ORIGINAL PAPER

doi: 10.5455/medarh.2021.75.291-296
MED ARCH. 2021 AUG; 75(4): 291-296
RECEIVED: JUL 17, 2021
ACCEPTED: AUG 18, 2021

The Relationship Between Fetal Weight with Sequestration of Infected Erythrocyte, Monocyte Infiltration, and Malaria Pigment Deposition in Placenta of Mother Giving Birth Suffering from Plasmodium Vivax Infection

Nugrahanti Prasetyorini[1,5], Nabila Erina Erwan[2,5], Rudi Priyo Utomo[3], Rivo Yudhinata Brian Nugraha[4,5], Loeki Enggar Fitri[4,5]

[1]Department of Obstetrics and Gynecology, Faculty of Medicine Universitas Brawijaya/dr Saiful Anwar Hospital, Malang, Indonesia

[2]Doctoral Program in Medical Science, Faculty of Medicine, Universitas Brawijaya, Malang, Indonesia

[3]Department Obstetrics and Gynecology, dr T.C. Hillers Hospital, Maumere, Sikka District, NTT, Indonesia

[4]Department of Parasitology, Faculty of Medicine, Universitas Brawijaya, Malang, Indonesia

[5]Malaria Research Group, Faculty of Medicine, Universitas Brawijaya, Malang, Indonesia

Corresponding author: Loeki Enggar Fitri, Department of Parasitology/Malaria Research Group, Faculty of Medicine, Universitas Brawijaya, Jl Veteran Malang, Indonesia E-mail address: lukief@ub.ac.id, ORCID ID: https://orcid.org/0000-0002-4880-1048.

ABSTRACT

Background: Malaria in pregnancy can cause fatal complications by parasite sequestration mechanism, which can cause monocyte infiltration in the intervillous space. *P. vivax* infection was significantly associated with malaria pigment in the placenta, indicating past subclinical infections **Objective:** This study aimed to determine the mechanism of *P. vivax* in the pathogenesis of placental malaria and its relationship with LBW. **Methods:** This study was observational analytic with a cross-sectional approach. Placental tissue samples were obtained from pregnant women with LBW babies during delivery in Maumere, Nusa Tenggara Timur. The samples used in this study were confirmed by a polymerase chain reaction and consisted of 25 samples with 12 positive and 13 negative samples. Placental tissue samples were made with Hematoxylin-Eosin staining and observed under 1000x magnification at 100 fields using a light microscope. Parasite density, monocyte infiltration, and parasite pigments deposition were calculated. **Results:** Microscopic observation revealed that there was a significant difference in infected erythrocytes sequestration between groups. Interestingly, monocyte and malaria pigments accumulation were found in malaria-positive and -negative groups, and no significant difference between groups. The correlation test showed no significant relationship between monocyte infiltration and LBW in the malaria-positive and -negative group and between parasite pigments and LBW in both groups. Moreover, there was no significant correlation between parasite density and LBW in the positive and negative groups. **Conclusion:** *P. vivax* infection causes acute, sub-acute, and chronic placental malaria in subclinical infected pregnant women in Maumere, Nusa Tenggara Timur that might cause an LBW baby.

Keywords: Placental Malaria, Erythrocyte Sequestration, Monocyte Infiltration, Malaria Pigment, Low Birth Weight (LBW).

1. BACKGROUND

Malaria is an infectious disease caused by *Plasmodium* and transmitted through the female *Anopheles* mosquito vector. Malaria is a life-threatening infectious disease that can cause various complications. It was reported that malaria causes millions of infection cases and 10,000 deaths in Indonesia every year (1), and it is also reported that malaria in Indonesia is mainly caused by *P. falciparum* (55%) and *P. vivax* (44%). There are 252,027 malaria cases reported in health facilities (2).

A critical factor in the pathogenesis of malaria is the cytoadherence process of *Plasmodium* in human cells, which have specific receptors in human organs. This cytoadherence process will trigger microvascular problems in the host's body. The attachment to the endothelium will trigger sequestration of infected erythrocytes in the small blood vessels of the organ. In other words, the infected erythrocytes will be trapped in the endothelium. The sequestration of infected erythrocytes in the microvasculature structure will obstruct

blood flow, endothelial damage and trigger an inflammatory process (3).

