Relationship between Malaria and Hypertensive Disorders in Pregnant Women in East Nusa Tenggara (Case Report)

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ABSTRACT

East Nusa Tenggara is one of high endemic malaria area in Indonesia. Because of malaria infection, many pregnant women suffer severe complications in pregnancy; one of them is hypertensive disorders. Placental Malaria (PM) has a close relationship with hypertensive disorders in pregnancy. Two cases in Karitas Hospital, Southwest Sumba, East Nusa Tenggara, area with high endemic malaria, were reported: the first is hypertension in pregnancy and the other is preeclampsia. Both babies suffered from low birth weight. Early detection through regular ANC and improved community empowerment, will decrease maternal morbidity and mortality, prevents IUGR (Intrauterine Growth Retardation) and fetal death.

Keywords: pregnant women, malaria, hypertensive disorders, East Nusa Tenggara

INTRODUCTION

Indonesia has a population of 230 million in 2007. Since the last five years, Indonesia have had nearly 350,000 confirmed cases and 1.25 million – 2.50 million probable malaria cases, 45%–50% of them are Plasmodium falciparum cases; around 500 confirmed malaria deaths are reported every year. Cases of malaria are caused by all four known species of human Plasmodium with the highest concentration in eastern part of Indonesia, such as Nusa Tenggara, Maluku, and Papua. Plasmodium falciparum and vivax are the most common species. Karitas Hospital medical file records both falciparum and vivax.

Malaria in pregnancy cause several problems for the mother and her baby. Roll Back Malaria, a global partnership to reduce malaria, notes that “Pregnant women resident in areas of low or unstable malaria transmission are at a two- or threefold higher risk of developing severe disease as a result of malaria infection than are non-pregnant adults living in the same area”. This condition can cause spontaneous abortion, neonatal death, and Low Birth Weight (LBW). In high and moderate (stable) areas of malaria transmission, pregnant women usually suffer malaria-related anemia, placental malaria, neonatal death, and Low Birth Weight (LBW). Pregnant women with malaria infection have serious problems, such as severe anemia, hypertension, preeclampsia, neonatal death, and IUGR (Intrauterine Growth Retardation).

This paper analyzes two cases of malaria and hypertensive disorders in Karitas Hospital. The findings were compared with various literatures.

RELATIONSHIP BETWEEN MALARIA AND HYPERTENSIVE DISORDERS IN PREGNANCY

1. Plasmodium falciparum sequestration in placenta

Hypertensive disorders in pregnancy are caused by many factors that influence the attachment and condition of placenta. One of those factors is Placental Malaria (PM). Placental Malaria is caused by Plasmodium falciparum infection in pregnancy. Parasite antigens expressed on the surface of infected erythrocytes bind to specific adhesion receptors in placenta, especially chondroitin sulphate A, and result in parasite sequestration in placenta, which is responsible for many harmful effects of malaria during pregnancy. Plasmodium sequestration can thicken basal membranes and induce infiltration of monocytes in the intervillus...
spaces of placenta (intervillositis). Those histopathological changes increased barriers to the oxygen transport across placenta that will lead to placental and fetal hypoxia.

Placental malaria usually affects primigravida because they do not have enough antibodies to prevent adherence of infected erythrocytes. It also causes low birth weight (LBW) in newborn babies. Women with sub-microscopic level of P. falciparum infection (detected by real-time PCR) at delivery had a 13-fold increased risk of delivering a child with low birth weight compared with non-infected pregnant women. Women with microscopically detectable P. falciparum infection also have a 2-fold increased risk for low birth weight compared with women with a sub-microscopic infection.

2. Malaria and its correlation with hypertensive disorders (hypertension and preeclampsia)

Hypertension and preeclampsia are two kinds of hypertensive disorders in pregnancy. Large amount of protein in urine, low protein level in blood, and body edema were found in preeclampsia. In Sri Lanka (1935), “Epidemic of . . . toxemic pregnancies followed in the wake of malaria epidemic, with hypertension in 20%, albuminuria in 40%, edema in 50%, and death in 13% of 357 infected women”.

