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Risk Factors of Miscarriage in Malaria-Endemic Region: A Case-Control Study in Eastern Indonesia

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Abstract

Background: To date, there are still 242 districts in Indonesia which remain endemic for malaria, mostly in the eastern region of the country. East Nusa Tenggara Province is one of the regions with the highest Annual Parasite Incidence (API) per 1,000 population, with none of the districts or cities being able to achieve malaria elimination even once. Hence, most of the pregnant women who live in the Asia-Pacific countries are at risk of Plasmodium vivax infection. There is also a notion that malaria infection could increase the risk of miscarriage. Therefore, we aimed to assess the risk factors of miscarriage in the malaria-endemic regions in Eastern Indonesia.

Methods: A case-control study was conducted using data from the previous malaria study in East Nusa Tenggara. This study included 37 respondents with a history of miscarriage and 74 control subjects matched by age (±5 years) and sub-district. We assessed the correlation of socioeconomic status, malaria, anemia, body mass index, and glucose-6-phosphate dehydrogenase (G6PD) deficiency with miscarriage. Data were analyzed using bivariate and multivariate analysis with p-value <0.05 indicates that the variable has a significant effect.

Results: A total of 111 women were included in this study with 37 respondents being the case group and 74 being the control group. The risk of developing miscarriage increased in lower socioeconomic status (OR 1.05; 95% CI: 0.45-2.44), in malaria-positive (OR 1.40; 95% CI: 0.60-3.26), in the presence of anemia (OR 1.90; 95% CI: 0.82-4.45), and in abnormal BMI (OR 1.08; 95% CI: 0.47-2.46).

Conclusion: Lower socioeconomic status, malaria-positive, anemia, and abnormal BMI showed a positive correlation with miscarriage in the malaria-endemic area of East Nusa Tenggara, Indonesia.
Keywords: Eastern Indonesia, malaria-endemic region, miscarriage

Introduction

Malaria is an endemic disease predominantly in tropical and subtropical regions that is caused by *Plasmodium.* The disease is transmitted by the female *Anopheles* mosquito.[1], [2] In 2018, approximately 228 million malaria cases were reported across the world with 7.9 million (3.4%) cases distributed in South-East Asia.[3] In Indonesia, 242 districts or cities remain as malaria-endemic regions, and they are mostly resided in the eastern regions of the country.[4] East Nusa Tenggara Province is one of the regions with the highest Annual Parasite Incidence (API) per 1,000 population (3.42) in Indonesia after Papua (52.99) and West Papua (8.49), with none of the districts or cities having ever reached the status of malaria-eliminated area. South Central Timor District is one of the 10 regions in East Nusa Tenggara with the highest number of malaria cases.[5], [6]

According to a study conducted by Dellicour *et al.* in 2007, 91 million pregnancies occurred in malaria-endemic countries that fall under the regional office of the World Health Organization (WHO) for the South East Asian (SEARO) and the Western Pacific Region (WPRO). That means most of the pregnant women who live in these countries are at risk of *Plasmodium vivax* infection.[7], [8] Pregnant women are the vulnerable population for malaria infection due to the pregnancy-related immune system suppression.[9] In 2008, East Nusa Tenggara has the highest malaria cases for pregnant women in Indonesia.[10] Meanwhile, there is a notion that the infection could harm pregnancies as reported by various studies. Miscarriage is defined as the termination of pregnancy before 20 weeks of gestation or when the fetus is born weighing less than 500 grams without medical or mechanical intervention.[12] A study by McGready *et al.* in Thailand found that malaria could increase the risk of miscarriage.[11] In another study, Moore *et al.* in Thai-Myanmar border found that the risk of miscarriage increased 1.61 times following an initial first-trimester of falciparum episode, 3.24 times after the recurrent of falciparum malaria, and 2.44 times after the recurrent of symptomatic vivax malaria.[13]

To date, there are still few studies about the correlation of miscarriage and malaria infection, and almost none for East Nusa Tenggara as a malaria-endemic region in eastern Indonesia. We seek out to investigate various factors involved in the reported miscarriage cases from the region and to assess the risk of miscarriage in infected women with the history of miscarriage in those endemic regions.

