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A tale of two lives, vivax malaria in pregnancy in Indonesia's Heartland: A case series

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Abstract

Background: East Nusa Tenggara, an endemic region for malaria with the third-highest prevalence in Indonesia, increases the susceptibility of pregnant women to infection and related complications.

Case: Two new cases of vivax malaria in pregnancy were identified in the first semester of 2024, both experiencing complications during pregnancy and the puerperium period. Both patients were nulliparous women from rural backgrounds, presented with evening fever, chills, heavy sweating, headache, myalgia, and arthralgia. The first case involved a singleton pregnancy in the third trimester, complicated by anemia and thrombocytopenia, which led to a malaria relapse a month post-delivery. The second case involved multiple pregnancies in the second trimester, presenting with thrombocytopenia, premature labor, and low birth weight post-treatment. Both patients received a three-day course of dihydroartemisinin-piperaquine (DHP), resulting in negative follow-up blood smears on days 3 and 7.

Discussion: Plasmodium infects erythrocytes, sequesters in the placenta, and induces placental insufficiency, thereby contributing to maternal anemia, low birth weight, premature delivery, and infant mortality. DHP exhibits high efficacy and tolerability in pregnant women during the second and third trimesters, as evidenced by negative results in blood smears on days 3 and 7 post-treatment. However, the absence of a 14-day primaquine regimen leads to relapse in the first case.

Conclusion: Early detection and treatment of malaria during pregnancy are essential in endemic regions to reduce maternal and neonatal complications.

Keywords: Malaria; *Plasmodium vivax*; Pregnancy; Complications; Endemic

1. Introduction

Malaria ranks as the second leading cause of death from infectious diseases worldwide, surpassed only by tuberculosis [1]. As many as 125 million pregnant women are at risk infected by malaria leading to 200.000 infant deaths and 10.000 maternal deaths every year [2]. Two significant parasite infections that emerge with adverse effects are *Plasmodium falciparum* and *Plasmodium vivax* [3]. In 2022, there were 443.530 cases of malaria in Indonesia with 34.18% infected by *Plasmodium vivax*, the second-highest parasite but dominantly infected in endemic regions [4]. East Nusa Tenggara has the highest risk of vivax malaria in Indonesia [5]. Alor has the fifth position of malaria burden with 331 cases in

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2023, where the number of pregnant women suffering from malaria has increased from 2022 to 2024 which found 3 cases, 4 cases, and 6 cases respectively [6, 7].

Malaria transmission occurs through the bite of an infected *Anopheles* mosquito, which injects *Plasmodium* sporozoites from its salivary glands into the human bloodstream. The sporozoites subsequently migrate to the liver, where they undergo maturation and replication to continue their life cycle [1]. In *P. falciparum*, parasites infect the erythrocyte and sequester in the placenta mainly at the intervillous space assisted by the protein exported, VAR2CSA, which later induces inflammation [8]. This mechanism leads to placental destruction ensuing poor neonatal outcomes. However, *P. vivax* involvement in pregnancy is still unclearly understood. It is stated that changes in placental structure, leukocyte infiltration, and angiogenic imbalance are caused by cytokines such as TNF-α and IFN-γ that induce systemic inflammation. Nevertheless, IL-10 is linked to a better prognosis [9]. Other studies elaborate that the placenta infected by *P. vivax* are different compared with *P. falciparum*, it showed a thicker barrier and have more monocytes and syncytial knots. Parasite sequestration also found absent in contrast with *P. falciparum* [10].

As an endemic area of malaria, pregnant women are one of the most susceptible infected by malaria. Higher risk factor of being infected included the primigravidae, younger maternal age, and during the second trimester [11]. Despite *P. vivax* infection being less severe than *P. falciparum*, it can lead to several complications [12]. The adverse effect of malaria infection includes maternal anemia, severe maternal morbidity (such as renal failure, pulmonary edema, and cerebral malaria), until death. Therefore, miscarriage, stillbirth, neonatal death, low birth weight, preterm birth, and fetal growth restriction can also occur [13]. Moreover, *P. vivax* and *P. ovale* are the only *Plasmodium* species that can induce relapse, owing to the presence of dormant liver stages known as hypnozoites [14].