It was reported that malaria in pregnancy is the most significant cause of maternal mortality globally and harms the baby (4). Malaria in pregnancy includes placental malaria and congenital malaria. Placental malaria is characterized by the accumulation of infected erythrocytes in the placenta with various adverse consequences for the mother and fetus. Placental malaria is associated with the sequestration of infected erythrocytes in the intervillous space of the placenta. Malaria infection in pregnant women can cause spontaneous abortion, premature birth, stillbirth, severe maternal anemia, and responsible for the birth of babies with Low Birth Weight (LBW) (5, 6).

LBW is a public health problem globally and has short-term and long-term consequences. The consequences of LBW include fetal and neonatal morbidity and mortality, poor cognitive development, and an increased risk of chronic disease in the future. LBW problems are very complex and include preterm neonates, neonates with small gestational age, and a combination of both, which has the worst impact on LBW (7). LBW babies with a small gestational age are said to have fetal growth restriction and have a high risk of dying after birth (8).

Several studies stated that severe complications of malaria occur due to *P. falciparum* infection only, but in reality, *P. vivax* is reported can also cause placental malaria (9-13). *P.vivax* is currently considered to be the cause of severe and fatal malaria (14). Because the placental malaria research related to *P. vivax* infection is limited, research is needed to determine the mechanism of *P. vivax* in the pathogenesis of placental malaria.

2. OBJECTIVE

This study aimed to determine the mechanism of *P.vivax* in the pathogenesis of placental malaria and its relationship with LBW.

3. MATERIALS AND METHODS

Study Design

The design of this study was observational analytic with a cross-sectional approach. The research sample used in this study was placental tissue of pregnant women obtained from a research of Nugrahanti Prasetyorini, MD, Obstetrics and Gynecology Department of Saiful Anwar Hospital, Malang, Indonesia. The samples used were 25 samples consisting of 12 negative samples and 13 positive samples infected with *P. vivax* confirmed by Polymerase Chain Reaction (PCR). Sampling in this study was carried out by informed consent and permission to the local Health Office beforehand. This research was conducted at the Laboratory of Parasitology, Laboratory of Pathological Anatomy, and Biomedical Central Laboratory, Faculty of Medicine, Universitas Brawijaya, Malang, Indonesia. The research was conducted from November 2018 to December 2018. The ethics clearance of this research was approved by the Faculty of Medicine Universitas Brawijaya Ethics Committee with number 307A/EC/KEPK/11/2018. All participants had been informed and gave consent as the subject of this study.

Malaria Parasite Examination

Examination of malaria parasites was conducted by making a blood smear with Giemsa staining with a ratio of 1:8 between Giemsa and the buffer, then allowed to stand for 20 minutes. After staining, the object-glass was rinsed using water and dried, then observed with a microscope using immersion oil and 1000x magnification.

Polymerase Chain Reaction (PCR) Examination

PCR examination was performed at the Biomedical Central Laboratory, Faculty of Medicine, Universitas Brawijaya, Malang, Indonesia, as described previously (15).

Placental Histology Preparations

Placental histology preparation was conducted at the Laboratory of Pathological Anatomy, Faculty of Medicine, Universitas Brawijaya, Malang, Indonesia. The sample was inserted into the container and processed using the Tissue Tex Processor tool. The paraffin block process was carried out using a tool. Then, the sample was cooled in a freezer and was cut with a microtome. The sample was placed in the incubator. Then the sample was deparaffinized. Hematoxylin-Eosin staining was performed using a Tissue Tex DRS tool. Histopathological analysis was carried out using a light microscope.

Sequestration of Infected Erythrocytes, Monocyte Infiltration, and Parasite Pigments Examination

The examination was performed by using a light microscope with 1000x magnification. Sequestration of infected erythrocytes (parasite density), monocyte infiltration, and parasitic pigments accumulation calculated on 100 fields.

Statistical analysis

Statistical analysis was conducted using SPSS 22 software program. Then, the techniques for analyzing data include the normality test of data using the Shapiro Wilk test to determine the normal data distribution and the Levene test to determine the homogeneity of data. Independent-T to test the significance of the results in this study for data that are normally distributed and homogeneous and Mann Whitney test for non-homogeneous data. The correlation test among the variables in this study used a Pearson test for homogeneous data and the Spearman test for non-homogeneous data. Data analysis was carried out with a confidence level of 95% and a degree of significance by $p \leq 0.005$. A computer program did the data analysis.

