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Original Article

The association between maternal malaria infection and poor birth outcomes in a remote community in Papua, Indonesia

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Abstract

Background Sikari is a remote district in Papua, Indonesia, which is malaria-endemic. Malaria infection during pregnancy has been linked to poor birth outcomes.

Objective To evaluate for an association between malaria infection in pregnancy and birth outcome.

Methods This cohort study compared the outcomes of newborns from mothers infected with malaria during pregnancy vs. uninfected controls. We included clinical data of 82 pregnant women from January to December 2020 at the Batavia Public Health Center, Sikari District, Mamberamo Raya, Papua. Malaria diagnosis was established based on the *World Health Organization* (WHO) criteria and positive rapid diagnostic tests. The maternal and infant characteristics analyzed were years of formal education, antenatal care (ANC) visits, gestational age, obstetric history, diagnosis of malaria, birth weight, APGAR score, and newborn mortality.

Results Forty-six mothers (56.1%) were diagnosed with malaria during pregnancy, of whom 33 (71.7%) had tropical malaria, 7 (15.2%) had tertian malaria, and 6 (13.0%) had mixed malaria. Malaria infections of any type were associated with an increased risk of preterm birth (OR 5.34; 95%CI 1.10 to 25.91; P=0.04), low birth weight (LBW) (OR 49.00; 95%CI 28.62 to 838.89; P=0.00), newborn mortality (OR 13.86; 95%CI 0.76 to 251.37; P=0.04), and low 5-minute APGAR score (OR 23.65; 95%CI 1.34 to 416.61; P=0.03). Tropical malaria was associated with a higher risk of preterm birth (OR 5.44; 95%CI 1.06 to 27.86; P=0.04), LBW (OR 15.22; 95%CI 1.82 to 127.02; P=0.01), newborn mortality (OR 14.09; 95%CI 0.75 to 265.48; P=0.04), and low APGAR (OR 24.33; 95%CI 1.34 to 440.77; P=0.03). Mixed malaria was associated with a higher risk of LBW (OR 35.00; 95%CI 2.73 to 449.10; P=0.01) and low APGAR score (OR 40.56; 95%CI 1.67 to 985.39; P=0.02).

Conclusion Malaria infections are associated with an increased risk of preterm birth, low birth weight, newborn mortality, and low 5-minute APGAR scores. **[Paediatr Indones. 2023;63:1-6; DOI: 10.14238/pi63.1.2022.1-6**].

Keywords: *poor birth outcome; malaria infection; remote area*

Malaria is a worldwide public health issue and a leading cause of death in tropical regions.[1] In 2019, the WHO reported that around 229 million cases of malaria and 409,000 deaths from malaria occurred worldwide, of which 94% were reported in Africa, followed by 4% in Southeast Asia, the Eastern Mediterranean, as well as several countries in the Americas and the Western Pacific.[2] Malaria infection is more common in pregnant women, with an estimated 125 million women globally at risk during pregnancy.[1,3] Studies have reported that low birth weight associated with malaria infection causes approximately 100,000 newborn deaths annually in malaria-endemic countries.[4,5]

Malaria infection in pregnant women in malaria-endemic countries has been reported to significantly impact newborns, and has been associated with an increased risk of spontaneous abortion, preterm delivery, newborn mortality, fetal death, low birth weight, fetal growth retardation, or child developmental delay.[1,6] Several studies have shown that primigravid mothers

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with malaria infection have a two- to sevenfold risk of giving birth to low birth weight (LBW) infants. Other associated poor outcomes include maternal anemia and preterm delivery.[6,7] The LBW reflects intrauterine fetal growth retardation and prematurity, indicating newborn morbidity. It has been associated with mortality in newborns, poor cognitive development, and the risk of developing non-communicable diseases in the future.[6,8]

Sikari is a remote district, newly expanded in July 2017, in Mamberamo Raya Regency, Papua Province. Mamberamo Raya is an underdeveloped regency and is classified as an area with high malaria endemicity. To the best of our knowledge, no study has reported a possible association between malaria infection in pregnant women and pregnancy outcomes, especially in such a remote and economically disadvantaged area. Therefore, we aimed to examine the association between malaria infection during pregnancy and the risk of LBW, preterm delivery, and newborn mortality in Sikari District, Mamberamo Raya Regency, Papua Province.

