Severe malaria in a pregnant woman successfully treated with Artemisinin-based Combination Therapy (ACT)*

By Stephanie Marie S. Aquino, MD and Angela A. Du, MD, FPOGS

Department of Obstetrics and Gynecology, Manila Doctors Hospital

ABSTRACT

Malaria is suspected in pregnant women with fever of unknown origin who come from areas with high transmission of the disease. Pregnant women are at greater risk of infection due to a weakened immune response and higher parasite burden because of placental sequestration. A 26-year-old Sudanese primigravid 23 6/7 weeks of gestation presented at our institution with mixed infection of malaria, with severe features (hypotension and anemia). Malaria was highly suspected due to her country of origin, which was highly endemic and has high transmission of the disease. Fetal surveillance to monitor fetal well-being was done since malaria is known to cause perinatal adverse outcomes. Intrauterine growth restriction, preterm labor and stillbirth are the most common perinatal morbidity from malaria. These are not present in the patient due to the prompt initiation of artemisinin-based combination therapy, which significantly decreased the parasite load, leading to successful outcome.

Keywords: Malaria, Malaria in Pregnancy, artemisinin combination therapy

INTRODUCTION

Malaria is one of the most severe public health problems worldwide. It occurs most commonly in the poor, tropical and subtropical areas of the world. In the Philippines, it has been said that malaria cases declined to at least 83% reduction from 2005 to 2013 and of the 53 known provinces that are endemic of the disease, 27 of which have been declared malaria-free (Cavite, Batangas, Marinduque, Catanduanes, Albay, Masbate, Sorsogon, Camarines Sur, Iloilo, Aklan, Capiz, Guimaras, Bohol, Cebu, Siquijor, Western Samar, Eastern Samar, Northern Samar, Northern Leyte, Southern Leyte, Biliran, Camiguin, Surigao Del Norte, Benguet, Romblon, Batanes, and Dinagat Islands).

Malaria is transmitted through the bite of infected female Anopheles mosquitoes. The problems that malaria infection causes differ by the type of malaria transmission area. Persons who live in an area with high transmission of the infection have developed immunity against it, causing a lesser degree of morbidity and mortality. Moreover, those who live in areas with low transmission have no immunity against it, causing severe and fatal malaria disease. Pregnant women are at higher risk of having the infection because of a weakened immune response, thereby causing fatal disease and contribute to as much as 15% of maternal anemia, 14% of low birth weight infants, 30% of preventable low birth weight, 70% of intrauterine growth retardation, 36% of premature deliveries and 8% of infant mortality. Placental sequestration of the parasite, also known as placental malaria, is the main reason why these complications happen. Higher parasite burden is observed in pregnant patients, causing severe disease, warranting prompt treatment.

This paper presents a case of malaria in pregnancy seen in a tertiary hospital Obstetrics and Gynecology Department successfully treated with Artemisinin-Based Combination Therapy (ACT).

CASE REPORT

This is a case of MT, a 26-year-old, 23 6/7 weeks of gestation, primigravid resident and citizen of Khartoum, Sudan, came to the emergency room due to intermittent fever, associated with one episode of nonbilous and nonbloody vomiting. It is not associated with chills, cough, dysuria, hypogastric pain nor diarrhea. Past medical history, family history and personal/social history were all unremarkable.

On assessment, patient was febrile at 39˚C, tachycardic at 142bpm, with BP of 100/60mmHg. She was initially managed by emergency medicine service, hydrated and given paracetamol 600mg/IV. Laboratory tests showed mild anemia with haemoglobin of 101g/L, hematocrit of 30%, and thrombocytopenia at 107,000, normal urinalysis results. Patient was tested for Dengue and showed negative results. Since patient originated from Sudan, which is highly endemic to malaria, malaria rapid antigen test was requested and showed positive for

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P. falciparum and non-*P. falciparum* species, suggestive of mixed infection. For confirmation, malarial blood smear was requested and showed 7,400,000 ring forms/uL of blood.

