CASE REPORT

Complicated vivax malaria in pregnancy: A case report in rural area of Indonesia

Raymond Surya[1], **Edward Sugito Manurung**[1], **Yudianto Budi Saroyo**[2]*
[1]Obstetrics and Gynecology Specialist, RSUD SoE, Timor Tengah Selatan District, East Nusa Tenggara, Indonesia
[2]Department of Obstetrics and Gynecology, Dr. Cipto Mangunkusumo Hospital, Faculty of Medicine, Universitas Indonesia, Jakarta, Indonesia

Article Info
Received May 11, 2023
Revised Aug 2, 2023
Accepted Aug 11, 2023
Published Dec 1, 2023

***Corresponding author:**
Yudianto Budi Saroyo
yudibs@gmail.com

Keywords:
Vivax malaria
Complication
Education
Anemia
Pregnancy
Maternal health

ABSTRACT

Objective: This study aimed to report a preterm delivery and anemia as part of *P. vivax* malaria infection complications in a pregnant woman in Timor Tengah Selatan regency, East Nusa Tenggara, Indonesia.

Case report: A 42-year-old pregnant woman, gravida 6 para 5,36-week of gestational age pregnant woman came with complaints of water breaking since one day before admission. She had fever with chills for three days, especially at night along with muscle, headache, joint soreness, dizziness, and palpitations. Rapid diagnostic test for malaria showed positive result. Peripheral blood smear examination revealed microcytic hypochromic due to iron deficiency or chronic infection and presence of trophozoites-ring form of *P. vivax* with 4,235 parasitemia. A baby boy was born with weight of 2,470 grams (percentile 28%), fetal head 31 cm (percentile 13%), birth length 43 cm (percentile 4%), and Apgar Score (AS) 8 and 9 at 1 and 5 minutes, respectively. The treatment was provided according to anti-malarial guideline in Indonesia using dihydroartemisin 120 mg and piperaquine phosphate 960 mg fixed dose as DHP for 3 days and primaquine 15 mg for 14 days.

Conclusion: Anemia as part of vivax malaria complication in pregnancy contributes to preterm delivery.

How to cite: Surya R, Manurung ES, Saroyo YB. Complicated vivax malaria in pregnancy: A case report in rural area of Indonesia. Majalah Obstetri & Ginekologi (Journal of Obstetrics & Gynecology Science). 2023;31(3):162-166. doi: 10.20473/mog.V31I32023.162-166.

Highlights:

1. In malaria endemic area, pregnant women are highly prone to suffer from malaria infection.
2. Vivax malaria in pregnancy can contribute to anemia and preterm delivery.

INTRODUCTION

World Health Organization (WHO) reported there were 247 million cases of malaria with 619,000 death cases in 2021.[1] Around 90% of the population at risk of *Plasmodium vivax* (*P. vivax*) infection lives in the Asia and Pacific regions.[2] In Indonesia, the prevalence of diagnosed and treated malaria in pregnant women was 2,650 cases.[3] *P. vivax* infection in pregnancy is associated with stillbirth, preterm delivery, low birthweight, and anemia.[4–6] However, this infection is

less severe than *P. falciparum* because it infects only reticulocytes; thus, there are parasites densities.[7]

In endemic area of malaria, pregnant women are highly prone to suffer from malaria infection.[8] *P. vivax* infection in pregnancy is associated with maternal anemia and hepatic dysfunction, miscarriage, congenital malaria, preterm delivery, and development to severe disease.[6,9,10] A significant burden and impact of *P. vivax* infection in pregnancy needs a strategy to prevent and control the spread of the infection. Unfortunately, *P. vivax* and *P. ovale* are the only malaria species which have the ability to relapse because of the dormant liver stages known as hynozoites. In acute stage of vivax malaria, schizontocidal agent chloroquine (CHQ) is the key of treatment and it is also safe for pregnancy.[11] To prevent the occurrence of relapse, both 8-aminoquinolines prima-quine (PMQ) or tafenoquine (TQ) are active against hypnozoites stage of *P. vivax*. However, it is contraindicated in pregnancy because the glucose-6-phosphate dehydrogenase (G6PD) status of the fetus cannot be determined antenatally in most malaria endemic settings.[11,12]

Therefore, this study aimed to report a preterm delivery and anemia as part of *P. vivax* malaria infection complications in a pregnant woman in endemic areas of malaria in Indonesia, the Timor Tengah Selatan regency, East Nusa Tenggara.