Methods

This retrospective, single-center cohort study was conducted at Batavia Public Health Center. The health center is located on the bank of Mamberamo River, Sikari District, Mamberamo Raya Regency, Papua Province, Indonesia, covering five villages: Sikari, Iri, Muara Suaki, Batu Tengah, and Pintu Angin. Sikari has an estimated population of 1,700 and an average of 100 births per year. Communication between villages is by motor- or oar boats.

The study protocol was approved by the Health Research Ethics Committee, Faculty of Medicine, University of Lampung. A simple random sampling method was applied to select 82 pregnant women. We excluded one suspected tuberculosis patient and seven patients with incomplete medical records of who were lost to follow-up. Clinical data and malaria status of subjects were followed up regularly and extracted from their medical records from January to December 2020. The diagnosis of malaria was established based on the *World Health Organization* (WHO) diagnostic criteria and positive rapid diagnostic tests from peripheral blood specimens.[9] Pregnant women with tuberculosis, who died, and whose infants' birth weight data were unavailable were excluded from the study.

We collected demographic and clinical data, including patient outcome data. From medical records, we obtained maternal data on pre-pregnancy body mass index (BMI), mid-upper arm circumference (MUAC), years of formal education, frequency of antenatal care (ANC) visits, gestational age, obstetric history, and malaria diagnosis, and infant data on birth weight, APGAR score, and mortality. LBW was defined as birth weight <2,500 grams. Late preterm birth was defined as birth between 32-37 weeks' gestation.[10] A 5-minute APGAR score of <7 as categorized as low.

Malaria was categorized as tropical, tertian, or mixed. Diagnoses were made according to WHO diagnostic criteria of flu-like syndrome with positive rapid diagnostic test (RDT) results in endemic areas. We used capillary or venous blood specimens for the RDT (*First Response,* Premier Medical Corporation, Sarigam, India). We classified patients who tested positive for histidine-rich protein-2 (HRP2) antigen as tropical malaria, those positive for lactate dehydrogenase (pLDH) as tertian malaria, and those positive for both as mixed malaria.[9]

Categorical variables were described as percentages and frequencies. Continuous variables with normal distribution were expressed as means with standard deviations (SD), while variables with abnormal distribution were expressed as medians with interquartile range (IQR). The t-test was applied when comparing normally distributed data; otherwise, the Mann-Whitney test was used. The chi-square test was used to analyze proportions for categorical variables, and the Fisher's exact test was utilized when data were limited. We calculated odds ratios (OR) with 95% confidence intervals (95%CI); P values ≤0.05 were considered statistically significant and served as the condition to enter variables into the multivariate model. For all statistical studies, *SPSS version 25* (*IBM,* Armonk, New York) was used.

Results

We included 82 pregnant women in the study and categorized them into two groups, with and without malaria. Of the maternal subjects, 79 (96.3%) were

aged 20-35 years; the remaining three (3.7%) were >35 years of age. The characteristics of maternal subjects are described in **Table 1**.

Forty-six (56.1%) subjects were diagnosed with malaria infection during pregnancy. Of the 46 malaria-infected mothers, 33 (71.7%) had tropical malaria, 7 (15.2%) had tertian malaria, and 6 (13.0%) had mixed malaria. Pregnant women with malaria infection had a significantly higher incidence of late preterm birth (23.9% *vs.* 5.6%, respectively; P=0.04), LBW (30.4% vs 2.8%, respectively; P=0.00), newborn mortality (15.2% *vs.* 0.0%, respectively; P=0.04) and low APGAR score (23.9% *vs.* 0.0%, respectively; P=0.03) than uninfected mothers (**Table 2**).