Malaria during pregnancy is associated with hypertension in young primigravida, but not in older or multigravida. Hypertensive PM-positive women were significantly younger than normotensive PM-positive women, and also had a trend toward lower parity. Maternal-fetal conflict involving the VEGF pathways occurs during PM, and that sVEGFR1 (placentally derived soluble vascular endothelial growth factor receptor 1) may be involved in the relationship between chronic PM and hypertension in first-time mothers. Serum levels of sVEGFR1 are elevated prior to and during preeclampsia. Levin et al. and Maynard et al. notes this agent causes systemic endothelial dysfunction by binding and sequestering free serum vascular endothelial growth factor (VEGF) and placental growth factor. Another research conducted by Ndoo et al. in Senegal found that prevalence of PMI (Placental Malaria Infection) was 4.6% for eclampsia (severe preeclampsia), 4.0% for preeclampsia, and 11.6% for gestational hypertension. In multivariate analysis, PMI appeared to be an independent risk factor for gestational hypertension (adjOR = 2.7%, 95%CI: 1.0, 7.6). They also found an association between PMI and nonproteinuric hypertension in women living in a malaria-hypo endemic area.

3. Pathophysiology of hypertensive disorders (hypertension and preeclampsia) caused by malaria infection

Hypertension diseases (gestational hypertension, preeclampsia, and eclampsia) are the most common medical disorders during pregnancy. In West Africa, hypertension during pregnancy is the third leading cause of maternal severe morbidity (after hemorrhage and dystocia) and the second leading cause of maternal death principally due to eclampsia. Preeclampsia cases is about 5-15% of all pregnancy in the world. In Cipto Mangunkusumo Hospital, there are 400-500 cases/4000-5000 pregnancy per year.

The pathophysiologic mechanisms of preeclampsia and PMI (Placental Malaria Infection) are similar, including placental ischemia, endothelial dysfunction, and production of pro-inflammatory cytokines. More recently, in 2006 in Tanzania, Muehlenbachs et al. have suggested that maternal-fetal conflict involving the inflammatory mediator, vascular endothelial growth factor pathway, occurs during placentar malaria and that its inhibitior, soluble vascular endothelial growth factor receptor 1, may be involved in a possible relation between chronic PMI (Placental Malaria Infection) and hypertension in primigravidas.

Recently, endothelial dysfunction is considered as a causing factor in the pathogenesis of preeclampsia. An endothelial dysfunction caused by several factors such as hemodynamic shear stress, oxidative stress, inflammatory cytokines, and hypercholesterolemia, may disrupt the regulatory function. This condition may disrupt vasomotor substance balance and hypertension can occur. If there is an endothelial dysfunction, vascular cell adhesion molecule-1 (VCAM-1) and intercellular cell adhesion molecule-1 (ICAM-1) will be expressed in the surface of the endothelium, increasing vascular permeability and causing edema and proteinuria.

In most preeclampsia patients, sVCAM-1, vWF (von Willebrand factor) were increased and monomer fibrin was also found. It is concluded that endothelial dysfunction occured in preeclampsia. It is also suggested that there was a correlation between endothelial dysfunction (marked by increasing of sVCAM-1 and vWF) and severity of the disease (as indicated by systolic and diastolic blood pressure and severity of proteinuria).

Malaria Prevention During Pregnancy

Malaria during pregnancy can be prevented, reduced, and managed with appropriate, low-cost interventions through providing Focused Antenatal Care (ANC) with health education on malaria, using intermittent preventive treatment (IPT), insecticide-treated bed nets (ITNs), and also case management.

The interventions must emphasize on two approaches. Those approaches focus on appropriate preventive measures in asymptomatic pregnant women during antenatal care and effective case management for all clinical cases.