This study reports two instances of complicated malaria in pregnancy from Alor, East Nusa Tenggara, Indonesia, a malaria-endemic area. The first case involved a relapse of *P. vivax* infection during a singleton pregnancy, whereas the second case resulted in preterm birth and low birth weight in a twin pregnancy, culminating in neonatal mortality. Both cases received treatment with dihydroartemisinin-piperaquine (DHP), with subsequent malaria tests returning negative; however, the complications persisted after the completion of the treatment.

2. Case reports

2.1. Case 1

A 32-year-old nulliparous woman at 34-36 weeks of gestation was admitted to Kalabahi Regional Public Hospital, Alor, East Nusa Tenggara presenting with an 8-day history of fever, chills, arthralgia, and myalgia. The fever occurred predominantly in the evenings, accompanied by heavy sweating, and exhibited an intermittent pattern with febrile-free days. Laboratory tests revealed normocytic anemia (hemoglobin 8 g/dL), thrombocytopenia (69,000/μL), and a positive peripheral blood smear for *Plasmodium vivax* (+2). Serum dengue (IgM and IgG) tests were negative, and urinalysis was normal. The patient was treated with a three-day course of dihydroartemisinin-piperaquine (DHP), consisting of dihydroartemisinin 120 mg and piperaquine phosphate 960 mg. Follow-up evaluations on days 3 and 7 post-treatment showed negative peripheral blood smear results. Other therapies include symptomatic drugs such as antipyretic and one-bag transfusion of Packed Red Cells (PRC). One-month post-therapy, the patient spontaneously delivered an infant weighing 4,010 grams and measuring 50 cm in length, with an APGAR score of 8/9 and no signs of respiratory distress. One month postpartum, the patient was readmitted to the hospital after experiencing four days of fever and chills, followed by headache, myalgia, and arthralgia, which did not resolve with antipyretic medication. Laboratory tests revealed anemia, thrombocytopenia, and a positive result for *Plasmodium vivax* (+3), shown in Figure 1. The patient was treated with a three-day course of dihydroartemisinin-piperaquine (DHP) and 15 mg of primaquine, with the recommendation to abstain from breastfeeding during treatment. Peripheral blood smear for malaria conducted three days post-treatment returned negative.

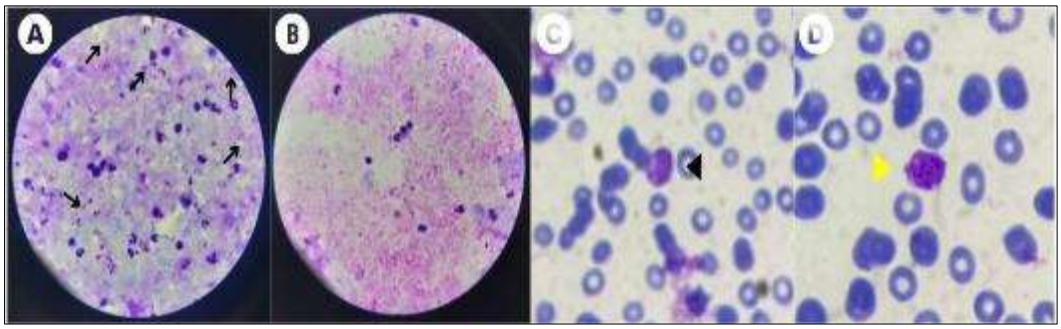

Figure 1 Microscopic examination of patient 1 blood smear with Giemsa

Note: (A) Multiple rings (black arrow) were observed in a thick blood smear in the first examination. (B) No *Plasmodium vivax* was found in the thick blood smear on the 3rd day of evaluation. (C-D) Mature trophozoite (black arrowhead) and schizont (yellow arrowhead) were seen in an enlarged and distorted infected RBC in a thin blood smear during the episode of relapse.