4. RESULTS

Peripheral blood smear of 25 samples used in this study was observed and showed negative for malaria. Malaria was then diagnosed using PCR examination.

	Malaria	N	Mean	Std. Deviation	Std. Error Mean
BBW (gram)	Positif	12	2175.00	327.178	94.448
	Negatif	13	2130.77	249.615	69.231

Table 1. Data of Baby's Birth Weight (N=25)

The PCR examination detected 12 samples of *P. vivax* infection as malaria-positive and 13 samples as malaria-negative. The positive finding using PCR examination suggesting the parasite density in the samples was at a submicroscopic level. In this study, all of the samples were pregnant women with full-term pregnancies without any signs and symptoms of malaria and stated to be in subclinical malaria condition.

Observation with a light microscope 1000x magnification at 100 fields found erythrocytes containing parasites with or without parasite pigments called hemozoin, representing *Plasmodium*-infected erythrocytes. Monocyte infiltrations were found in the placental intervillous space. Parasite pigments were found to be free, attach to fibrin, white blood cells in the intervillous space, or macrophages covered by fibrin. These histopathological changes were observed in all malaria-positive groups (100%) - observations on malaria-positive groups as shown in Figure. 1.

On malaria-negative samples, infected erythrocytes with ring-form *Plasmodium* were found in 4 of 13 malaria-negative samples (30.8%). Monocyte infiltration, white blood cells such as lymphocytes and neutrophils, and parasite pigments deposition, entangled in fibrin or free in intervillous space in several visual fields, were found in 11 of 13 samples (84.6%) as in Figure. 2.

Microscopic examination of sequestration of infected erythrocytes (parasite density), monocyte infiltration, and parasite pigments in the placenta was calculated as shown in Figure 3. The data of the baby's birth weight is in Table 1.

Based on the Shapiro-Wilk test from LBW data and observations of infected erythrocyte sequestration (parasite density), monocyte infiltration, and parasite pigments carried out in this study were normally distributed ($p>0.05$) with the significance values were 0.456, 0.582, 0.681, and 0.850. Based on the Levene test, BBW and monocyte infiltration data were homogenously distributed ($p>0.05$) with a significance value of 0.826 and 0.747, respectively. In contrast, sequestration of infected erythrocytes (parasitic density) and parasite pigment data were not homogenously distributed ($p<0.05$) with a significance value of 0,000 and 0.034, respectively, thus requiring non-parametric statistical analysis. Furthermore, the data were analyzed using the Independent T-test for BBW and monocyte infiltration data and the Mann Whitney test for parasite density and parasitic pigment data.

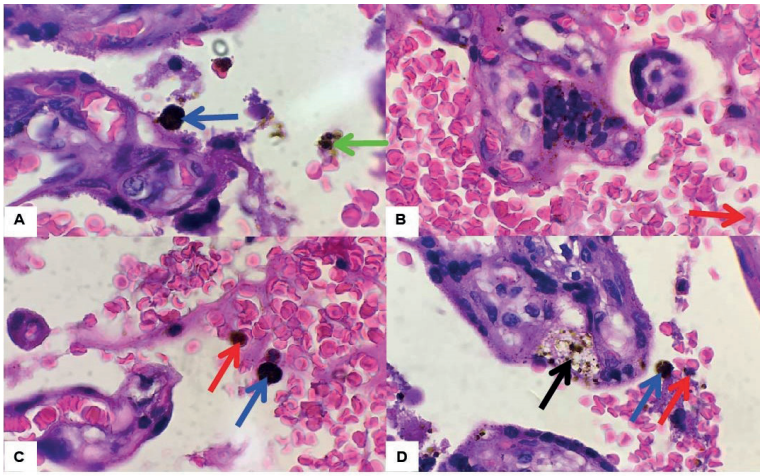

Figure 1. Placental tissue in the malaria-positive group. A: Monocyte infiltration (blue arrow) and free parasite pigment in the intervillous space (green arrow); B) Sequestration of infected erythrocyte with ring-form parasites (red arrow); C: Monocyte infiltration and sequestration of infected erythrocyte; D: Parasite pigment in the placental tissue (black arrow), monocyte infiltration, and sequestration of infected erythrocyte (1000x magnification)