The goals of Focus on Antenatal Care (ANC) are to promote maternal and neonatal health and survival through early detection and treatment of problems and complications, prevention of complications and disease, birth preparedness and complication readiness, and health promotion. They also add essential elements of a birth plan such as facility or place of birth, skilled provider, provider/facility contact information, transportation, funds, decision-making, family and community support, blood donors, needed items, dangers signs/signs of advanced labor.

Intermittent preventive treatment (IPT) is another intervention to reduce malaria in pregnancy. All pregnant women in areas of stable transmission (recommended, in areas of unstable transmission), should take a single dose of SP (Sulfadoxin-pyrimethamin) (three tablets, each containing 500 mg of sulfadoxin and 25 mg pyrimethamin at the first antenatal visit after fetal movement begins (quickening) and at each subsequent antenatal care visit; but no more often than monthly until delivery. 
Insecticide-treated bed nets (ITN) can also be used for intervention in pregnant women; it will kill mosquitoes that touch the net's surface.  

In endemic areas, case management also plays an important part in reducing malaria in pregnancy. Screening for malaria signs and symptoms should be a routine part of antenatal care. Women with uncomplicated malaria (fever with or without symptoms such as chills, headache, body/joint pain, and loss of appetite) should be treated with antimalarial and iron/folate with intensive monitoring. Severe malaria (fever/recent history of fever with complications such as unconsciousness or convulsions, rapid or difficult breathing, severe vomiting and/or dehydration, weakness/fatigue, pulmonary edema or hypoglycemia) need doctor consultation for stabilization, administration of antimalarials and iron/folate, blood transfusion, and other life-saving measures.  

**CASE REPORT**  

This paper will report two cases in Karitas Hospital, East Nusa Tenggara. The first case is a 30-year-old primigravida, 7 months pregnant, with severe headache, fever, and nausea. Her vital sign shows high blood pressure (170/100 mmHg) and high body temperature (39°C). *Plasmodium falciparum* was found in peripheral blood examination (+++). The second case is a 25-year-old primigravida, 8 months pregnant, with fever, nausea, vomiting, general edema, and blurred vision. Vital sign shows high blood pressure (200/100 mmHg) and high body temperature (38°C). Urinalysis shows proteinuria (++++)+. No plasmodium was found in blood examination.  

Both are primigravidas who have a greater risk of being infected by *Plasmodium falciparum* and one have a high level of parasitemia. They also have lower antibodies to prevent plasmodium sequestration in placenta.  

They all have clinical symptoms of malaria: fever, shivering, nausea, and vomiting, but *Plasmodium falciparum* is found in only one patient. In areas of intense and stable transmission, the absence of evidence of plasmodia in the peripheral blood on a single occasion does not exclude diagnosis of infection. Parasitemia can fluctuate and be kept under the level of detection (total biomass about 10⁸ parasites) by acquired immunity or self-medication, and *Plasmodium falciparum* can sequester in the placenta.  

Both patients were given treatments for hypertension and *Plasmodium falciparum* infection. Nifedipine and Magnesium Sulfate (MgSO₄) were given to lower blood pressure and prevent convulsion. Those patients were given nifedipine 5 mg sublingually. In addition, 4 g of MgSO₄ 20% was given intravenously, slowly over 5 minutes, followed immediately with 10 g of 50% MgSO₄ solution, 5 g in each buttock as deep IM injection with 1 ml of 20% lignocaine in the same syringe. Intravenous quinine was administered to eliminate parasites. The dose was 20 mg/kg body weight in 500 ml dextrose 5% solution in the first 4 hours, then for the second 4 hours only dextrose 5% solution was given. Maintenance dose 10 mg/kg body weight of quinine in 500 ml dextrose 5% solution was administered for another 4 hours. Paracetamol tablets 500 mg 3 times a day was also given to relieve fever.  