2.2. Case 2

A 21-year-old nulliparous woman at 26-28 weeks of gestation with multiple pregnancies was admitted to Kalabahi Regional Public Hospital, Alor, East Nusa Tenggara presenting with a 7-day history of fever, chills, arthralgia, and myalgia unresponsive to antipyretic treatment. The fever was primarily experienced daily at 2-3 am. The patient also reported dysuria with intermittent episodes over the past month, accompanied by a clear, non-pruritic vaginal discharge. Laboratory tests revealed thrombocytopenia (105,000/μL) and leukocyturia (+3) on urinalysis, with negative serum tests for dengue (IgM and IgG) and typhoid (IgM and IgG). The rapid diagnostic test (RDT) for malaria was positive (+2). The patient was treated with a three-day course of DHP, resulting in negative malaria tests on days 3 and 7 post-treatment, as shown in Figure 2. Three weeks post-admission, the patient delivered preterm infants spontaneously. The first infant had a very low birth weight, asphyxia neonatorum, and moderate respiratory distress (weight: 1,490 grams, length: 40 cm, APGAR score: 6/8, Downe score: 6) and died after two days of treatment. The second infant had an extremely low birth weight, small for gestational age, and mild respiratory distress (weight: 990 grams, length: 34.1 cm, APGAR score: 8/9, Downe score: 2) and died after 13 days of treatment.

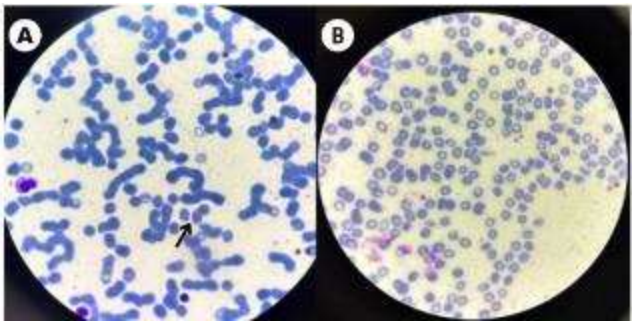

Figure 2 Microscopic examination of patient 2 blood smear with Giemsa

Note: (A) Ring (black arrow) in an enlarged and distorted infected RBC in a thin blood smear (B) No Plasmodium vivax was found in the thin blood smear on the 3rd day of evaluation.

3. Discussion

Malaria that caused by *Plasmodium vivax* transmitted by an infected *Anopheles* mosquito, which has various pattern fever symptoms. Fever occurs from infected red blood cells (RBC) that rupture and release inflammatory cytokines [15]. After RBC is infected by merozoites, the life cycle inside the erythrocytes begins until 48 hours, and the schizont ruptures. This underlined that vivax malaria is called “tertian fever”. Moreover, the symptoms of vivax malaria are milder compared to falciparum malaria, such as headache, anorexia, nausea, and myalgia, as occurred in both cases. Other symptom variations are seen as follows: dizziness, cough, vomiting, splenomegaly, epistaxis, urticaria, diarrhea, jaundice, and hepatomegaly [16]. Alor is a regency in East Nusa Tenggara, Indonesia, which is an endemic region of malaria where pregnant women are susceptible to getting infected.

Both cases also presented thrombocytopenia. Thrombocytopenia is a common hematological alteration in vivax malaria, with several hypothesized pathomechanisms. The primary mechanism involves the excessive removal of platelets or damaged thrombocytes. Possible contributing factors include oxidative stress, macrophage colony-stimulating factor, immunoglobulin G (IgG) binding to platelet-bound malaria antigens, spleen pooling, and platelet phagocytosis [17]. Thrombocytopenia in pregnancy with vivax malaria is also triggered by the infection mechanism. The malaria parasite, *Plasmodium vivax*, induces an inflammatory response and immune activation, leading to the destruction and decreased production of platelets. The sequestration of infected erythrocytes in the microvasculature, including the placenta, exacerbates this condition by creating localized inflammation and disrupting normal hematopoiesis. Furthermore, pregnancy itself is a state of immune modulation, which can intensify the effects of malaria infection on the hematological system, resulting in lower platelet counts and increased risk of complications [8]. Another study states that the cause of decreased thrombocytes during malaria infection was caused by platelet activation, splenic pooling, and decreased life span of platelets (normal 7 – 10 days, and reduced to 2 – 3 days at malaria vivax infection) [18].

Thrombocytopenia in pregnancy due to vivax malaria can closely mimic dengue fever, particularly in regions where dengue is more prevalent. This diagnostic challenge arises because both conditions present with fever and low platelet counts, making it easy to misinterpret malaria as dengue. According to the study by Karunaratna et al., thrombocytopenia is a common feature in malaria infections, with over 86% of patients exhibiting low platelet counts. Misdiagnosis can delay appropriate malaria treatment, as clinicians might initially test for dengue, especially when dengue outbreaks are common. Thus, laboratory test of IgM and IgG dengue was conducted and proven negative in both cases [19].