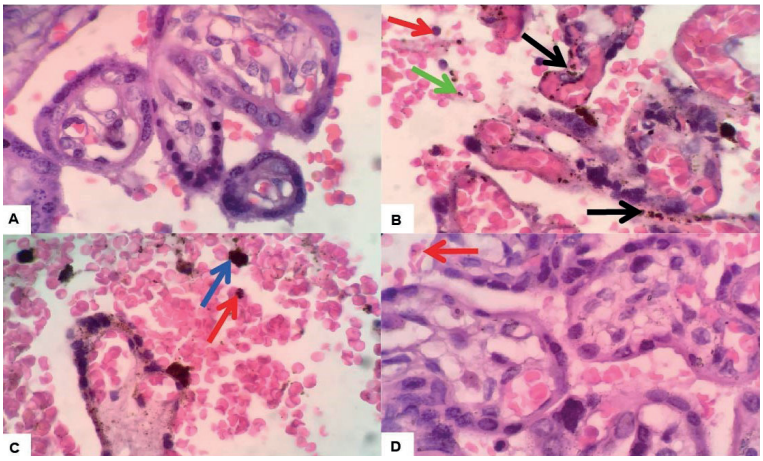

Figure 2. Placental tissue in the malaria-negative group. A: Normal placental tissue; B: Parasite pigment in placenta (black arrow) and Intervillous space (green arrow), sequestration of infected erythrocyte (red arrow); C: Monocyte Infiltration (blue arrow) and infected erythrocyte; D: Sequestration of infected erythrocyte with ring-form parasite (1000x magnification)

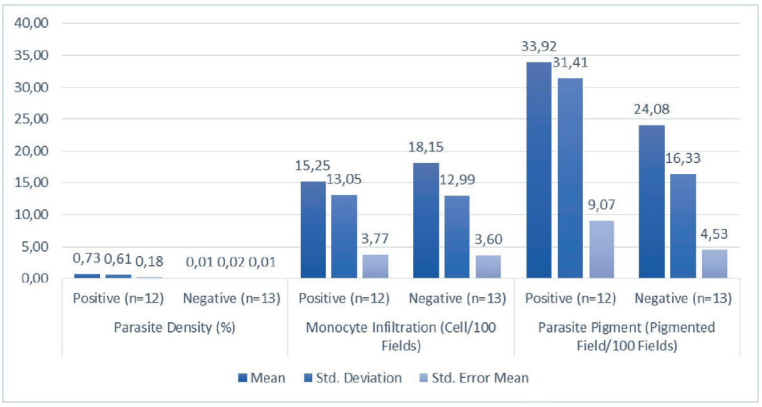

Figure 3.

Independent T-test showed no significant difference in Baby's Birth Weight (BBW) and the monocyte infiltration between the malaria-positive and negative groups ($p=0.706$ and 0.583, respectively). The Mann-Whitney test showed a significant difference in parasite density between the malaria-positive and negative groups ($p=0,000$). No significant difference in parasite pigments

was found between the malaria-positive and negative groups (p=0.723).

Based on the Pearson test, there was no significant relationship between monocyte infiltration and LBW babies from pregnant women infected with *P. vivax* in the malaria-positive (p=0.626) and negative groups (p=0.862). Based on Spearman's test on the malaria-positive group, there was no significant correlation between parasite density and parasite pigment with LBW babies of pregnant women infected with *P. vivax* (p=0.404 and 0.324, respectively). Likewise, there was no significant correlation between parasite density and parasite pigment in the negative-malaria group with LBW babies (p=1,000 and 0,181, respectively).

5. DISCUSSION

Sequestration of infected erythrocytes, monocyte infiltration, and parasite pigments deposition is a histological sign of placental malaria (11, 13, 16). The pathological hallmark of placental malaria has been well reported in *P. falciparum* infection. The cytoadherence mechanism of infected erythrocytes into a specific receptor in the placenta showed as the pathomechanism. Sequestration of infected erythrocytes did not occur in high shear stress conditions in the systemic circulation. However, when infected erythrocytes were attached to Chondroitin Sulfate A (CSA) and Hyaluronic Acid (HA), the infected erythrocytes were more resistant to the increased shear stress. Sequestration of *P. vivax* infected erythrocytes occurs in low shear stress conditions in the intervillous space of the placenta and causes a local placental inflammatory process, thus disrupting placental circulation and transfer of nutrients from the placenta to the fetus (17).