Methods

This was a case-control study using data from the previous malaria study by Hutagalung *et al.*[14] The previous study was carried out from August 2013 to September 2014 in five sub-districts in South Central Timor District, East Nusa Tenggara Province. The five areas had been chosen based on the Annual Parasitic Incidence (API) number as follows: Oe'ekam (API>5), Oinlasi (API>5), Batu Putih (API 1-5), Panite (API 1-5), and Oenino (API<1). This study had been approved by the Medical Research Ethical Committee, Faculty of Medicine, Universitas Padjadjaran with the ethic license number 936/UN6.KEP/EC/2020.

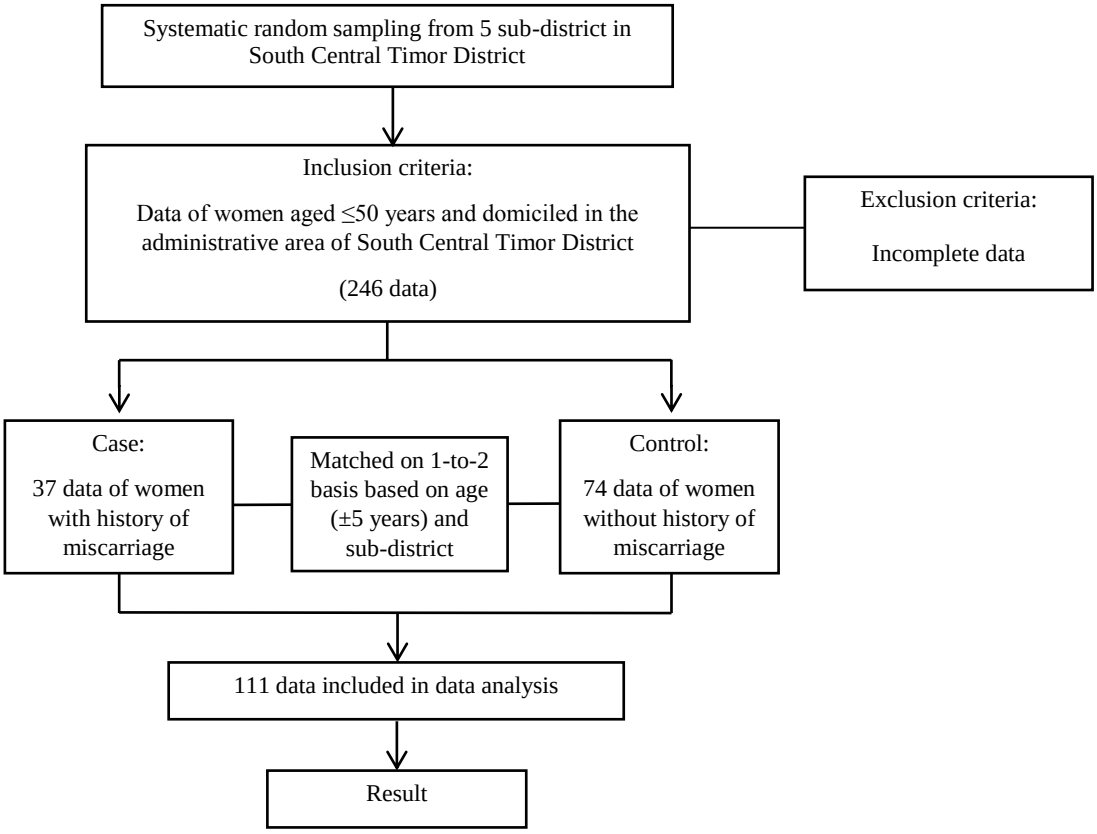

Figure 1. Research Flowchart

1. Data Collection

In the primary research, subjects were selected through systematic random sampling based on the household data from each sub-district. The data included in this study were selected based on inclusion criteria: data of women aged ≤50 years and domiciled in the administrative area of South Central Timor District, while incomplete data would be excluded. The cases were defined as women with a history of miscarriage based on interviews and data from maternal and child health book, while the controls were women without a history of miscarriage. To minimize bias, we matched each case with two control subjects based on age (±5 years) and sub-district.

Socioeconomic status (SES) was determined by the need for a minimum area of space per person following the Decree of The Minister of Residence

and Regional Infrastructure Number: 403/KPTS/M/2002.[15] Lower SES was represented by a person who lives in a house with a minimum area of space per person <9 m^2, while a person who lives in a house with a minimum area of space per person ≥9m^2 was categorized as higher SES.