Multivariate analysis of malaria subtypes compared to uninfected pregnant women revealed that infants of mothers with tropical malaria had a significantly higher risk of late preterm birth (24.2% *vs.* 5.6%, respectively; OR 5.44; 95%CI 1.06 to 27.86, P=0.04), LBW (30.3% *vs.* 2.8%, respectively; OR 15.22; 95%CI 1.82 to 127.02; P=0.01), newborn mortality (15.2% *vs.* 0.0%, respectively; OR 14.09; 95%CI 0.75 to 265.48; P=0.04), and low 5-minute APGAR score (24.2% *vs.* 0.0%, respectively; OR 24.33; 95%CI 1.34 to 440.77; P=0.03). Infants born from mothers with mixed malaria infection had a significantly higher risk of LBW (50.0% *vs.* 2.8%, respectively; OR 35.00; 95%CI 2.73 to 449.10; P=0.01) and low 5-minute APGAR score (33.3% *vs.* 0.0%, respectively; OR 40.56; 95%CI 1.67 to 985.39; P=0.02) compared to those from uninfected mothers; there were no significant differences in the risk of preterm birth and newborn mortality between these groups. There were no significant differences between

Table 1. Baseline characteristics of pregnant women with and without malaria infection

Variables	All mothers (n=82)	Maternal malaria infection (n=46)	Uninfected (n=36)	Z/x^2 values	P value
Maternal age, n (%)				2.44	0.12
20-35 years	79 (96.3)	43 (93.5)	36		
>35 years	3 (3.7)	3 (6.5)	0		
Pre-pregnancy maternal BMI, n (%)				1.65	0.20
Normoweight	78 (95.1)	45 (97.8)	33		
Overweight	4 (4.9)	1 (2.2)	3		
Median maternal MUAC (IQR)*	24.0 (23.5-25.0)	24.0 (23.8-25.0)	24.3 (24.0-25.0)	-1.37	0.17
Years of formal education, n (%)				5.00	0.08
No formal education	18 (22.0)	14 (30.4)	4		
≤6 years	39 (47.5)	21 (45.7)	18		
6-12 years	25 (30.5)	11 (23.9)	14		
Parity, n (%)					
Nulligravida	5 (6.1)	3 (6.5)	2	0,18	0.86
Primigravida	16 (19.5)	3 (6.5)	13	-3,03	0.00
Multigravida	55 (67.1)	35 (76.1)	20	1.94	0.05
Grande multigravida	6 (7.3)	5 (10.9)	1	1.29	0.19
History of abortion, n (%)				3.29	0.07
No	78 (95.1)	42 (91.3)	36		
Yes	4 (4.9)	4 (8.7)	0		
No. of ANC visits, n (%)				2.13	0.34
≥4	9 (11.0)	7 (15.2)	2		
1-3	63 (76.8)	33 (71.7)	30		
None	10 (12.2)	6 (13.0)	4		

Note: Chi-square test (X^2 values) for categorical variables; Mann-Whitney test (Z values) for non-parametric test marker with *; BMI=body mass index; MUAC=mid-upper arm circumference; IQR=interquartile range

the tertian malaria group and the uninfected group in the incidence of preterm birth, LBW, low 5-minute APGAR score, or newborn mortality (**Table 3**).

Discussion

This retrospective, single-center cohort study was conducted at Batavia Public Health Center, Sikari District, Mamberamo Raya Regency, Papua Province, Indonesia. We evaluated the prevalence of malaria

Table 2. Analysis of malaria infection and birth outcomes

Variables	All newborns (n=82)	Maternal malaria infection (n=46)	Uninfected mothers (n=36)	Z/X^2 values	P value
Gestational age, n(%)					
Full term birth	69 (84.1)	35 (76.1)	34 (94.4)	3.14	0.00
Preterm birth	13 (15.9)	11 (23.9)	2 (5.6)		
Birth weight, n(%)					
Normal	67 (81.7)	32 (69.6)	35 (97.2)	1.22	0.00
LBW	15 (18.3)	14 (30.4)	1 (2.8)		
Median (IQR), kg	2.85 (2.68-3.00)	2.70 (2.28-2.90)	3.00 (2.80-3.13)	-3.61	0.00
Apgar score, n(%)					
<7	11 (13.4)	11 (23.9)	0 (0)	3.07	0.00
≥7	71 (86.6)	35 (76.1)	36 (100.0)		
Birth outcome, n(%)					
Survived	75 (91.5)	39 (84.8)	36 (100.0)	2.62	0.00
Died	7 (8.5)	7 (15.2)	0 (0)		

Note: IQR=interquartile range. Chi-square test (X^2 values) for categorical variables; Mann-Whitney test (Z values) for non-parametric test marker with*