The cytoadherence mechanism of infected erythrocytes with *P. vivax* is constantly being explored. New evidence related to this pathomechanism was urgently needed to accomplish the concept of this infection. The cytoadherence process of infected erythrocytes with *P. vivax* is related to Intercellular Adhesion Molecule-1 (ICAM-1) and CSA as in *P.falciparum* infection (18). However, this statement remains controversial. In contrast to erythrocytes infected with *P. falciparum,* which have *P.falciparum* Erythrocyte Membrane Protein-1 (PfEMP-1), *P. vivax*-infected erythrocytes do not have homologous protein like PfEMP-1. *P. vivax*-infected erythrocytes express a group of variable proteins called VIR protein, which is not clonally expressed and can be found on these infected erythrocytes, indicating that VIR proteins have a different function with PfEMP-1. The role of VIR protein is still being studied further, and the functional analysis of this protein reveals different subcellular localizations and functions. It can mediate the adhesion of infected erythrocytes to ICAM-1, particularly VIR14 (17, 19-21). It was also stated that erythrocytes infected with *P. vivax* could form rosettes by the interaction between infected erythrocytes and the glycophorin C receptor present in normal erythrocytes. The rosettes formed by *P. vivax* infection contribute to the sequestration process of *P. vivax* in the microvasculature (17, 20, 21). Marın-Menendez et al. stated that rosetting was the cytoadherence phenotype of *P. vivax* infection (21). The adhesive force of infected erythrocyte by *P.vivax* forms a rosette as strong as *P. falciparum* characteristic, but the specific mechanism of rosette formation in *P. vivax* malaria is unestablished (22).

A recent study from Albrecht et al. showed the role of rosette integrity in *P. vivax* infection as an evasion mechanism from being phagocytized. *P. vivax* rosetting was dependent on plasma components that are yet to be identified, as in previous evidence of the *P. falciparum* rosetting process associated with immunoglobulin M. The limitation of opsonization and phagocytosis already observed in *P. vivax* rosetting. However, the adhesion phenotypes regarding immunoglobulin components have not been untangled yet. The rosetting was also related to Interleukin (IL)-6, IL-10, and IgM (22). Rosetting in *P. vivax* infection may play an essential role in the sequestration process, which elucidates parasite subpopulation in a specific organ, induces prolonged infection by the significant protection from the host immune system, and becomes a latent infection.

The research related to the *P. vivax* cytoadherence mechanism has become an attractive concern thus far. The actual pathological process has not been unsolved yet. The recent cytoadherence evidence was also mentioned to be associated with extracellular vesicles uptake by spleen fibroblasts which signal the NF-kB transcription factor translocation and ICAM-1 surface expression upregulation. This condition supports the parasite to adhere and multiply on the organ while not in the systemic circulation (23).

During the acute phase of infection, the only histopathological features found were sequestration of infected erythrocytes. Along with the progress of the malaria disease, the hemolysis process occurs, including infected erythrocytes in the placenta, which will cause the deposition of parasite pigments. Although only infected erythrocytes can be detected in the acute condition, mild pigment deposition can still be found. In chronic infection, apart from infected erythrocytes, monocyte infiltration, and pigment deposition, other placental tissue damage can also be found, such as thickening of the basal trophoblast membrane, fibrinoid necrosis, and syncytial knots in the histopathological features of the placenta (10). In previous infections, pigment deposition will only be found without parasites found in infected erythrocytes (24, 25).

This study indicates that the presence of *P. vivax* infection in pregnant women causes histopathological changes in the placenta. The relationship between sequestration of infected erythrocytes, monocyte infiltration, and parasite pigment deposition with LBW in the baby born to pregnant women infected with *P. vivax* statistically did not significantly influence. It is shown by the insignificant difference in baby's birth weight between the groups of malaria-positive and -negative. Increased parasite density, monocyte infiltration, and parasite pigment in both groups were not followed by a decrease in the baby's birth weight. However, all the LBW babies

were born to mothers whose histopathological changes in the placenta. The histopathological findings showed an infection process, either acute, subacute, or chronic infection. As mentioned in the previous study, the infected placenta will show different appearances than the uninfected placenta because of tissue and physiological mediator alteration (26).

