Fetal Heart Rate of 148 beats per minute, cephalic presentation. Vaginal examination found no fluxus and no opening of the cervix.

The blood test showed normochromic normocytic anemia (Hb 7.4 g/dL), thrombocytopenia (72,000/µL), and hypokalemia (2,97mmol/L). The Serum Iron and Total Iron Binding Capacity are low (15 µg/dL and 176 µg/dL). ICT rapid test was positive for P.v*ivax*. Parasite malaria was found in microscopic blood smear examination. There was a formation of trophozoite and schizont of P.v*ivax* and parasitemia index 1%. Peripheral blood smear showed normochromic normocytic anisopoikilocytosis and thrombocytopenia. Molecular genotyping cannot be done. The patient was diagnosed with recurrent vivax malaria accompanied by anemia and thrombocytopenia in pregnancy.




**Picture 1.Schizont and trophozoite of *Plasmodium vivax***

Dihidroartemisin-Piperaquin (DHP) 4 tablets a day for 3 days without primaquine was given. Supportive treatment including high calorie and high protein diet and 1 bag of packed red cells transfusion per day until the hemoglobin rise to 10 g/d. Folic acid 400 µg once a day and Ferrous fumarate 180 mg once a day were given due to iron deficiency anemia. A slow-release potassium tablet was administered three times 600 mg a day for 3 days due to mild hypokalemia.

Microscopic examination on the 3rd day was negative for malaria. The patient was discharged on day 6 after all workup examinations appeared to be normal. She was advised to maintain good health during pregnancy to prevent relapse of malaria since this patient did not get chemoprophylaxis chloroquine during pregnancy. She was advised to visit the outpatient clinic to have a microscopic examination on the 7th, 14th, 21st, and 28th day. Her disease did not relapse

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until delivery. She delivered her baby in a full-term pregnancy, but her baby was underweight. After breastfeeding time, complete doses were planned to be given to prevent relapse.

## DISCUSSION

Malaria is caused by a parasite called *Plasmodium sp.* Plasmodium infects red blood cells through female *Anopheles* mosquito bites (WHO, 2010; Kemenkes, 2018a).

Malaria causes a fever that is commonly preceded by shivering then followed by high fever and sweating. The characteristic of the fever is typical depends on the species. These classic symptoms are usually found in non-immune people from a non-endemic area. Otherwise, the symptoms in immune people living in the endemic area are usually unclear, such as headache, nausea, vomiting, diarrhea, and muscle pain. The clinical presentation of malaria is even less clear in patients having a history of previous malaria infections. Physical examination may found pale conjunctiva or pale hands, icteric sclera, spleen enlargement, and liver enlargement. (WHO 2010; WHO, 2015a).

Vivax malaria is caused by Plasmodium vivax. In contrast to malaria caused by P. falciparum, P malariae, and P knowlesi, P.vivax form hypnozoite, a latent liver stage, that remain dormant for weeks or months before awakening dan makes relapse of malaria. The patient can have a subsequent infection without reinfection. A large number of mosquito bites can increase the number of relapses dan shorten the interval between primary infection and the first relapse. (Chu & White, 2016).*Plasmodium vivax* has two general forms, tropical and temperate form. The tropical form causes relapses at the frequent interval, typically every 3 weeks, 5-7 weeks after primary infection, and tends to be less susceptible to primaquine. The temperate form causes relapses around 9 months after primary infection and more sensitive to primaquine (WHO, 2015a).

Recurrent vivax malaria can be caused by relapse (hypnozoite reactivation), recrudescence (due to inadequate anti-malarial treatment to clear partially resistant blood stages beyond day 28 of treatment), or re-infection (new infection transmitted by a mosquito). It is hard to distinguish between recrudescence, reinfection, and relapse. Molecular genotyping should be done to determine the genotype of the parasite (WHO, 2015a). In this case, we cannot distinguish between the three because we don't do molecular genotyping. Recrudescence is still possible because of 1 month's previous history of malaria with inadequate anti-malarial treatment. The patient received second-line treatment but was incomplete because of low adherence due to drug's side effect. Relapse also possible because the time interval between the primary infection with the secondary infection is more than 3 weeks (refers to tropical form). This case could be a new infection because the patient had fever on the $4^{th}$ day since arrival from Papua. The incubation period for malaria vivax is 12-17 days, so it can be assumed that the patient is in the incubation period when the patient returns from Papua.