Table 3. Sub-group multivariate analysis of malarial infection type and birth outcomes

Variables	Maternal malaria infection (n=46)	Uninfected mothers (n=36)	OR (95% CI)	P value
All malaria infection, n (%)				
Preterm birth	11 (23.9)	2	5.34 (1.10-25.91)	0.04
LBW	14 (30.4)	1	49.00 (28.62-838.89)	0.00
Low APGAR score	11 (23.9)	0	23.65 (1.34-416.61)	0.03
Newborn mortality	7 (15.2)	0	13.86 (0.76-251.37)	0.04
Tropical malaria, n (%				
Preterm birth	8 (24.2)	2	5.44 (1.06-27.86)	0.04
LBW	10 (30.3)	1	15.22 (1.82-127.02)	0.01
Low APGAR score	8 (24.2)	0	24.33 (1.34-440.77)	0.03
Newborn mortality	5 (15.2)	0	14.09 (0.75-265.48)	0.04
Tertian malaria, n (%)				
Preterm birth	2 (28.6)	2	6.80 (0.77-59.75)	0.08
LBW	1 (14.3)	1	5.83 (0.32-106.44)	0.23
Low APGAR score	1 (14.3)	0	16.85 (0.62-460.22)	0.09
Newborn mortality	1 (14.3)	0	16.85 (0.62-460.22)	0.09
Mixed malaria, n (%				
Preterm birth	1 (16.7)	2	3.40 (0.26-44.76)	0.35
LBW	3 (50.0)	1	35.00 (2.73-449.10)	0.01
Low APGAR score	2 (33.3)	0	40.56 (1.67-985.39)	0.02
Newborn mortality	1 (16.7)	0	19.91 (0.72-552.78)	0.08

Note: data are presented in n (%); OR=odds ratio; CI=confidence interval

infection in pregnant women and its association with clinical outcomes. In previous studies in Africa, maternal malaria infection had a varied prevalence.[6,11] Several studies reported that the high incidence of malaria in pregnancy was associated with susceptibility to malaria infection due to a combination of host and parasitic factors as well as factors involving local epidemic control policies.[12,13] In agreement with previous studies, more than half of the pregnant women in our study were infected with malaria, with falciparum malaria (tropical malaria) being the most common subtype. The Republic of Indonesia Ministry of Health also reported a high endemicity of malaria infection in the Mamberamo Raya Regency.[14]

Several factors contribute to LBW and neonatal mortality, including socioeconomic, environmental, nutritional, and clinical factors during pregnancy.[5] Low birth weight can result from premature birth and intrauterine growth restriction.[15] Although the government family planning program promotes the importance of reproductive health and contraceptive use,[17] we found that 67% of our subjects had a history of multiparity and 7.3% were grande multipara. The WHO also recommended that pregnant women have at least four ANC visits.[16] The application of these recommendations is still far from being attained, as only 11% of patients had four or more ANC visits. The level of education in our study population remains low; most subjects had no or less than six years of formal education. Another study also revealed that low educational level was associated with an increased likelihood of seeking infrequent and inappropriate ANC.[17] Local governments should address the issues of low maternal education level, infrequent ANC, and multiparity by promoting reproductive health awareness and services.

Malaria infection during pregnancy has been linked to poor neonatal outcomes.[5,12,18] Infected erythrocytes have specific surface antigens that mediate binding to placental receptors leading to the recruitment and activation of various immune cells, which might cause a cascade of downstream inflammatory processes. These inflammatory events have been linked to decreased placental nutrient transfer, which contributes to placental insufficiency.[19,20] We found significant associations between malaria infection and an increased risk of preterm birth, LBW, low APGAR score, and newborn mortality. Cottrell et al. showed that Plasmodium falciparum infections were associated with maternal anemia, premature birth, and LBW.[21] In addition, mixed malaria infection was associated with LBW and low APGAR score. Unfortunately, we could not perform microscopic examination of thick and thin blood films due to resource limitations in our primary health care centers.

In conclusion, maternal malaria infection is associated with an increased risk of preterm birth, LBW, low 5-minute APGAR score, and newborn mortality. Further studies using a larger scale and proper diagnostic tools are needed to assess the prevalence of birth outcomes in pregnant patients with malaria.

Conflict of interest

None declared.

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