CASE REPORT

A 42-year-old pregnant woman, gravida 6 para 5,36-week of gestational age pregnant woman was admitted to a rural hospital in SoE, East Nusa Tenggara, Indonesia with complaints of water breaking in the past one day before admission. She had fever with chills for three days, especially at night along with muscle, headache, joint soreness, dizziness, and palpitations. No history of malaria infection before. The patient had a BP of 110/70 mmHg, pulse 105 bpm, RR 20 bpm, temperature 102^0F, and saturation of 98% without oxygen support. Physical examination revealed normal range. On obstetrical status, there was head presentation at station -1 and 2 cm dilatation without intact membrane. Ultrasound examination showed oligo-hydramnios with estimated fetal weight (EFW) of 2,500 grams.

The patient had Hb 8.3 g/dL, leucocyte 12,400/uL, platelet 229,000/uL, mean corpuscular volume (MCV) 76/um, mean corpuscular hemoglobin (MCH) 25 pg, granulocyte 69%, lymphocyte 23%, monocyte 8%, random blood glucose (RBG) 112 mg/dL, aspartate aminotransferase (AST) 28 U/L, alanine aminotransferase (ALT) 24 U/L, urea 13 mg/dL, creatinine 0.4 mg/dL. Rapid diagnostic test for malaria showed positive result. Peripheral blood smear examination revealed microcytic hypochromic due to iron deficiency or chronic infection and presence of trophozoites-ring form of *P. vivax*. Malaria smear showed 4,235 *P. vivax* parasitemia with trophozoite-ring form stage of the parasite present (Figure 1).

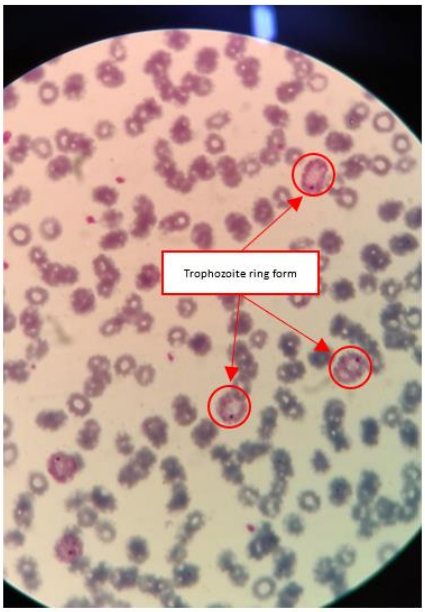

Figure 1. Trophozoite-ring form stage of *P. vivax* parasitemia.

After observation for 12 hours, a baby boy was born with a weight of 2,470 grams (percentile 28%), fetal head 31 cm (percentile 13%), birth length 43 cm (percentile 4%), and Apgar Score (AS) 8 and 9 at 1 and 5 minutes, respectively. Examination on the Fenton growth curve revealed that it was still appropriate for gestational age (AGA). Neonatal and cord blood smears were negative for malaria parasites.

The treatment was in line with anti-malarial guideline in Indonesia using dihydroartemisin 120 mg and piperaquine phosphate 960 mg fixed dose as DHP for 3 days and PMQ 15 mg for 14 days. Paracetamol in divided doses was given to control the fever. The fever clearance time was 12 hours, and the clinical symptoms was resolved after day 1. The patient was hospitalized for three days to obtain DHP administration. The patient was well and she was to be discharged. Evaluation after 7, 14, and 21 days of treatment revealed no *P. vivax* on peripheral blood smear (Figure 2).

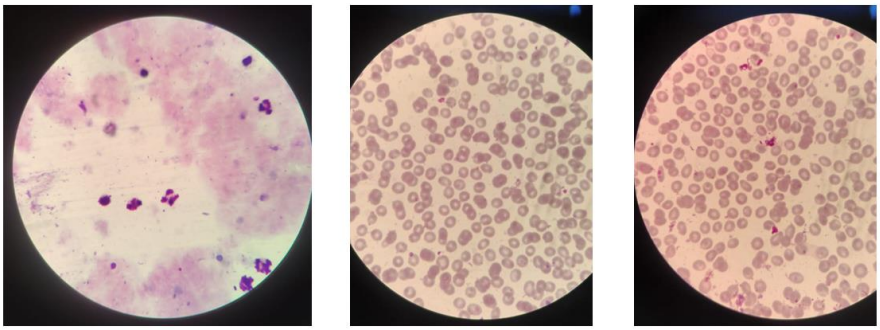

Figure 2. Blood smear evaluation after 7 (left), 14 (center), and 21 (right) days of treatment with no *P. vivax* parasitemia found.