Nested-PCR was carried out for malaria assessment as described in the protocol by Snounou *et al*.[16] Hemoglobin (Hb) levels were measured by Bene-Check Hemoglobin Stick Test. Based on the WHO classification, hemoglobin levels were classified as anemia (Hb <11g/dl) and non-anemia (Hb ≥11g/dl).[17] Data of body mass index (BMI) were obtained by calculating the body weight and height according to the formula and the classification used by the Ministry of Health of the Republic of Indonesia. The BMI data were then classified into two main groups: abnormal (skinny and fat) and normal.[18] G6PD deficiency was screened using a quantitative G6PD test kit following the Randox G6PD test protocols.[19]

2. Data Analysis

The data that has been collected were processed and analyzed using Microsoft® Excel 2010 and IBM® SPSS® Version 25. Bivariate and multivariate analysis was used to assess the association of SES, malaria, anemia, BMI, and G6PD deficiency on miscarriage. P-value <0.05 indicates that the variable has a significant effect on miscarriage.

Results

1. Characteristics of Respondents

A total of 111 women were included in this study with 37 respondents being the case group and 74 being the control group. Table 1 shows the distribution of both case and control groups. The mean age of the respondents was 35 years old with a range between 18 and 50 years old. The history of miscarriage was highest in the 36-40-year-old group and mostly found in respondents who came from Oe'ekam and Oenino (respectively 27%). Also, the majority of respondents (61.3%) and the cases (59.5%) came from the lower SES. Among the malaria-positive respondents, 22 were positive for *P. vivax* (56.4%), 9 were positive for *P. falciparum* (23.1%), and 8 were positive for mixed infection (20.5%). The mean hemoglobin level in the case group was lower than the control group (10.9 g/dl and 11.54 g/dl, respectively).

Table 1. The Distribution of Case and Control Groups

Characteristics	Cases n = 37 (%)	Controls n = 74 (%)	Total n = 111 (%)
Age (years old)			
≤20	2 (5.4)	3 (4.1)	5 (4.5)
21-25	4 (10.8)	9 (12.2)	13 (11.7)

26-30	3 (8.1)	7 (9.5)	10 (9.0)
31-35	8 (21.6)	16 (21.6)	24 (21.6)
36-40	9 (24.3)	17 (23.0)	26 (23.4)
41-45	7 (18.9)	18 (24.3)	25 (22.5)
46-50	4 (10.8)	4 (5.4)	8 (7.2)
Sub-district			
Oinlasi	7 (18.9)	14 (18.9)	21 (18.9)
Oe'ekam	10 (27.0)	20 (27.0)	30 (27.0)
Panite	5 (13.5)	10 (13.5)	15 (13.5)
Batu Putih	5 (13.5)	10 (13.5)	15 (13.5)
Oenino	10 (27.0)	20 (27.0)	30 (27.0)
Socioeconomic status (SES)			
Higher	15 (40.5)	28 (37.8)	43 (38.7)
Lower	22 (59.5)	46 (62.2)	68 (61.3)
Malaria			
Positive	15 (40.5)	24 (32.4)	39 (35.1)
Negative	22 (59.5)	50 (67.6)	72 (64.9)
Anemia			
Yes (<11 g/dL)	20 (54.1)	26 (35.1)	46 (41.4)
No (≥11 g/dL)	17 (45.9)	48 (64.9)	65 (58.6)

2. Bivariate Analysis

The bivariate analysis result as shown in Table 2, indicated no significant association between miscarriage history with SES, malaria, anemia, BMI, and G6PD deficiency.

Table 2. Result of Bivariate Analysis

Variables	Cases n=37 (%)	Controls n=74 (%)	Total n=111 (%)	p-value	OR	95%CI	
						Lower	Upper
Socioeconomic status (SES)							
Higher	15 (40.5)	28 (37.8)	43 (38.7)	0.783	0.893	0.398	2.001
Lower	22 (59.5)	46 (62.2)	68 (61.3)				
Malaria							
Negative	22 (59.5)	50 (67.6)	72 (64.9)	0.399	1.420	0.672	3.216
Positive	15 (40.5)	24 (32.4)	39 (35.1)				
Anemia							
No (≥11 g/dl)	17 (45.9)	48 (64.9)	65 (58.6)	0.056	2.172	0.972	4.851