With the patient's history of recent travel to different countries, including Dubai, the diagnosis of *Ebola, Zika* and *MersCoV* were considered. She was asked to fill up a *"Triage Screening Form"*, which screens for these possible infections. These were ruled out because the signs and symptoms of the said disease such as, abdominal pain, headache, anorexia, bleeding from any site, sore throat, cough or other respiratory symptoms were absent in the patient. Also, patient did not come from countries that are endemic for the disease: Guinea, Liberia, Sierra Leone, Nigeria, with no exposure to persons or animals that were infected with the disease. Patient was then admitted under the service of OBGYN, comanaged with OBGYN-Infectious Disease, with admitting diagnosis of G1P0 Pregnancy Uterine 23 6/7 weeks Age of gestation, not in labor, malarial infection.

Upon admission, patient is still febrile at 38.4˚C, tachycardic at 142bpm, BP of 100/60mmHg, with unremarkable physical examination findings. Abdomen was globular with fundic height of 24 cm and fetal heart tones of 150 bpm. Patient was hydrated with IV fluids and was started on the following medications: clindamycin 450mg every 8 hours, hydroxychloroquine 500mg OD 400mg for 3 days (Source: WHO Treatment Guidelines) and paracetamol 500mg for fever. Fetal heart tones were monitored closely. Nonstress test was reactive with category I tracing of FHT 145-150bpm, moderate variability, with accelerations, no decelerations, with good fetal movement and no uterine contractions noted. Ultrasound to ensure fetal well-being was done showing, "Single live intrauterine pregnancy, 23 5/7 AOG, Breech presentation, good cardiac (FHR 140 bpm) and somatic activity, Estimated fetal weight 636 grams (p10-50), Adequate amniotic fluid volume (SVP=6.57cm), Placenta posterior, grade II, high lying", given multivitamins for the pregnancy. 24 hours later, repeat CBC showed a drop of haemoglobin from 108 to 81 and haematocrit from 30% to 23%, still with thrombocytopenia at 60,000. Two units packed RBC were transfused. Post-blood transfusion showed hemoglobin of 90 and haematocrit of 25%. CBG monitoring was done every 6 hours, with no hypoglycemic episodes noted.

On the 2nd hospital day, patient still had febrile episodes, with highest temperature of 40˚C, with hypotensive episodes of 100/40mmHg. Blood pressure trends were observed, with BP range of 90-100/40-60mmHg. 24 hours after hydrochloroquine and clindamycin, repeat peripheral smear showed increase in ring forms of 13,980,000 ring forms/uL of blood. Patient was referred to IM-Infectious Disease service, who recommended artemisinin-combination therapy (artemether-lumefantrine) based on the National Protocol for Treatment of Malaria in Khartoum, Sudan. However, artemisinin combination therapy is not readily available in the National Capital Region, Philippines, so treatment was delayed. ACT was only made available through the Department of Health at the 5th hospital day.

On the fourth hospital day, patient still febrile with one episode of vomiting, associated with epigastric pain, with poor appetite, and headache. Patient was put on small, frequent feedings. Electrolytes were requested with note of hypokalemia of 2.1mmol/L, correction was started with KCl drip, with post-correction value of 2.9mmol/L. She was started on oral KCl once vomiting ceased.

Treatment with ACT (artemether-lumefantrine) was started at the recommended dosage and frequency at the 5th hospital day. The other medications: hydroxchloroquine and clindamycin were discontinued. On assessment for the pregnancy, there were 2 moderate to strong uterine contractions noted in 15 minute palpation, with good fetal movement, FHT 160s. Nonstress test showed reactive with category I tracing, with BFHR of 150-155bpm, moderate variability, with accelerations, no decelerations, with uterine contractions every 2-4 minutes, mild to moderate. On internal examination, cervix is closed, soft, and 2.5cm long. She was started on nifedipine 10mg every 8 hours. Post-nifedipine tracing was reactive with BFHR of 150-155bpm, moderate variability, with accelerations, no decelerations, no uterine contractions.

