Prevalence of pregnant women with malaria in Aceh, symptoms and fetomaternal outcome

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ABSTRACT

WHO estimates that as many as 300 to 500 million people are infected with malaria each year. There are around 3 million severe malaria cases (complicated malaria) and deaths due to malaria. Other sources revealed that as many as 1.5 million to 2.7 million people die every year, especially children and pregnant women. Malaria is a disease that is emerging and continues to affect the people of Aceh. Malaria in pregnancy is a serious problem considering its effects on the mother and fetus, which can increase maternal and neonatal mortality rates if not treated quickly and accurately. Prevention of malaria in pregnancy can be started early through ANC visits by providing health education about malaria prevention and prophylactic treatment for those living in endemic areas. The purpose of this review is to discuss the classification of the Aceh Province according to the level of susceptibility to malaria was based on the API value criteria, to discuss prompt treatment of malaria to improve maternal and fetal outcomes.

Keywords: Fetal Maternal Outcome, Malaria, Pregnancy.

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INTRODUCTION

Indonesia is one of the countries at risk for malaria cases with a prevalence of 1.4% and an incidence rate of 0.3% with an Annual Parasite Incidence (API) in 2015 of 0.85%.

One of the indicators in the health development target is the number of districts/cities with malaria elimination certification. WHO estimates that as many as 300 to 500 million people are infected with malaria each year. There are around 3 million severe malaria cases (complicated malaria) and deaths due to malaria. Other sources say that as many as 1.5 million to 2.7 million people die every year, especially children and pregnant women. Outbreaks (KLB) of malaria cases occur in almost all continents, increasing public health problems and causing death, reducing work productivity, and gives rise to other economic impacts, including reduced tourism due to imported malaria. Imported malaria is a malaria case in a person who visits an area prone to malaria disease and then returns to his/her home area, which is not an endemic malaria area. Some malaria outbreaks are caused by changes in the environment where the potential breeding grounds for malaria mosquito vectors expand or increase.

There were 1,038 malaria cases between 2015-2018 in Aceh, and Plasmodium vivax is a primary cause of malarial with 703 cases (67.73%). Most of them were found in Aceh Jaya and Aceh Selatan district. One of the first steps in assisting Aceh and district/city governments in identifying and eliminating malaria cases is by researching the types of plasmodium parasites that cause malaria and classifying areas prone to malaria to work more on areas with a high level of vulnerability to malaria. The purpose of this review is to discuss the classification of the Aceh Province according to the level of susceptibility to malaria was based on the API value criteria to discuss prompt treatment of malaria to improve maternal and fetal outcomes.

ACEH PROVINCIAL CLASSIFICATION BASED ON MALARIA VULNERABILITY LEVEL

In this case, the classification of the Aceh Province according to the level of susceptibility to malaria was based on the API value criteria. API is an indicator to determine the number of people free of malaria in a certain area. The API value is obtained from the number of malaria cases in a year divided by the population and multiplied by 1000. The data used is the API data for all districts/cities in the Aceh Province, from 2015 to 2018. API indicators have four categories, namely No Case Incidence (API = 0), Low Case Incidence (LCI) if the API value is less than 1, Moderate Case Incidence (MCI) if the API value is between 1 to 5, and High Case Incidence if the API value is more than 5. However, districts/cities in Aceh Province only have three API categories.

Gayo Lues District is the only district in Aceh Province that does not have malaria cases or is included in category 1. Furthermore, Aceh Jaya District is the only district with the highest number of malaria cases in Aceh Province with an API value <5 and is included in the category. 3. Meanwhile, the other 21 districts/cities fall into category 2, with API values varying from 0 to 1, making it possible to divide these districts/cities into new clusters. Regions in one cluster will have adjacent API values, while regions with different clusters will have distant API values. This clustering is carried
Table 1. Classification of districts/cities in Aceh Province based on the API indicator