The presence of monocyte infiltration and parasite pigment deposition in the malaria-negative group was referred to as the condition of subclinical or submicroscopic malaria infection (12, 26). This condition may occur due to a history of previous infection or chronic infection in the malaria-negative group. The presence of prolonged infection causes an inflammatory reaction and host immune response to malaria, which can be seen in the host's tissue and chemical mediator profile.

The pathomechanism that underlies the increased inflammatory reaction and the immune response in the host is the presence of infected erythrocyte sequestration, which stimulates maternal mononuclear cells for the secretion of β-chemokine as chemotactic compounds for monocytes and macrophages, including Macrophage-Inflammatory Protein-1α and β (MIP-1α and β), Interferon-inducible Protein-10 (IP-10), and Monocyte Chemoattractant Protein-1 (MCP-1) (25). Activation of the immune response due to *Plasmodium* infection will increase the release of other proinflammatory cytokines from macrophages, monocytes, T cells, smooth muscle cells, adipocytes, and fibroblasts such as Tumor Necrosis Factor Alpha (TNF)-α (27), Interferon-γ, Interleukin-1β, and Interleukin-2 (28). In pregnant women infected with *Plasmodium*, there is an imbalance of cytokines in the placenta to increase the phagocytosis process by macrophages, forming reactive oxygen intermediates and L-arginine-derived nitric oxide, and stimulate T cell proliferation. Excessive production of these proinflammatory cytokines can endanger pregnancy (28) and provoke a destructive effect on the mother and the fetus (29). The destructive effects are LBW due to fetal-growth restriction, premature birth, spontaneous abortion, and maternal anemia (21, 28).

Previous infections that have received inadequate therapy will still provide histopathological features of placental malaria (16). Parasite pigment deposition resulting from an immune response in the form of phagocytosis of macrophages to parasitic material provides an immunomodulatory effect directly that will further increase proinflammatory cytokines in placental tissue. As a result, there was an increase in placental damage, disrupting maternal-fetal blood flow (16, 24). Therefore, although there was no active infection from *P. vivax*, previous infections with inadequate therapy will allow the impact of placental malaria in the form of LBW. This finding consistent with previous studies which explained the cytoadherence mechanism of *P. vivax* and concluded that sequestered *P. vivax* subpopulations in several organs elucidate the reason for low peripheral blood parasitemia in subclinical infection with marked severe disease (23). A placental malaria is a form of severe malaria that shows severe consequences associated with maternal and fetal well-being.

The absence of a significant effect between sequestration of infected erythrocytes (parasitic density), monocyte infiltration, and parasite pigments deposition against LBW in this study was caused by several factors. The first factor was the limited number of samples used in this study. Then, both groups of samples found the presence of parasitic density, monocyte infiltration, and parasite pigments. In the malaria-negative group, infected erythrocytes were found. This finding can be explained by the evidence of the parasite population sequestration in a specific organ and not circulating in peripheral blood (23), while the PCR blood sample used in this study was obtained from peripheral blood. A subpopulation of parasites in some organs becomes a diagnostic challenge of malaria which can be neglected and permit chronic infection. Several consequences arise in response to such chronic inflammatory conditions, including maternal and fetal impact in malaria placenta. This study presents the consistency features of the *P. vivax* pathological profile as mentioned in previous studies, which is *P.vivax* as pathogenic as *P. falciparum* (20, 26)

However, in addition to placental factors, LBW is influenced by maternal and fetal factors. Lack of maternal nutritional intake during pregnancy, maternal weight, eating disorders, mothers with short stature, and history of teratogenic drugs consumption during pregnancy are maternal factors that influence LBW. At the same time, the fetal factors are fetal malformations and genetic abnormalities (8). These factors can be the confounding factors in this study.

6. CONCLUSION

From this study, infected erythrocyte, monocyte infiltration, and parasite pigment deposition were found in malaria-negative groups placental histopathology, which may be due to previous malaria infections. The infected erythrocyte inside the intervillous space of the placenta in this study exhibit evidence of *P. vivax* sequestration. These findings represent that *P. vivax* may be as pathogenic as *P. falciparum* and reveal that *P. vivax* infection causes acute, subacute, and chronic placental malaria of subclinical infected pregnant women in Maumere, NTT that might cause LBW baby. Further research needs to be carried out with larger research samples. It is necessary to observe the sequestration of infected erythrocytes, monocyte infiltration, and parasite pigments by other tissue staining methods to find out more clearly the description of malaria infection. In addition, to see parasite pigments that give rise to birefringent images, observations are needed by using a polarized light microscope.