One day after ACT was started, patient was afebrile with no recurrence of vomiting and no hypotensive episodes. Daily malarial parasite count showed a significant decline after one day of therapy from 13,980,000 ring forms to 4,980,000 ring forms/uL. This suggests that the parasite was susceptible to ACT. In Sudan where our patient is from, chloroquine-resistant malaria is present, hence, artemisinin-based combination therapy is the treatment of choice.

On the sixth hospital day, patient was afebrile with no subjective complaints and no perceived uterine contractions. Malarial parasite count progressively declined to 785,454 ring forms / uL of blood. Potassium was normal at 4.9mmol/L. Patient was eventually discharged on the 3rd day of artemether-lumefantrine, improved and stable.

CASE DISCUSSION

Malaria is an infection with Plasmodium species with the female Anopheles mosquito as the vector. Rupture of red blood cells during the erythrocytic stage of the life cycle of the parasite is responsible for the clinical symptoms. If

severe, this may cause haemolytic anemia and jaundice, which are worsened by splenic sequestration of infected red blood cells. When exposed to the parasite, splenic macrophages release pro-inflammatory cytokines (TNF-alpha, IL-1B) which causes nonspecific symptoms, such as fever, chills, generalized malaise and headache, which are all similar to any minor viral illness.

Of the four plasmodium species, Plasmodium falciparum is the specie that can cause the most severe disease because of its microvascular effects. The falciparum-infected red blood cells express surface proteins, which will cause attachment of the RBCs to the adhesion molecules in the vascular endothelium. This will cause adherence of infected RBCs to uninfected RBCs forming a rosette pattern and agglutination. These agglutinated cells will cause obstruction of the vessels, leukocyte infiltration in the tissues, thereby local inflammation and edema. Obstruction of vessels in different organs is the main pathogenesis of the different complications of malaria, such as cerebral malaria causing brain edema that can be fatal, pulmonary edema that can cause acute respiratory distress syndrome, renal impairment causing metabolic acidosis and placental malaria that cause pregnancy complications and poor birth outcomes.

According to Mesbnick, et.al (2008), the adhesion molecule that is associated with placental malaria is chondroitin sulphate A (CSA) and hyaluronic acid, which are expressed by the syncytiotrophoblast that line the placenta intervillous spaces. There are three specific changes in the placenta once infected: 1) the mature trophozoites and schizont parasite accumulate in the intervillous spaces, 2) intervillous infiltrates of monocytes and macrophages, some containing with the malarial pigment (hemozoin), 3) malarial pigments in fibrin deposits that can persist after resolution of episodes of infection. These changes are associated with poor birth outcomes. Placental sequestration of the infected RBCs will cause obstruction of flow from the maternal to the fetal circulation, causing fetal hypoxia, decreased nutrient uptake, impaired growth and vascularization, intrauterine growth retardation and preterm delivery, thereby causing low birth weight.

Malaria in pregnancy causes risk to both pregnant women and baby. It causes more mortality and morbidity than those of non-pregnant women. This is due to the reduced immunity during the pregnant state, leading to more relapses, hyperparasitemia and worse clinical conditions. The most common manifestations of malaria in pregnancy are fever, anemia, splenomegaly, acute pulmonary edema, hyopglycemia and secondary infections.

For this case, the patient was classified with severe malaria, with the following clinical signs and symptoms: episodes of circulatory collapse (blood pressure <90/60mmHg), thrombocytopenia (61,000), severe anemia (as low as 80g/dL) and hyperparasitemia (>2% parasitized red blood cells).