Condition of fetus was examined with USG (Ultrasoundography). The estimation of fetus weight was 2,450 grams for patient A and 2,300 grams for patient B. The heart rates were normal. Patients delivered their babies normally. The babies’ weights were 2,450 grams and 2,300 grams; slight low birth weight (< 2,500 grams). They cried directly after birth, showing no hypoxia, and had normal heart rates.  

Both patients had severe hypertension (170/100 mmHg and 200/100 mmHg) with signs and symptoms of preeclampsia (headache, edema, blurred vision, and severe proteinuria). They also have malaria infection. Malaria may become the possible risk factor for hypertensive disorders such as hypertension and preeclampsia.  

**DISCUSSION**  

It is important to diagnose malaria in pregnant women who have clinical symptoms of malaria but *Plasmodium falciparum* cannot be found in their peripheral blood examination. It is also important to confirm *Plasmodium falciparum* infection either by microscopic examination (the current gold standard) or by use of a rapid diagnostic test that detects a specific parasite antigen. This confirmation has two benefits. First, if they are infected, they have a greater risk having placental malaria that will harm their babies. Placental malaria can be prevented using appropriate drugs for *Plasmodium falciparum* infection to prevent placental hypoxia, fetal hypoxia, and fetal growth retardation (FGR). The other benefit is to avoid unnecessary exposure of mother and fetus to antimalarial drugs.  

Peripheral blood examination (microscopic test) for confirmation of *Plasmodium falciparum* infection in pregnant women seems insufficient because many asymptomatic cases with low parasite densities and parasites sequestered in placenta cannot be detected. Recently, rapid diagnostic tests have been developed. Such tests are practical but do not have the sensitivity needed in pregnancy. PCR is used in research settings for genotyping and detection of malaria parasites and is marginally more sensitive than microscopy.  

Microscopic blood examination or rapid diagnostic test can be done on pregnant woman presents with symptoms (or a history of symptoms) compatible with malaria, or as part of systemic antenatal screening (bearing in mind on the limitations in detection). In all malarious area, blood test for malaria should be done in a pregnant woman during every antenatal consultation and positive cases are treated appropriately.  

**CONCLUSION**  

Both patients show clinical symptoms of malaria and hypertensive disorder, but plasmodium was found only in one patient. Since plasmodium sequestrated in placenta, it might not appear in blood; placental histopathological examination should be conducted. These two cases also illustrates that malaria infection affects mothers and their babies. The mothers suffered from hypertension and preeclampsia, while the babies had low birth weight.  

Malaria in pregnancy, especially *Plasmodium falciparum*, increases morbidity and mortality of mother and babies. *Plasmodium falciparum* infection and hypertensive disorder have a close relationship.  

Clinicians must be aware and pay attention to pregnant women with clinical symptoms of malaria even when plasmodium is not found. Patients have to be advised and
given explanation on signs and symptoms of hypertensive disorder and should go to the nearer health services as soon as possible for treatment. Early detection of hypertensive disorder can decrease maternal morbidity and maternal mortality rate. It also prevents IUGR (Intrauterine Growth Retardation) and fetal death.

Most maternal death in Sumba Island is caused by three delays: delay in making decision, delay in reaching health care services, and delay in receiving health care services. Many women do not know symptoms of high risk pregnancy and come very late to hospital. In addition, the infrastructure (road and transportation) in that area is bad; it takes 3 to 4 hours to reach the hospital. The key solution to tackle these three delays is ANC (Antenatal Care) Program. This program will increase their knowledge on high risk pregnancy and effects of malaria on their pregnancy. During visit, the condition of pregnancy can also be examined. Community empowerment is another way to solve these three delays. Families of the pregnant women are taught in high risk pregnancy symptoms and to prepare patient’s transportation in case of emergency. Early detection and treatment can prevent serious problems and complications. Prevention, early detection, and early treatment of malaria infection are also important for pregnant women to reduce complications.

BIBLIOGRAPHY