DISCUSSION

The classic *P. vivax* malaria symptoms consist of fever, headache, and chills which usually occur after 10-15 days after getting bitten by an infected mosquito.[1] The high frequency of headache combined with fever in *P. vivax* infection requires the malarial rapid diagnostic test at antenatal check-up, especially in endemic area.[13] In our case, a woman came with fever and headache so that the midwives performed malarial rapid diagnostic test. *P. vivax* microscopic monoinfection is defined as the presence of asexual *P. vivax* parasites of any densities and no other of Plasmodium species found on the blood smear. Congenital malaria is defined as the presence of asexual Plasmodium parasites in the peripheral of neonates or cord blood at delivery without regarding the clinical symptoms and signs.[6]

In Asia, infection of both *P. falciparum* and *P. vivax* in pregnancy are prevalent, while *P. vivax* infection is considered to be benign and results in less morbidity than *P. falciparum*.[14] A study in Papua showed that high drug-resistant malaria and the ability to relapse of *P. vivax* infection caused 34% of infections in pregnancy,[8] which was higher than that reported in a study from Thailand with the prevalence of 17%.[15] The higher transmission rate might be supported by good immunity to suppress both symptoms and parasitemia, resulted in persistent infection, whether it is undetected and untreated. In addition, lower parasitemia density in *P. vivax* infection, as compared to infection with *P. falciparum*, results in less symptom presentations. Therefore, women who search for treatment are less.[8] In our case, the woman came to the health facility due to obstetrics reason with suspicious symptoms of malaria. She underwent rapid positive malarial test and was continued with *P. vivax* infection on peripheral blood smear. There was 4,235 *P. vivax* parasitemia, higher than that in a study in Papua which showed lower average of *P. vivax* parasitemia (632 parasites/uL). Thus, our patient revealed classic symptoms of malaria corresponding to higher parasitemia level.[8]

The risk of anemia, small for gestational age (SGA), and preterm delivery is increasing along with *P. vivax* infection. A study by Bardaji et al.[6] revealed that clinical *P. vivax* infection increased the risk of maternal anemia (OR 5.48; 95% CI 1.83-16.41; p=0.009). Meanwhile, another study in Venezuela stated that 84.6% of women with malaria came with mild to severe anemia, where the severe anemia as the most frequent complication of around 23%, which was corresponding to some studies in Brazil.[16,17] Vivax malaria infection is associated with the increased of SGA (OR 1.27; 95% CI 1.21-1.33).[18] Meanwhile, vivax malaria infection at each gestational age is related to preterm birth (OR 1.23-1.79).[18] In our case, the woman suffered from vivax malaria at 36 weeks of gestational age with clinical symptoms of microcytic hypochromic anemia, AGA, and preterm delivery due to obstetrical indication of water breaking. On peripheral blood smear, we found microcytic hypo-chromic smear due to iron deficiency or chronic infection or malaria infection. Whether *P. vivax* infection causes preterm birth or SGA is still debatable. There are some evidences that *P. vivax* is able to sequester in the placenta, regardless of placental inflammation as one of factors contributing to preterm birth.[18] In *P. vivax* infection, systemic inflammation is more common than local placental inflammation which is proved by modest placental pathology and absent of sequestration.[19] In our case, the history of malaria infection was unknown. The possibility of preterm birth in our case might be caused by maternal anemia impacting to vivax-associated SGA.[18] Besides, anemia in malaria is often normocytic and normochromic without spherocytes or schistocytes. However, micro-cytic hypochromic anemia in our case was related to malaria is because of high frequencies of hemoglobin-

opathies and iron deficiency in endemic countries. Therefore, malaria infection combined with iron deficiency anemia is the most common problem in pregnancy, resulting in preterm birth through preterm premature rupture of membrane.