| Category       | Regency / City                                                                 | Information |
|----------------|-------------------------------------------------------------------------------|-------------|
| Category 1     | No Case Incidence                                                             | There are no cases |
| Category 2     | Low Cluster 1                                                                 | Low Cluster 1 |
| Incidence Cluster 1 | Regency: Gayo Lues, Regency: Simeulue, Kab. Aceh Singkil, Kab. Southeast Aceh, Kab. East Aceh, Kab. Central Aceh, Kab. West Aceh, Kab. Aceh Besar, Kab. Pidie, Kab. Bireuen, Kab. North Aceh, Kab. Southwest Aceh, Kab. Aceh Tamiang, Kab. Nagan Raya, Kab. Bener Meriah, Kab. Pidie Jaya, Banda Aceh City, Langsa City, Lhokseumawe City, Subulussalam City Regency. South Aceh | Low Cluster 2 |
| Category 3     | Low Cluster 2                                                                 | Low Cluster 3 |
| Incidence Cluster 2 | Kab. South Aceh, Kab. Aceh Jaya, Kab. Sabang City                              | Moderate |
| Incidence Cluster 3 | Kab. South Aceh, Kab. Aceh Jaya, Kab. Sabang City                              | Moderate |

out to facilitate related parties, such as the Aceh Provincial and District/City Health Offices, to identify areas prone to malaria disease so that malaria prevention programs can be focused on areas with a higher level of vulnerability. The number of clusters used in this study was 3 clusters, namely Low Case Incidence Cluster 1, Low Case Incidence Cluster 2 and Low Case Incidence Cluster 3. Cluster 1 is the area with the lowest level of vulnerability, and cluster 3 is the area with the highest vulnerability level. Low Case Incidence categories are used so that the malaria prevention program can focus on areas with a higher level of vulnerability.

K-means clustering analysis is based on the distance between observations or data. The closest distance between data and a particular cluster will determine where the data is located in the available clusters. The clustering results of 21 districts/cities included in the Low Case Incidence (LCI) category are shown in Table 1 in category 2. Table 1 lists the districts/cities included in category 1 (No Case Incidence) and 3 (Moderate Case Incidence). Districts/cities that are included in categories 1 and 3 are not included in the K-means clustering analysis.

Based on Table 1 in category 2, it is known that of the 21 districts/cities analyzed, 19 districts/cities are included in cluster 1 (Low Case Incidence Cluster 1), namely Kab. Simeulue, Kab. Aceh Singkil, Kab. Southeast Aceh, Kab. East Aceh, Kab. Central Aceh, Kab. West Aceh, Kab. Aceh Besar, Kab. Pidie, Kab. Bireuen, Kab. North Aceh, Kab. Southwest Aceh, Kab. Aceh Tamiang, Kab. Nagan Raya, Kab. Bener Meriah, Kab. Pidie Jaya, Banda Aceh City, Langsa City, Lhokseumawe City, Subulussalam City Regency. South Aceh.

**IMMUNOPATHOLOGY OF RESPONSE IMMUNE AGAINST MALARIA INFECTION DURING PREGNANCY**

Response Specific immunity consists of cellular immunity carried out by T lymphocytes, and humoral immunity carried out by B lymphocytes. These cytokines play a role in activating humoral immunity. CD4+ functions as a regulator by helping produce antibodies and activation of other phagocytes, while CD8+ acts as a direct cause for parasitic phagocytosis and inhibits parasite development by producing IFN-γ. In this case, the parasite antigen epitopes will bind to B lymphocyte receptors that act as antigen-presenting cells to T lymphocytes, CD4+. Furthermore, T cells will differentiate into Th-1 and Th-2 cells. Th-2 cells will produce IL-4 and IL-5, which promote the formation of Ig by B lymphocytes. These Ig also increase the phagocytosis ability of macrophages. Th-1 cells produce IFN-γ and TNF-α, which activate cellular immunity components such as macrophages, monocytes, and NK cells.