The complications of malaria in pregnancy include algid malaria or shock, anemia, bleeding or coagulopathy, hemoglobinuria, acute renal failure and acute pulmonary edema. In the management of severe malaria in pregnancy, of importance is the management for anemia, hypoglycaemia and acute pulmonary edema. The patient only presented with shock, presented with hypotensive epidoses as low as 80/50mmHg and anemia with a haemoglobin of 80g/dL. For this, patient was hydrated and transfused with packed red cells.

Anaemia is a common presentation in malaria and it may be due to hemolysis of infected erythrocytes, which may be so significant that it may aggravate folic acid deficiency, and increased demands during pregnancy. According to Uneke (2008), anemia increases the risk of perinatal mortality and maternal morbidity and mortality. During labor, patients with severe anemia may not be able to tolerate mild to moderate blood loss, and failure of compensatory mechanisms may happen which can lead to maternal morbidity and mortality. Infants may be at risk for intrauterine growth retardation, stillbirth and low birth weight. Also, may cause iron deficiency to the infants, which may affect their behavioural and cognitive development. Malaria may affect iron status by decreasing iron absorption in the intestines, sequestrating iron in the malarial hemozoin, consuming iron for its metabolism, mobilization of iron stores and releasing it to the circulation during hemolysis.

In patients with malaria, hypoglycaemia is a complication of the infection due to the hypercatabolic state of the infecting parasite. CBG ranges were maintained to normal and no hypoglycemic episodes were noted in the patient. According to Ali, et.al (2011), glucose metabolism during malaria infection is due to multiple factors, such as drug treatment, fever, parasite metabolism, hormonal changes, cytokines, fasting and gastrointestinal disturbances. Patients who present with hypoglycaemia have higher mortality rates. Therefore, it is important to monitor glucose levels in patients with malaria because it can significantly affect its outcome.

Electrolyte disturbances are also common in patients infected with falciparum malaria. In a retrospective study made by Thanachartwet, et.al, (2008), 81% of the study population with uncomplicated malaria had electrolyte imbalances. The most common disturbance noted was hypokalemia (<3.4mmol.L), and hyperkalemia (>5,1mmol.L) in children, especially with those infected with P.vivax. Most of the patients present as clinically hypovolemic. They found out that volume depletion

is the most predominant risk factor in hypokalemia. They concluded that such disturbance in potassium is multifactorial and could be due to the urinary loss and shift of potassium from extracellular to intracellular. The factors that were noted to be associated with hypokalemia include Plasmodium vivax infection, female gender, fever before admission, hypovolemia, BUN:Cr ratio >15, hyponatremia and glucose >100mgdL. It is prudent to correct potassium concentration since it may cause increased risk of arrhythmias.

Treating the infection is of utmost importance. According to the WHO Guidelines for Malaria Treatment, first line in pregnant patients in all trimesters of pregnancy is oral quinine. In second and third trimester of pregnancy, quinine is combined with sulfadoxine-pyrimethamine or a combination of artesunate tablets. Antimalarial drugs that are safe in the first trimester of pregnancy include quinine, cholorquine, clindamycin and proguanil.

In uncomplicated malaria in pregnancy on the first trimester, seven days of quinine and clindamycin is recommended. According to WHO, the safest treatment regimen for pregnant women in the first trimester with uncomplicated malaria is quinine + clindamycin for 7 days. In the second or third trimesters, artemisinin derivatives are recommended. However, in patients with severe malaria, IV Quinine or IM Artemether is the treatment all throughout pregnancy. If patient can tolerate oral therapy, treatment may be completed for 3 days of artemisinin combination therapy (ACT). Since the patient had a mixed infection of falciparum and non-falciparum species, the treatment of choice is still ACT, that is, artemether-lumefantrine. Also, since the patient is from Sudan where 95% of the parasite is chloroquine-resistant, ACT is still the treatment of choice.