Yes (<11 g/dl)	20 (54.1)	26 (35.1)	46 (41.4)				
BMI							
Normal	20 (54.1)	41 (55.4)	61 (55.0)	0.893	1.056	0.478	2.333
Abnormal	17 (45.9)	33 (44.6)	50 (45.0)				
G6PD deficiency							
No	34 (91.9)	61 (82.4)	95 (85.6)	0.181	0.414	0.11	1.555
Yes	3 (8.1)	13 (17.6)	16 (14.4)				

OR odds ratio, *BMI* body mass index, *G6PD* glucose-6-phosphate dehydrogenase

3. Multivariate analysis

Logistic regression was performed to assess the possible contributing factors to miscarriage. As shown in Table 3, SES, malaria, anemia, G6PD deficiency, and BMI had a positive relationship with miscarriage although not statistically significant (p>0.05). The risk of developing miscarriage increased by 1.05 in lower SES (95% CI: 0.45-2.44), 1.4 times in malaria-positive (95% CI: 0.60-3.26), 1.9 times in the presence of anemia (95% CI: 0.82-4.45), and 1.08 times in abnormal BMI (95% CI: 0.47-2.46). Meanwhile, the risk of miscarriage will decrease by 47% if the patient has G6PD deficiency (B -0.64, OR 0.53, 95% CI: 0.13-2.11).

Table 3. Result of Multivariate Analysis

Variables	B	p-value	OR	95% CI	
				Lower	Upper
Constant	-1.088	0.032	0.337		
Socioeconomic status (SES)	0.047	0.913	1.048	0.451	2.438
Malaria	0.338	0.432	1.402	0.603	3.258
Anemia	0.644	0.137	1.904	0.815	4.445
BMI	0.077	0.854	1.080	0.474	2.460
G6PD deficiency	-0.637	0.368	0.529	0.132	2.113

B coefficients regression, *OR* odds ratio, *BMI* body mass index, *G6PD* glucose-6-phosphate dehydrogenase

Discussion

This study found that several factors contributed to the reported miscarriages in malaria-endemic regions such as East Nusa Tenggara, Indonesia. Lower SES, malaria-positive, anemia, and abnormal BMI had all positive correlation with miscarriages. However, they did not reach the level of statistical significance (p> 0.05), presumably because the number of exposures in the case group in this study was too small.

The percentage of the poor population (low SES) in East Nusa Tenggara is high. In 2014, the percentage of the poor population at the national level reached 10.96 percent, while in East Nusa Tenggara it was 19.8 percent.[20] In this study, we also found that most of the respondents had lower SES (61.3%, n = 68) and this condition increases the risk of miscarriage by 1.05 times. Similarly, the previous study in South Korea found that women with low SES were more likely to have a miscarriage than women with higher SES (OR 1.40; 95% CI: 1.31-1.50).[21] Lower SES can be associated with a lower likelihood of seeking antenatal care, poor nutrition, and lower levels of education that are associated with age at pregnancy.[21]–[23]

Pregnant women are prone to malaria because of their immunological tolerance, which reduces their effectiveness in clearing the malaria parasite.[9] The majority of pregnant women living in the Asia Pacific region are at risk of *Plasmodium vivax* infection.[8] In this study, the proportion of women with malaria was also largely due to *P. vivax* (56.4%), but here we only assessed the odds of malaria on miscarriage compared to non-malaria without differentiating the causative species. Our study found that malaria increased the risk of miscarriage by 1.40 times. Similar to a study in Thailand, showing that women with asymptomatic and symptomatic malaria are at higher risk of miscarriage compared to non-malaria women (aOR 2.70, 95% CI: 2.04-3.59 and aOR 3.99, 95% CI 3.10-5.13, respectively).[11] Plasmodium may bind to chondroitin sulphate A that expressed on trophoblasts and triggers local parasitemia in the placenta.[24] Antigen stimulation in malaria infection will activate macrophages then triggering the production of reactive oxygen species (ROS) to destroy intracellular parasites, leading to the damage of cells lining of blood vessels and trophoblast cells in the placenta.[9] In addition, malaria can also cause maternal anemia that may contribute to the poor outcome of pregnancy.[25]

Maternal anemia was associated with the poor outcome of pregnancy.[26] In this study, 54.1% (20/37) of respondents in the case group had anemia. The mean hemoglobin levels in the case group were lower than the control group (10.9 g/dl and 11.54 g/dl, respectively). We found that the presence of anemia increasing the risk of miscarriage by 1.9 times and contribute most to miscarriage (64.4%). In another study in India, it was stated that the prevalence of miscarriage in the group of pregnant women with severe anemia (74.7%) was statistically significantly higher ($p < 0.05$) compared to moderate and mild anemia.[27] Anemia may occur due to an increase in iron demand, inadequate iron intake, poor nutrition status, and can also occur due to infection such as malaria. Maternal anemia can cause death in the product of conception which in turn can lead to miscarriage.[28], [29]