Pregnant women are more likely to develop falciparum malaria that is found more severe compared to nonpregnant women. Concentrations of erythrocytes infected with parasites are found in the placenta, so that it is suspected that the immune response to parasites in that area is suppressed. This is related to the
suppression of the immune system, both humoral and cellular, during pregnancy due to the presence of the fetus as a “foreign object” in the mother’s body.9

Suppression of the immune system during pregnancy is related to the hormonal state. The progesterone hormone concentration, which increases during pregnancy, inhibits T lymphocyte activation against antigen stimulation. Also, the immunosuppression effect of cortisol plays a role in inhibiting immune response.9

**CLINICAL SYMPTOMS**

The main symptom of malaria infection is fever which is thought to be associated with the schizogony process (rupture of merozoites/schizonts) and cytokines and/or other toxins. In hyperendemic areas, patients with parasitemia are often found without fever symptoms. The characteristic features of malaria are periodic fever, anemia, and splenomegaly. There are frequent prodromal symptoms such as malaise, headache, bone/muscle pain, anorexia and mild diarrhea. The effects of malaria on pregnancy can be divided into two groups: the effects on the mother and the effects on the fetus. Effect on mothers there are anemia, circulatory system disorders, orthostatic hypotension is common, pulmonary edema, hypoglycemia, placenta infection, electrolyte disturbances, cerebral malaria. Effect on the fetus there are fetal death in utero, abortion, premature birth, low birth weight, placental malaria. However, the clinical effect of malaria on pregnant women depends more on the level of immunity of pregnant women against the disease, while immunity to malaria is determined more by the level of malaria transmission where pregnant women live/originate, which is divided into two major groups.10

1) Stable transmission, or endemic (example: Sub-Saharan Africa)
   a. People in this area are constantly exposed to malaria because they often receive an effective mosquito bite every month.
   b. Immunity to malaria builds up significantly.10

2) Unstable transmission/transmission is unstable, epidemic or non-endemic (example: Southeast Asia and South America)
   a. People in these areas are rarely exposed to malaria and only receive an average of <1 infective mosquito bite/year. Pregnant women (semi-immune) in areas of stable/high endemic transmission will experience:
      b. Increase in parasite rate (in primigravida in Africa, parasite rate in pregnant women increases 30-40% compared to nonpregnant women)
      c. Increased density of peripheral parasitemia. It causes fewer clinical effects, except for maternal anemia as the main complication that often occurs in primigravida. The anemia can worsen, causing serious consequences for both the mother and the fetus.10

   On the other hand, in unstable/non-endemic/low-endemic areas where most of the population are not immune to malaria, pregnancy will increase the risk of severe mental illness, fetal death, preterm birth and death. Pregnant women suffering from severe malaria in this area have a more than ten times possibly fatal risk than nonpregnant women suffering from severe malaria in the same area.

**ETIOLOGY**

Malaria is an infectious disease caused by Plasmodium parasites that enter the human body, transmitted by the anopheline tina mosquito (WHO 1981). The four Plasmodium species that cause malaria in humans are: *Plasmodium falciparum* (P. falciparum), *Plasmodium vivax* (P. vivax), *Plasmodium ovale* (P. ovale), *Plasmodium malariae* (P. malariae). The types of Plasmodium commonly found in Indonesia are P. falciparum and P. vivax or a mixture of both, while P. malariae is only found in East Nusa Tenggara and P. ovale is found in Papua.11

**DIAGNOSIS OF MALARIA IN PREGNANCY**

Malaria in pregnancy is confirmed by finding the malaria parasite in maternal blood and placental blood through biopsy. The clinical findings of malaria in nonimmune women (in non-endemic areas) varies from mild malaria without complications (uncomplicated malaria) with high fever, until severe malaria (complicated malaria) with a high risk for both mother and fetus (20-50% maternal mortality rate and often fatal to the fetus).11