Besides thrombocytopenia, hematological disturbance also occurred such as anemia in the first case with the level of hemoglobin at 8 mg/dl. Anemia in pregnancy with *P. vivax* malaria occurs primarily due to several key mechanisms involving the destruction and impaired production of RBC that is infected by the merozoite, the destruction of non-infected RBC, and inadequate erythropoiesis due to the involvement of cytokines and/or various mediator of inflammation [20]. *Plasmodium vivax* causes hemolysis, leading to the destruction of red blood cells. Additionally, the infection results in increased splenic clearance of erythrocytes, further exacerbating the reduction in red blood cell count. The body's response to infection often includes a reduction in the production of new red blood cells [21]. Anemia in malaria also can induced or aggravated by iron deficiency, thus also decreasing RBC levels [13]. In this case, iron deficiency anemia was excluded considering the hematological laboratory test showed a normocytic anemia.

Maternal complications may arise from multiple episodes of *P. vivax* malaria due to reinfection. The risk of recurrent malaria episodes is exacerbated by the contraindication of primaquine treatment during pregnancy, attributed to its teratogenic effects. Studies have indicated that the modulation of inflammatory responses during pregnancy can facilitate *P. vivax* proliferation and subsequent reinfection. Unlike *P. falciparum*, where maternal complications are associated with placental sequestration of infected erythrocytes, *P. vivax*-related complications are driven by placental inflammation. Inflammatory responses against *P. vivax* may lead to placental damage and insufficiency through altered angiogenic and vascular remodeling mechanisms, thereby resulting in adverse pregnancy outcomes despite the early administration of antimalarial agents [9]. Moreover, *P. vivax* reinfection can occur post-treatment during pregnancy, as hypnozoites residing in the liver may reactivate, causing subsequent infections [14].

Besides the hypnozoites stage of vivax malaria, reinfection could result from the recrudescence that happened because of treatment failure in blood stage antimalaria or if the patients are in the endemic area, such as the case above. The relapse of vivax malaria infection could occur after 3 to 4 weeks after treatment with antimalarial agents. However, the probability of vivax malaria reinfection depends on the parasite's susceptibility to drugs and the biomass at the start of the drug administration, as well as the host's immunity [22]. Thus, the postpartum time could increase the probability of reinfection caused by the mother's immunity that hasn't returned to the normal immune function, which normally may take 3 to 4 months to return to normal condition after labor [23].

Previous studies have demonstrated that antenatal infection with *P. vivax* at any trimester can adversely impact fetal development, with recurrent parasite exposure during pregnancy exacerbating these effects [9]. Infection with *P. vivax* is associated with adverse outcomes including preterm delivery, low birth weight, oligohydramnios, spontaneous abortion, and fetal death. Complications in infants are primarily attributed to placental inflammation and local homeostasis dysregulation, leading to placental tissue damage [24]. Additionally, *P. vivax* infection during pregnancy can induce placental reactions due to the clogging of the placental intervillous space with *Plasmodium*-infected erythrocytes and macrophages, particularly during the second trimester. This obstruction compromises placental function, including nutrient provision to the fetus leading to a low birth weight [20]. A preterm birth, low birth weight,

and respiratory distress induced by vivax malaria complications in the second case led to the mortality of both twin neonates.

4. Conclusion

Malaria, particularly caused by *Plasmodium vivax*, poses significant risks to pregnant women, leading to severe maternal and neonatal complications. The cases from Alor, East Nusa Tenggara, illustrate the serious implications of *P. vivax* infection during pregnancy, including anemia, thrombocytopenia, and adverse pregnancy outcomes such as preterm birth and low birth weight. Despite treatment with dihydroartemisinin-piperaquine (DHP), these cases highlight the challenges of managing malaria in endemic regions, where reinfection and relapse can occur due to the dormant liver stages of the parasite. Effective malaria control and management strategies are crucial to mitigate the impact of malaria on maternal and neonatal health, especially in endemic areas. Enhanced diagnostic capabilities, timely treatment, and preventive measures are essential to reduce the morbidity and mortality associated with malaria in pregnancy.

Compliance with ethical standards

Disclosure of conflict of interest

The authors declare that there are no conflicts of interest regarding the publication of this case series.

Statement of informed consent

Informed consent was obtained from all individual participants included in the study.

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