In endemic areas of malaria, routine screening at antenatal visit and optical microscopy should be used for case detection of malaria infection.[20] WHO recommends all suspected cases of malaria having to be confirmed by diagnostic testing using parasite-based microscopy or rapid diagnostic test. The treatment of malaria needs multiple medicines based on type of malaria, drug-resistance, weight or age of infected person with malaria, and pregnancy status.[1] In *P. vivax* infection, dormant hypnozoites leading to relapses weeks or months later, prevention of relapses is the most important strategy for disrupting transmission.[21] PMQ is the only drug licensed for prevention of relapses. However, it is contraindicated in pregnancy due to safety reasons. It imposes to higher risk of clinical relapses.[22] Pregnant woman often serve as asymptomatic parasite reservoirs so that it limits for effective malaria control and elimination. Fortunately, our patient delivered after 12 hours of observation and she was administered with PMQ after delivery. Before PMQ administration, a mother should have been tested for G6PD deficiency. Side effects such as abdominal pain and risk of drug-induced hemolysis are part of complications in G6PD-deficient individuals.[22,23] WHO conditionally recommends for radical cure postpartum after 6 months of age.[24]

This study was conducted in an endemic area of malaria in Indonesia. Thus, the analysis both in hospital and primary health care was used to examine malaria through peripheral blood smear. Besides, this study depicted the classical symptoms of malaria in pregnancy as well as the complication of the pregnancy. However, due to the limitation of laboratory tests in remote area, there was no availability of iron profile test such as serum iron, ferritin, transferrin, and total iron binding capacity (TIBC) and hemoglobin electrophoresis to rule out the differential diagnosis of microcytic hypo-chromic anemia.

CONCLUSION

Anemia as one of vivax malaria complications in pregnancy contributes to preterm delivery. PMQ is the drug for preventing relapses in vivax malaria. However, it is contraindicated in pregnancy.

DISCLOSURES

Acknowledgment

Thank you to all parties involved in this research.

Conflict of interest

All authors have no conflict of interest.

Patient consent for publication

The patient has agreed that her case is to be published in a case report.

Funding

This research has received no external funding.

Author contribution

All authors have contributed to all process in this research, including preparation, data gathering and analysis, drafting and approval for publication of this manuscript.

REFERENCES

1. World Health Organization. Malaria [Internet]. 2023 [cited 2023 Apr 4]. Available from: https://www.who.int/news-room/fact-sheets/detail/malaria
2. Hay SI, Guerra CA, Tatem AJ, et al. The global distribution and population at risk of malaria: past, present, and future. Lancet Infect Dis. 2004;4(6): 327-36. doi: 10.1016/S1473-3099(04)01043-6. PMID: 15172341; PMCID: PMC3145123.
3. Ministry of Health, Republic of Indonesia. Brief overview situasi malaria di Indonesia dan beban pada ibu hamil dan anak [Brief overview on malaria situation in Indonesia and burden among pregnant women and children] [Internet]. 2022 [cited 2023 Apr 4]. Available from: https://p2pm.kemkes.go.id/storage/publikasi/media/publikasi_media_18_20230112054415
4. Moore KA, Simpson JA, Scoullar MJL, et al. Quantification of the association between malaria in pregnancy and stillbirth: a systematic review and meta-analysis. Lancet Glob Health. 2017;5(11): e1101-e1112. doi: 10.1016/S2214-109X(17)30340-6. Epub 2017 Sep 26. PMID: 28967610.
5. Rijken MJ, McGready R, Boel ME, et al. Malaria in pregnancy in the Asia-Pacific region. Lancet Infect Dis. 2012;12(1):75-88. doi: 10.1016/S1473-3099(11)70315-2. PMID: 22192132.