The spectrum of disease of *Plasmodiumvivax* infection ranges from asymptomatic parasitemia to severe malaria. *Plasmodium vivax* causes paroxysmal fever with a periodicity of 24-48 hours, usually preceded by chills and rigor. Anemia may only be present in persistent and recurrent infections (WHO 2010; WHO,2015b). The patient, in this case, suffered from typical malaria fever. She also had a previous history of vivax malaria a month before and lives in an endemic area of malaria.

The diagnosis of malaria should be defined by microscopic examination or Rapid Diagnostic Test (RDT). Microscopic examination is a gold standard to diagnose malaria. Examination of blood material with thick and thin preparation with the microscope aims to determine the presence of

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parasite malaria, the species, the stage, and the density of the parasite (Kemenkes, 2018a). RDT is used to detect antigens of malaria using immunochromatography. However, the use of RDTs in pregnancy gave varying results. Vivax malaria may be difficult to diagnose because it occurs at low parasite densities below microscopically detectable levels. Besides, the parasites can confine in the spleen and bone marrow so that it is difficult to detect although there is large parasite biomass associated with severe malaria (WHO, 2015b).

Malaria is classified into uncomplicated malaria and severe malaria based on the clinical manifestation. The clinical signs of severe malaria are impaired consciousness (GCS less than 11), general weakness, multiple convulsions, acidosis, hypoglycemia, severe anemia, renal impairment, jaundice, pulmonary edema, significant bleeding, shock, hyper parasitemia, and black water fever. A patient with uncomplicated malaria has no features of severe malaria (WHO, 2015a; Kemenkes, 2018a; WHO, 2015b). The patient, in this case, is classified as uncomplicated vivax malaria.

Anemia is the most common hematological abnormal finding in pregnancy. It affects more than 40% of pregnant women worldwide, half of this due to iron deficiency. Deficiencies in iron and folic acid during pregnancy can potentially negatively impact the health of the mother and her pregnancy. As pregnancy can reduce a woman's immunity, this condition making pregnant women more susceptible to malaria infection.(WHO, 2016). Maternal anemia in malaria is the contribution of the placental process, especially in the first pregnancy. In vivax malaria where there is no placental sequestration, the severity of anemia observed with low parasitemia may also be due to the cumulative impact of multiple P.vivax relapses (Rogerson et al., 2007). In this patient, anemia is caused by a combination process of iron deficiency anemia related to pregnancy and malaria.

Thrombocytopenia occurs in 5% to 10% of women during pregnancy due to gestational thrombocytopenia (Cines& Levine, 2018). It is not associated with adverse outcomes for the mother and baby, and usually self-limiting in 1-2 months after delivery (Ciobanu*et al*, 2016). The thrombocytopenia can be caused by acute malaria infection. The study showed that 18.7% of patients with *Vivax* malaria had platelet counts less than 150,000/$mm^3$ and 10.1% of these had either severe or very severe thrombocytopenia. Platelets play role in innate immunity against malaria. The factors affecting thrombocytopenia in malaria are endemicity, accessibility to the treatment, and immunity (Naing&Whitteker, 2018; Coelho et al., 2013). In this patient, as the disease resolves, the thrombocyte count increased so thrombocytopenia in this patient was more likely related to malaria than to pregnancy. However, this thrombocytopenia has no significant effect on the prognosis, since the thrombocytopenia does not cause clinical manifestation.

Immunity is an important factor affecting manifestation and severity. Several variables affecting this immunity, such as continuous transmission, age, and pregnancy (WHO, 2015a). A pregnant woman has a greater risk when getting malaria, especially primigravida and early pregnancy. Parasitemia usually occurs in 9-16 weeks. This may be due to hormonal or immunologic rather than the placental sequestration process. Malaria in pregnancy has a risk of placental malaria and maternal anemia. Placental malaria leads to neonatal mortality and low birth weight, while maternal anemia increases the risk of perinatal mortality (Rogerson*et al*., 2007). Vivax malaria is known as a factor causing spontaneous abortion and IUGR in pregnant women although *Plasmodium vivax* does not sequester in the placenta (WHO, 2015b; Fried & Duffy, 2017). The outcome of low birth weight babies from vivax malaria is caused by systemic effects rather than placental changes (Rogerson*et al*., 2007).