- **Declaration of patient consent**: The authors certify that the research had obtained all participant consent.
- **Author's Contribution**: All authors were involved in the preparation of this article. Final proofreading was made by the first author.

- **Conflicts of interest**: There are no conflicts of interest.
- **Financial support and sponsorship**: From PNBP Faculty of Medicine Universitas Brawijaya and Universitas Brawijaya.

REFERENCES

1. Centers for Disease Control and Prevention (CDC). The Rapid Assessment of the Burden of Malaria during Pregnancy: A Toolkit [Internet]. The Rapid Assessment of the Burden of Malaria during Pregnancy: A Toolkit. 2015. p. 1. Available from: https://www.cdc.gov/malaria/tools_for_tomorrow/pregnancy_toolkit.html.
2. World Health Organization. Guideline for The Treatment of Malaria-3rd edition [Internet]. Geneva; 2015. Available from: http://apps.who.int/iris/bitstream/10665/162441/1/9789241549127_eng.pdf
3. Milner Danny A. Pathogenesis of malaria [Internet]. Uptodate. 2011 [cited 2017 May 20]. Available from: http://www.uptodate.com/contents/pathogenesis-of-malaria?view=print
4. Chedraui P, Daily J, Wylie B, Weller P, Ramin S, Barss V. Overview of malaria in Pregnancy. Uptodate. 2012.
5. World Health Organization. World Malaria Report 2016 [Internet]. Geneva; 2016. Available from: https://apps.who.int/iris/bitstream/handle/10665/252038/9789241511711-eng.pdf?sequence=1
6. WHO Report. World Malaria Report 2017 [Internet]. World Health Organization. 2017. Available from: http://apps.who.int/iris/bitstream/handle/10665/259492/9789241565523-eng.pdf;jsessionid=3B05B30235850B-2B29A7FFFDD8A874D8?sequence=1
7. World Health Organization. Global Nutrition Targets 2025: Low Birth Weight Policy Brief [Internet]. 2014. Available from: http://apps.who.int/iris/bitstream/handle/10665/149020/WHO_NMH_NHD_14.5_eng.pdf?ua=1
8. Cunningham FG, Leveno K, Bloom S, Spong C, Dashe J, Hoffman B, et al. Williams Obstetrics. 24th editi. Cunningham FG, editor. New York: McGraw-Hill Education/Medical; 2014. 1358 p.
9. Salih MM, Mohammed AH, Mohmmed AA, Adam GK, Elbashir MI, Adam I. Monocytes and macrophages and placental malaria infections in an area of unstable malaria transmission in eastern Sudan. Diagn Pathol. 2011; 6(1): 1-6.
10. Chaikitgosiyakul S, Rijken MJ, Muehlenbachs A, Lee SJ, Chaisri U, Viriyavejakul P, et al. A morphometric and histological study of placental malaria shows significant changes to villous architecture in both Plasmodium falciparum and Plasmodium vivax infection. Malar J. 2014; 13(1): 1-13.
11. Souza RM, Ataíde R, Dombrowski JG, Ippólito V, Aitken EH, Valle SN, et al. Placental Histopathological Changes Associated with Plasmodium vivax Infection during Pregnancy. PLoS Negl Trop Dis. 2013; 7(2): 1–11.
12. Parekh FK, Davison BB, Gamboa D, Hernandez J, Branch OH. Placental histopathologic changes associated with subclinical malaria infection and its impact on the fetal environment. Am J Trop Med Hyg. 2010; 83(5): 973-980.
13. Carmona-Fonseca J, Arango E, Maestre A. Placental malaria in Colombia: Histopathologic findings in Plasmodium vivax and P. falciparum infections. Am J Trop Med Hyg. 2013; 88(6): 1093-1101.
14. Anstey NM, Russell B, Yeo TW, Price RN. The pathophysiology of vivax malaria. Trends Parasitol. 2009; 25(5): 220-227.