We also found that abnormal BMI had a positive correlation on miscarriage. In the recent study, the risk of miscarriage increasing by 1.08 in abnormal BMI. In another study, it was also stated that underweight, overweight,

and obese increased the risk of miscarriage. [30]–[32] Miscarriage in an underweight woman may be caused by the downregulation of hormones or the direct result of undernutrition.[32] Meanwhile, overweight and obesity were associated with various endocrine and paracrine changes, that lead to hormonal disturbances, impaired trophoblastic invasion, and diminished endometrial receptivity, which could interfere the embryonic development and fetoplacental function.[31]

Furthermore, we also assessed the effect of G6PD deficiency on the prevalence of miscarriage. It is estimated that 400 million people in the world have G6PD deficiency and epidemiologically the prevalence of G6PD deficiency is commonly found in the malaria-endemic region.[33] G6PD is an enzyme that catalyzes the oxidation of glucose-6-phosphate to 6-phosphoglucono-□-lactone. This process generates nicotinamide adenine dinucleotide phosphate hydrogen (NADPH) from nicotinamide adenine dinucleotide phosphate (NADP). NADPH is important in the regeneration of glutathione which is an antioxidant that helps against oxidative stress.[34] Oxygen pressure in the placenta increases at 10-12 weeks of gestation and may cause oxidative stress on the trophoblasts. Trophoblast degeneration due to oxidative stress can occur if the antioxidant capacity is lower than oxidants and triggers a miscarriage.[35] In a previous study in Surabaya, they assessed the activity of the G6PD enzyme of respondents who had a bad pregnancy history, such as miscarriage, intrauterine death, and stillbirth. Of 23 respondents, 43.5% (10/23) had G6PD deficiency and all of these respondents have a history of miscarriage.[35] In this study, we found that the risk of miscarriage will decrease by 47% if the patient has G6PD deficiency (B -0.64, OR 0.53), however this might occur because the number of G6PD deficiency in the case group was lower (3/16) than the control group (13/16). Research on the association of G6PD deficiency with miscarriage is scarce and further studies may be needed to confirm this finding.

In order to reduce the number of miscarriages in malaria-endemic regions, one effort that can be done is through antenatal care services. Antenatal care in Indonesia is quite comprehensive, includes the examination of hemoglobin levels, providing iron supplement tablets, malaria assessment in endemic regions, and measuring body height and body weight.[36] Through antenatal care, the factors that are known from this study can contribute to the development of miscarriage can be detected earlier through screening thus the management can be done if there are abnormalities, besides health workers also can provide education about the prevention. Therefore, we recommend the health workers provide a more frequent understanding of the importance of doing antenatal care for pregnant women. In Indonesia, antenatal care is included in the scope of universal health coverage services, thus it is necessary to increase cooperation between various parties, such as the Healthcare Program of Social Security Administrator (*Badan Penyelenggara Jaminan Sosial*, BPJS), public health centers (*pusat kesehatan*

masyarakat, puskesmas), and health workers, for being more frequent in providing education, especially for women who come from low socioeconomic status so that the use of antenatal care services will be increases.[37]

Management of the risk factors needs to be done from the biggest problem. In this study, we found that anemia contributes the most to miscarriage, thus we suggest that the management of anemia in pregnant women should be prioritized. In malaria-endemic regions, anemia can also be caused by malaria, so if pregnant women have anemia and malaria, malaria management is prioritized as a form of causative therapy.

This study has several limitations. The overall prevalence of miscarriage is low, thus the factors assessed in this study are not statistically significant although it may be clinically significant. The amount of data in the primary data is limited, so there may be other factors that have a greater influence on miscarriage than the factors assessed in this study. Also, we cannot confirm when the miscarriage occurred so that it may not be truly representative of the population of interest.

Conclusion

In conclusion, lower SES, malaria-positive, anemia, and abnormal BMI showed positive correlations with miscarriage. Therefore, early intervention could hopefully control the risk factors in the pregnant women to increase the chance of having a successful pregnancy, especially for those who live in a malaria-endemic region.

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