As pregnancy can reduce a woman's immunity, this condition making pregnant women more susceptible to malaria infection.(WHO, 2016). But in vivax malaria where there is no placental

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sequestration, the severity of anemia observed with low parasitemia may also be due to the cumulative impact of multiple *P.vivax* relapses (Rogerson*et al*., 2007). This patient has low immunity against malaria due to pregnancy and no exposure to malaria during her childhood. This condition leads to recurrent, anemia, and low birth weight.

The most challenging problem in the treatment of malaria in Indonesia is decreasing of efficacy some of the malaria drugs and the low adherence to treatment for people in Indonesia. One of the causes is the irrational use of medicine. The objective of antimalarial treatment for vivax malaria is to cure both blood-stage and liver-stage infection to prevent recrudescence and relapse. For blood-stage infection, Dihydroartemisinin–Piperaquine (DHP), an ACT can be used in both pregnant and nonpregnant patients. ACT doses are given once daily for 3 days. For liver-stage infection, primaquine is used as the only preventive treatment to prevent relapses in Indonesia (Kemenkes, 2018a). The new single-dose treatment for vivax malaria that was just approved by FDA in 2018, tafenoquine is used for radical cure also for prophylaxis. But neither primaquine nor tafenoquine can be given during pregnancy or breast-feeding, patients with G6PD deficiency and are not recommended in children < 6 months. The dose of primaquine is 0.25mg/kg BW/day given for 14 days and in relapse vivax malaria, the doses of primaquine increase to 0.5mg/kg BW/day. In the patient with G6PD deficiency, primaquine is given once a week for 8 weeks with closed monitoring. But tafenoquine cannot be used in G6PD deficiency or if the status of G6PD in the patient is unknown (CDC, 2019; Kemenkes, 2018a).

Since primaquine is contraindicated in pregnancy, uncomplicated vivax malaria in pregnancy should get weekly chloroquine prophylaxis post-treatment until delivery is recommended to prevent relapse during pregnancy. (WHO, 2015a). This recommendation cannot be applied in Indonesia due to chloroquine-resistant malaria found in Indonesia. Then microscopic blood evaluation is done on the 3$^{rd}$, 7$^{th}$, 14$^{th}$, 21$^{st}$, and 28$^{th}$ day concurrent with clinical assessment. For radical cure, complete doses of primaquine were planned to be given after breastfeeding time to prevent the next relapse (Kemenkes, 2018a).

Vector control, i.e. indoor residual spraying (IRS) and insecticide-treated mosquito nets (ITNs) should be done to prevent infection, although these methods are not always effectivebecause some important vectors in endemic areas have primarily early-biting, outdoor-feeding, and outdoor-resting behavior. Moreover, *P. vivax* can be transmitted from humans to mosquitoes before symptoms develop in the infected people. Vector control also has no impact on latent hypnozoite stage parasite in the liver (WHO, 2015b). Chemoprevention is needed to accompany vector control. Some antimalarial drugs inhibit pre-erythrocytic development and kill asexual blood stages that have potential. Three doses of IPT with SP (sulfadoxine-pyrimethamine) are recommended in pregnant women living in the endemic area as prevention, accompanied by strict antenatal visits. This chemoprevention starts in the second trimester with at least a 1-month interval. Insecticide-treated nets (ITNs) are also recommended (WHO, 2015c; WHO, 2007; WHO, 2015a). But in Indonesia, due to the decrease effication of chloroquine and sulfadoxine-pyrimethamine in malaria, this drug is not recommended for treatment or prevention of malaria (Kemenkes, 2018a). The strategy of malaria in Indonesia is the use of Long-Lasting Insecticidal Nets, Passive Case Detection and Single Screening and Treatment (Webster *et al*., 2018)

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