Artemisinin derivatives are the most effective antimalarials but are associated with terratogenic effects in animal studies especially in early pregnancy. However, according to Kovacs, et.al (2016), there was no increased pregnancy loss among women who received an artemisinin compared to women who received no antimalarial drug. ACT is recommended to be given to women, on the 2nd and third trimester of pregnancy, infected with malaria. However, in cases of mixed infection and severe malaria, it is given in early pregnancy since initiation of treatment outweighs the risk.

The regimen given to the patient is an artemisinin combination therapy (ACT). ACT is a combination of a rapidly acting artemisinin derivative with a longer acting partner drug. Artemisinin component rapidly clears the parasites from the blood, significantly decreasing parasite count. It is also active against the sexual stages of the parasite. The longer acting partner, which is lumefantrine in this case, clears the remaining parasites and provides protection against drug resistance.

It is important to decrease the parasite load of the mother so vertical transmission to the fetus is less. Congenital malaria is one of the complications of malaria in pregnancy where in transmission to the fetus occurs particularly when there is infection at the time of birth and the placenta and cord are blood film positive for malaria. Transplacental spread is deemed to be rare, especially in high-transmission areas, where immunity has been established. The placental barrier and immunoglobulin antibodies, cross the placenta, making the fetus immune to the infection. All four species of Plasmodium may cause congenital malaria. The newborn may present with fever, irritability, feeding problems, hepatosplenomegaly, anaemia, and jaundice.

The obstetrical dilemma here are, is it advantageous to tocolyze and control preterm labor? Is there benefit for induction of labor and termination of pregnancy?

Management of preterm labor in pregnant patients with malaria is the same as with those not infected with the disease. One of the main reasons of preterm labor is infection, so the main management in our case is to treat the underlying infection. According to Luxemberger et al, the risk of premature delivery and/or neonatal deaths was similar for other febrile illnesses such as acute respiratory infections or urinary tract infections, reflecting an effect of fever and illness rather than malaria per se. Therefore, routine obstetric management for preterm labor should be rendered to the patient. Also, according to the Royal College of Obstetrics and Gynecology Guideline, malaria is not a reason for induction of labor. Management of this case includes: treating the infection, controlling preterm labor, and surveillance of fetal well-being. Malaria during pregnancy is not a direct cause of neonatal mortality. It increases neonatal death indirectly by reducing birth weight, and low birth weight babies are more likely to die during the neonatal period.

In areas with high transmission rates of the infection, where women will have asymptomatic placental parasitemia, intermittent preventive treatment (IPT) is given to all pregnant women. According to the Sudan treatment guidelines, IPT includes therapeutic doses of sulfadoxine-pyrimethamine (SP), regardless of parasitemia status, under direct observation of a health care provider. The first dose is given at the first prenatal check-up after quickening at 16-20 weeks and the second dose is in the next prenatal visit at least four weeks apart from the first dose.

WHO updated the recommendation, increasing the number to three or more SP doses. In practice, women in areas of moderate to high malaria transmission should receive SP at each antenatal care visit during the second and third trimesters (because four visits are recommended), with 1 month intervals between dose.

Malaria causes preterm labor, fetal heart rate abnormalities, fetal compromise or intrauterine growth restriction. It has been estimated that malaria in pregnancy in settings with stable malaria transmission, it is potentially responsible for up to 70% of IUGR and 36% of preterm delivery. IUGR has been placental infection while preterm delivery correlates with systemic manifestations of malaria infection in the mother.

The main management in pregnant patients infected with malaria is to control the fever and treat the infection. High fever may induce uterine contractions that may result to preterm labor, of which antipyretics and hydration may be given. Fetal distress is the most common complication. Obstetric management involves regular antenatal care with assessment of fetal growth scans. Perinatal morbidity may be prevented with prompt diagnosis and treatment.

CONCLUSION

The management of malaria in pregnancy includes: treating the infection, controlling preterm labor, and surveillance of fetal well-being. Although the index patient has not yet delivered upon completion of this report and is now already in Sudan, the authors can only surmise that the pregnancy will have a successful outcome because prompt initiation of the prescribed management was given. ■