6. Bardají A, Martínez-Espinosa FE, Arévalo-Herrera M, et al.; PregVax Study Group. Burden and impact of *Plasmodium vivax* in pregnancy: A multi-centre prospective observational study. PLoS Negl Trop Dis. 2017;11(6):e0005606. doi: 10.1371/journal.pntd.0005606. PMID: 28604825; PMCID: PMC5481034.
7. Gore-Langton GR, Cano J, Simpson H, et al. Global estimates of pregnancies at risk of *Plasmodium falciparum* and *Plasmodium vivax* infection in 2020 and changes in risk patterns since 2000. PLOS Glob Public Health. 2022;2(11): e0001061. doi: 10.1371/journal.pgph.0001061. PMID: 36962612; PMCID: PMC10022219.
8. Poespoprodjo JR, Fobia W, Kenangalem E, et al. Adverse pregnancy outcomes in an area where multidrug-resistant *Plasmodium vivax* and *Plasmodium falciparum* infections are endemic. Clin Infect Dis. 2008;46(9):1374-81. doi: 10.1086/586743. PMID: 18419439; PMCID: PMC2875100.
9. Arévalo-Herrera M, Rengifo L, Lopez-Perez M, et al. Complicated malaria in children and adults from three settings of the Colombian Pacific Coast: A prospective study. PLoS One. 2017;12(9):e0185435. doi: 10.1371/journal.pone.0185435. PMID: 28945797; PMCID: PMC5612730.
10. Lopez-Perez M, Pacheco MA, Buriticá L, et al. Malaria in pregnancy: a passive surveillance study of pregnant women in low transmission areas of Colombia, Latin America. Malar J. 2016;15:66. doi:10.1186/s12936-016-1125-9. PMID: 26850108; PMCID: PMC4743125.
11. World Health Organization. Guidelines for the treatment of malaria. Third edition [Internet]. WHO | Regional Office for Africa. 2023 [cited 2023 Apr 5]. Available from: https://www.afro.who.int/publications/guidelines-treatment-malaria-third-edition
12. Watson J, Taylor WR, Menard D, et al. Modelling primaquine-induced haemolysis in G6PD deficiency. Elife. 2017 ;6:e23061. doi: 10.7554/eLife.23061. PMID: 28155819; PMCID: PMC5330681.
13. van Eijk AM, Hill J, Noor AM, et al. Prevalence of malaria infection in pregnant women compared with children for tracking malaria transmission in sub-Saharan Africa: a systematic review and meta-analysis. Lancet Glob Health. 2015;3(10):e617-28. doi: 10.1016/S2214-109X(15)00049-2. Epub 2015 Aug 19. PMID: 26296450; PMCID: PMC4673091.
14. Price RN, Tjitra E, Guerra CA, et al. Vivax malaria: neglected and not benign. Am J Trop Med Hyg. 2007;77(6 Suppl):79-87. PMID: 18165478; PMCID: PMC2653940.
15. Nosten F, ter Kuile F, Maelankirri L, et al. Malaria during pregnancy in an area of unstable endemicity. Trans R Soc Trop Med Hyg. 1991;85(4):424-9. doi: 10.1016/0035-9203(91)90205-d. PMID: 1836685.
16. Romero M, Leiba E, Carrión-Nessi FS, et al. Malaria in pregnancy complications in Southern Venezuela. Malar J. 2021;20(1):186. doi: 10.1186/s12936-021-03728-9. PMID: 33858446; PMCID: PMC8051027.
17. Bôtto-Menezes C, Silva Dos Santos MC, Lopes Simplício J, et al. *Plasmodium vivax* malaria in pregnant women in the Brazilian Amazon and the risk factors associated with prematurity and low birth weight: A descriptive study. PLoS One. 2015;10(12):e0144399. doi: 10.1371/journal.pone.0144399. PMID: 26675007; PMCID: PMC4687654.
18. Moore KA, Simpson JA, Wiladphaingern J, et al. Influence of the number and timing of malaria episodes during pregnancy on prematurity and small-for-gestational-age in an area of low transmission. BMC Med. 2017;15(1):117. doi: 10.1186/s12916-017-0877-6. PMID: 28633672; PMCID: PMC5479010.
19. McGready R, Davison BB, Stepniewska K, et al. The effects of *Plasmodium falciparum* and *P. vivax* infections on placental histopathology in an area of low malaria transmission. Am J Trop Med Hyg. 2004;70(4):398-407. PMID: 15100454.
20. World Health Organization. World malaria report 2014 [Internet]. 2014 [cited 2023 Apr 5]. Available from: https://www.who.int/publications-detail-redirect/9789241564830.
21. White NJ. Determinants of relapse periodicity in *Plasmodium vivax* malaria. Malar J. 2011;10:297. doi: 10.1186/1475-2875-10-297. PMID: 21989376; PMCID: PMC3228849.
22. Ashley EA, Recht J, White NJ. Primaquine: the risks and the benefits. Malar J. 2014;13:418. doi: 10.1186/1475-2875-13-418. PMID: 25363455; PMCID: PMC4230503.
23. Chu CS, Bancone G, Moore KA, et al. Haemolysis in G6PD heterozygous females treated with primaquine for *Plasmodium vivax* Malaria: A nested cohort in a trial of radical curative regimens. PLoS Med. 2017;14(2):e1002224. doi: 10.1371/journal.pmed.1002224. PMID: 28170391; PMCID: PMC5295665.
24. WHO Malaria Policy Advisory Committee and Secretariat. Malaria Policy Advisory Committee to the WHO: conclusions and recommendations of eighth biannual meeting (September 2015). Malar J. 2016;15:117. doi: 10.1186/s12936-016-1169-x. PMID: 26911803; PMCID: PMC4766637.