**Clinical diagnosis (without laboratory examination)**

1) Mild/uncomplicated clinical malaria. On the history, malaria should be suspected in a person from a malaria-endemic area with acute fever in all forms, with/without other symptoms, there is a history of travel to malaria-endemic areas in the last two weeks, or history of living in a malaria area or malaria treatment. On physical examination can be found temperature >37.5°C, an enlarged spleen and anemia. The typical classic malaria symptoms consist of 3 successive stages, namely chills (15 - 60 minutes), fever (2-6 hours), and sweating (2-4 hours). The classic symptoms above do not appear sequentially. Not all of these symptoms can be found. Apart from the classic symptoms above, other symptoms / local specific symptoms may also be accompanied, such as weakness, headaches, myalgia, abdominal pain, nausea/vomiting, and diarrhea.12

2) Severe clinical malaria / with complications. Severe malaria / complicated malaria is a serious and dangerous form of falciparum malaria, which requires immediate and intensive treatment. Therefore, it is very important to recognize the signs and symptoms of severe malaria for health service units to reduce malaria mortality. Some of the important diseases similar to severe malaria are meningitis, encephalitis, septicemia, typhoid fever, viral infection, etc. This causes laboratory tests to be urgently needed to add strength to the diagnosis.12

**Laboratory diagnosis (by examination of blood slides)**

Microscopic examination is still the most important examination in malaria because the interpretation of this examination can...
Table 2. Classification of antimalarial drugs

| Antimalarial drugs | Oral dosage | Safety in pregnant women |
|--------------------|-------------|--------------------------|
| Chloroquine        | 25 mg base / Kg for 3 days (10 mg/Kg day I-II, 5 mg/Kg day III) | Safe for all trimesters |
| Amodiaquin         | 25 mg base/Kg for 3 days | Not recommended for the 1st trimester |
| Sulfadoxine-Pyrimethamine (SP) | Sulfadoxine: 25 mg/Kg | Not recommended for the 1st trimester |
| Mefloquine         | Pyrimethamine: 1 mg/Kg | Not recommended for the 1st trimester |
| Kinin              | 10 mg salt / Kg every 8 hours or 5 - 7 days | Safe for all Trimester |
| Artesunate         | 10-12 mg / Kg per day for 2-3 days | Not recommended for the 1st trimester |

General treatment at stage I:
- For fever, if the rectal temperature is >39°C, then compress it and give an antipyretic (paracetamol 3-4x500 mg/day).
- Pregnant women with anemia may be given packed red cell (PRC) transfusions.
- Hypoglycemia (blood sugar levels <40 mg%) often occurs in pregnant women both before and after quinine therapy. Occurs due to increased metabolic requirements at fever, tissue hypoxia. Another cause is thought to be an increase in glucose uptake by the malaria parasite. Actions:
  1. Give 50 - 100 ml Glucose 40% IV by bolus injection.
  2. Infusion of 10% glucose slowly for maintenance / preventing recurrent hypoglycemia.
  3. Regular monitoring of blood sugar levels every 4-6 hours.
- Cerebral malaria. Sufferers must be cared for with care, fluid balance and level of consciousness considered. Can be given an injection of 10-15 mg/kg intramuscular sodium phenobarbium in a single dose, and if a seizure occurs, diazepam 0.15 mg/kg BW intravenously (maximum 10 mg) can be given.
- Pulmonary edema. This is a fatal complication that often leads to death because severe malaria should be treated to prevent pulmonary edema. The patient may cough, shortness of breath, rapid and shallow breathing. On auscultation, he hears full crackles in all parts of the lung. Chest X-ray shows a large infiltration across the lung field. If there are signs of acute pulmonary edema, the patient is immediately admitted to the intensive care unit (whenever possible).
- For patients with severe malaria infection, empirical treatment with quinine or SP is resistant;
- Close monitoring of uterine contractions and fetal heart rate (CTG monitoring) to monitor fetal emergencies early.
- If monitoring shows signs of fetal emergency at delivery, it is an indication to end with cesarean section.

identify the type of Plasmodium accurately and count the number of parasites so that the degree of parasitemia can be known.