15. Arifin S, Fitri LE, Sujuti H, Hermansyah B, Endharti AT, Sulistyaningsih E, et al. Sensitivity and Specificity of Nested PCR for Diagnosing Malaria: Cases in Several Areas of Indonesia. 2018;
16. Muehlenbachs A, Nabasumba C, McGready R, Turyakira E, Tumwebaze B, Dhorda M, et al. Artemether-lumefantrine to treat malaria in pregnancy is associated with reduced placental haemozoin deposition compared to quinine in a randomized controlled trial. Malar J. 2012; 11(1): 1-9.
17. Chotivanich K, Udomsangpetch R, Suwanarusk R, Pukrittayakamee S, Wilairatana P, Beeson JG, et al. Plasmodium vivax adherence to placental glycosaminoglycans. PLoS One. 2012; 7(4): e34509.
18. Carvalho BO, Lopes SCP, Nogueira PA, Orlandi PP, Bargieri DY, Blanco YC, et al. On the cytoadhesion of Plasmodium vivax–infected erythrocytes. J Infect Dis. 2010; 202(4): 638-647.
19. Bernabeu M, Lopez FJ, Ferrer M, Martin-Jaular L, Razaname A, Corradin G, et al. Functional analysis of Plasmodium vivax VIR proteins reveals different subcellular localizations and cytoadherence to the ICAM-1 endothelial receptor. Cell Microbiol. 2012; 14(3): 386-400.
20. Totino PR, Lopes SC. Insights into the Cytoadherence Phenomenon of Plasmodium vivax: The Putative Role of Phosphatidylserine. Front Immunol [Internet]. 2017 Sep 20;8:1148. Available from: https://pubmed.ncbi.nlm.nih.gov/28979260
21. Marín-Menéndez A, Bardají A, Martínez-Espinosa FE, Bôtto-Menezes C, Lacerda M V., Ortiz J, et al. Rosetting in Plasmodium vivax: A Cytoadhesion Phenotype Associated with Anaemia. PLoS Negl Trop Dis. 2013; 7(4): 1-8.
22. Albrecht L, Lopes SCP, da Silva ABIE, Barbosa V, Almeida RP, Siqueira AM, et al. Rosettes integrity protects Plasmodium vivax of being phagocytized. Sci Rep [Internet]. 2020 Oct 7; 10(1): 16706. Available from: https://pubmed.ncbi.nlm.nih.gov/33028898
23. Toda H, Diaz-Varela M, Segui-Barber J, Roobsoong W, Baro B, Garcia-Silva S, et al. Plasma-derived extracellular vesicles from Plasmodium vivax patients signal spleen fibroblasts via NF-kB facilitating parasite cytoadherence. Nat Commun. 2020; 11(1): 1-12.
24. Ismail MR, Ordi J, Menendez C, Ventura PJ, Aponte JJ, Kahigwa E, et al. Placental pathology in malaria: a histological, immunohistochemical, and quantitative study. Hum Pathol. 2000; 31(1): 85-93.
25. Rogerson SJ, Pollina E, Getachew A, Tadesse E, Lema VM, Molyneux ME. Placental monocyte infiltrates in response to Plasmodium falciparum malaria infection and their association with adverse pregnancy outcomes. Am J Trop Med Hyg. 2003; 68(1): 115-119.
26. López-Guzmán C, Carmona-Fonseca J. Submicroscopic placental malaria: histopathology and expression of physiological process mediators. Rev Peru Med Exp Salud Publica. 2020; 37(2): 220-228.
27. Popa C, Netea MG, Van Riel PLCM, Van Der Meer JWM, Stalenhoef AFH. The role of TNF-α in chronic inflammatory conditions, intermediary metabolism, and cardiovascular risk. J Lipid Res. 2007; 48(4): 751-762.
28. Rogerson SJ, Hviid L, Duffy PE, Leke RFG, Taylor DW. Malaria in pregnancy: pathogenesis and immunity. Lancet Infect Dis. 2007; 7(2): 105-117.
29. Suguitan Jr AL, Leke RGF, Fouda G, Zhou A, Thuita L, Metenou S, et al. Changes in the levels of chemokines and cytokines in the placentas of women with Plasmodium falciparum malaria. J Infect Dis. 2003; 188(7): 1074-1082.