One laboratory test is an examination by microscope:
1. Giemsa’s stain on the blood smear to look for parasites
2. Acidine Orange stain to look for infected erythrocytes
3. Quantitative Buffy Coat (QBC) Fluorescence Check

Meanwhile, examination of thick and thin blood samples at the health center/hospital is used to determine the threshold value and determine the density of parasites (especially hospitalized patients) in blood samples. In areas with laboratory facilities and microscope personnel, malaria diagnosis is based solely on clinical examination (history taking and physical examination) without laboratory examination.

MANAGEMENT OF MALARIA IN PREGNANCY

Management of malaria in pregnancy depends on the degree of transmission and the surveillance of the following factors during pregnancy in all health lines.
- Monitor maternal and fetal health, as well as pregnancy progress.
- Prompt (timely) diagnosis and treatment.
- Admission of chemoprophylactic drugs for the mother.
- Personal protection to prevent contact with vectors, for example, the use of a mosquito net.
- Pregnant women with severe malaria infection should be admitted to an intensive care unit (whenever possible).
- For fever, if the rectal temperature is >39°C, then compress it and give an antipyretic (paracetamol 3-4x500 mg/day).
- Pregnant women with anemia may be given packed red cell (PRC) transfusions.
- Hypoglycemia (blood sugar levels <40 mg%) often occurs in pregnant women both before and after quinine therapy. Occurs due to increased metabolic requirements at fever, tissue hypoxia. Another cause is thought to be an increase in glucose uptake by the malaria parasite. Actions:
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referred to them, and before that, the following actions are taken:
1) Administration of highly concentrated oxygen to correct hypoxia
2) Limitation of provision of fluids
3) If anemia is accompanied, give a PRC transfusion.
4) To reduce the burden on the right heart can be done:
   • Position of the patient ½ sitting.
   • Administered furosemide 40 mg iv if necessary repeated 1 hour later or the dose is increased to 200 mg (maximum) while monitoring the urine output and vital signs.
   • Venaseksi, remove the patient's blood into a transfusion/donor bag as much as 250-500 ml will greatly help reduce tightness. If the patient's condition is normal, the blood can be returned to the patient.
5) Chloroquine is the safest drug of choice given to pregnant women (safe in 3 trimesters of pregnancy) at a 25 mg/kgBW for 3 consecutive days or on days I-II as much as 600 and on day III as much as 300 mg. If chloroquine resistance is found, quinine can be given at a dose of 3x400 mg for 7 days.

Pregnant women with severe malaria are given an infusion of chloroquine at a dose of 10 mg/kgBW in isotonic fluids at a constant rate for 8 hours and followed by 15 mg/kgBW for the next 24 hours or with chloroquine at a dose of 5 mg/kgBW given by constant speed for 6 hours and repeated every 6 hours for a total of 5 doses. Another alternative can be given quinine dihydrochloride 20 mg/kgBW intravenously for 4 hours in 5% dextrose and a maintenance dose of 10 mg/kgBW every 8-12 hours until the patient receives the drug orally.

General treatment at stage II
Within the first 6 hours, then if there are no contraindications for vaginal delivery, the indication for delivery by vacuum extraction/forceps depends on the indication for the obstacle course.

Management of severe malaria in pregnancy
Treatment of severe malaria requires speed and accuracy in the earliest possible diagnosis. For each patient with severe malaria, the following actions/treatments need to be done are: general/symptomatic action, providing anti-malarial drugs, treatment of complications.

Improve the general condition of the patient (administration of fluids and general care). Administration of fluids is a very important factor in the management of severe malaria. If it is excessive, it will cause pulmonary edema. On the other hand, if it is not enough, it will cause acute tubular necrosis, which results in acute renal failure.

Monitoring of vital signs includes: general condition, awareness, respiration, blood pressure, temperature and pulse every 30 minutes (always recorded for progress), uterine contractions, and fetal heart sounds should also be monitored. Keep Street breath to avoid asphyxia. Give oxygen if necessary. Giving antipyretic to prevent hyperthermia: paracetamol 10 mg/kg BW / x, and compresses can be done.

If convulsions, give anti-convulsants: Diazepam 5-10 mg IV (slowly over 2 minutes) repeat 15 minutes later if still seizures. Do not give more than 100 mg/24 hours. If Diazepam is not available, as an alternative, Phenobarbital 100 mg IM/ x (adult) can be used twice a day. To confirm the diagnosis, perform a thick SD examination. Assessment according to microscopic diagnostic criteria. If adequate facilities are not available, prepare the patient for a higher level of health care that provides intensive care.

Chemoprophylaxis malaria in pregnancy
WHO recommends giving a dossier treatment (dose antimalarial therapy for all pregnant women in malaria-endemic areas at the first ANC visit, later followed by regular chemoprophylaxis. Currently, the malaria treatment policy in Indonesia requires only the use of chloroquine for prophylaxis in pregnancy. Pregnant women with nonimmune status should be avoided from entering malaria-endemic areas.

Prophylaxis is started 1 to 2 weeks before visiting endemic areas, with chloroquine (300 mg base) given once a week and continued for up to 4 weeks after returning to non-infectious areas (Bradley and Warhurst, 1995). Several studies have shown that chemoprophylaxis reduces maternal anemia and increases the weight of babies born.

PREVENTION MALARIA IN PREGNANCY

Contact between mothers and vectors can be prevented by wearing a mosquito net dipped with insecticide (e.g., permethrin), wearing long trousers and long-sleeved shirts, use of mosquito repellents, use of mosquito netting on doors and windows. Any woman who lives in endemic areas or will travel to endemic areas should be given chemoprophylaxis. Although this does not provide absolute protection against malaria infection, it can reduce parasitemia, prevent severe malaria complications, and increase baby body weight.

Chloroquine is the safest drug for pregnant women, with a dose of 300 mg base (2 tablets) every week. For pregnant women who will travel to malaria-endemic areas, the provision is started one week before leaving, while in the endemic area, up to 4 weeks after leaving the area.

Another effort to prevent malaria infection is to break the chain of transmission to the host, agent or environment by:

a) Reducing contact / Anopheles mosquito bite by using a mosquito net, mosquito repellent
b) Kills adult mosquitoes
   c) Kills mosquito larvae.
d) Increase power hold on the body through vaccination.

Severe complications of malaria is severe anemia, so the prevention of anemia begins at this point: give iron supplements: 300 mg ferrosus sulfas (60 mg elemental iron)/day, and 1 mg folic acid / day, for the treatment of moderate anemia (Hb 7-10 g / dl), a 2x-fold iron dose is given, check Hb every ANC control.

CONCLUSION

Based on the analysis that has been done, it can be concluded that the 3 types of
plasmodium parasites that cause the highest malaria cases in Aceh Province are plasmodium vivax, plasmodium falciparum and Plasmodium knowlesi. K-means clustering analysis shows that most areas of Aceh Province have a low level of vulnerability to malaria cases. The 3 areas most vulnerable to malaria cases in Aceh Province are Aceh Jaya District, Sabang City and South Aceh District. Recommendations that can be given to the Government of Aceh, especially the Aceh Provincial Health Office, to pay special attention to eliminating malaria cases in Aceh Jaya District, Sabang City and South Aceh District, the highest level of susceptibility to malaria cases compared to other districts/cities. For people who live in these three areas, it is hoped that they will be more concerned with the factors that cause malaria and participate in the success of government programs in efforts to eliminate malaria cases in Aceh Province.

Our study limitation was the results of this review article have a lack of data regarding the incidence of malaria in pregnancy in Aceh that has not been well documented, therefore the fetomaternal outcome from case to case cannot be evaluated directly, research is needed to better record malaria cases in this pregnancy.

CONFLICT OF INTEREST
The authors declare there is no conflict of interests.

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AUTHOR CONTRIBUTION
CRM as a specialist in obstetrics and gynecology, she’s the woman in charge of investigating this article review and final editing and review in drafting the manuscript. CMY as a fetomaternal consultant in obstetrics and gynecology prepares the design, and review the manuscript. DMA is a resident in obstetrics and gynecology department search the literature, clinical studies and editing manuscripts. All authors discussed the results and commented the manuscript.

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