Background: Malarial infection in pregnancy is uncommon in the United States but morbidity and mortality can be striking. “Severe” malarial infections in pregnancy are even rarer, with only eight reported cases in 2010. Primiparous women are at the greatest risk for significant parasitemia.

Case Presentation: A 33-year-old Nigerian G4P3003 at 34 and 2 weeks gestational age presents with a five day history of fevers, frontal headache, weakness, and diarrhea in setting of recent immigration to America. She was septic in the emergency room, with marked splenomegaly, thrombocytopenia, and electrolyte disturbances, requiring medical intensive care unit stabilization and treatment for *Plasmodium falciparum* malaria sepsis. After stabilization, continuous electronic fetal monitoring revealed multiple prolonged decelerations requiring delivery for fetal indications.

Conclusion: Malarial infection in pregnancy, although rare, is often caused by the most virulent species, *Plasmodium falciparum*, and decomposition can occur quickly more commonly in first pregnancies. “Severe” malarial infections in pregnancy with documentation through the postpartum course are exceedingly rare in the United States.

Keywords: *Plasmodium falciparum*, Parasitemia, Severe Malarial Infection, Sepsis.

List of Abbreviations

- *P. falciparum*: *Plasmodium falciparum*
- MICU: Medical Intensive Care Unit
- G6PD: Glucose-6-Phosphate Dehydrogenase
- HD#: Hospital Day Number
- NST: Non-stress Test

Background

Malaria is considered a rare diagnosis in the United States today. The number of reported malaria cases in the United States in 2010 was the highest it has been since 1980 according to a report from the Centers for Disease Control and Prevention which cited 1,691 reported cases in the United States over that year [1]. Malaria is caused by the intracellular parasite *Plasmodium*, with species including *Plasmodium falciparum*, *Plasmodium vivax*, *Plasmodium malariae*, and *Plasmodium ovale* [2]. All are transmitted to humans by the female *Anopheles* mosquito [2]. In a complex series of events, beyond the scope of discussion in this case report, malaria parasites are injected into humans, move to and propagate rapidly within hepatocytes causing cellular rupture, attach to red blood cells, invade and hydrolyze hemoglobin, and ultimately cause red blood cell lysis before infecting new red blood cells [2]. *Plasmodium falciparum* (*P. falciparum*) is the most virulent species infecting red blood cells at any age leading to the highest levels of parasitemia and the most significant anemia [2]. *P. falciparum* is also the most common species found in pregnant women. In the United States in 2010 this species infected all 19 pregnant women for which the species type was known contrasting with a 58.1% infection rate for all individuals reported [1]. Thus although malaria in pregnancy is rare in the United States, women infected are at high risk for the most virulent form which can lead to rapid decomposition.

The majority of malaria infections in pregnancy occur in individuals who either reside in, or have recently traveled to endemic areas [1]. The endemic countries of origin for most infections in 2010 in descending order were Nigeria, India, Haiti, and Ghana [1]. Data indicate that there were only forty-one cases reported in pregnant women in 2010 [1]. This represented almost triple the number reported in 2008 [1]. Further, there were only eight cases in pregnant women in 2010 which were considered clinically “severe” (severe criteria defined later in this report) and there was no information available on birth outcomes. This report describes a patient with “severe” malaria with sepsis requiring intensive care unit care, and a discussion of the antepartum course, birth, and postpartum recovery.

Case Presentation

A 33-year-old African American G4P3003 at 34 and 2 weeks...
gestational age based on an 18 and 2 week gestational age ultrasound presented to an outside hospital complaining of a five-day history of fevers, frontal headache, and increasing weakness. Over the preceding twenty-four hours she had begun to experience new onset nausea, vomiting, and watery diarrhea. The intensity of her current headache was rated 8/10 and was frontal only without radiation. She had moved from Nigeria to the United States eleven days prior. Although she had none of her prenatal records from Nigeria, she did carry with her the dating ultrasound report that was done in her native country. She had three previous normal spontaneous vaginal deliveries three, six, and nine years ago, all in Nigeria. She denied any history of sexually transmitted infections. She had no significant past medical or surgical history and was not on any medications. She denied ever having a malarial infection. She did not smoke, use alcohol, or use any other drugs. Her family history was unknown.

Her vital signs in the emergency room included a blood pressure of 90/60 mm Hg, tachycardia at 130s/min, and a maximum temperature of 103.8 degrees Fahrenheit. On physical exam she was noted to be “ill-appearing” with pallor, scleral icterus, and dry mucus membranes. Bilateral rhonchi were heard at the lung bases, heart rate was irregular and tachycardic, and capillary refill was greater than 2 seconds. A baseline complete blood count with differential, comprehensive metabolic panel, and urinalysis showed multiple abnormalities (Table 1). Rapid HIV testing was negative.

A peripheral blood smear noted mild microcytic, normochromic red cells with many intracellular parasitic ring forms present, morphologically consistent with Plasmodium species (Figure 1). The patient confided that she was diagnosed with malaria while in Nigeria. At that time, she was “3 months” pregnant and was treated with an unknown oral medication for 3 months. She was asymptomatic from treatment conclusion until now. The patient required an increased level of care and she was transferred to our Regional Medical Center.

On arrival at our institution, the physical exam findings above were confirmed. An electrocardiogram (EKG) showed atrial fibrillation with rapid ventricular response, and 6 hours later showed sinus tachycardia with no atrial fibrillation. Repeat labwork (as shown in Table 2) was significant for decreasing platelets, hemoglobin, hematocrit, and bicarbonate, as well as an elevated fibrinogen. With the diagnosis of acute malaria in the setting of sepsis, thrombocytopenia, leukopenia, acute kidney injury, and transient atrial fibrillation, she was admitted to the Medical Intensive Care Unit (MICU).

Initial parasitemia load was found to be greater than 7.5%. Only Pl. falciparum DNA was identified by real-time PCR. While in the MICU, the patient was started on quinidine 100mg/hour IV and clindamycin 400g IV Q8 hours for her malaria infection to continue until parasitemia load dropped to less than 1% where upon she would be switched to quinine 600mg PO TID and clindamycin.
450mg PO TID. Tylenol was used to control her fever. Due to the ability of quinidine to produce prolonged QT syndrome, a repeat EKG was performed showing only sinus tachycardia. Blood glucose, complete blood count, and comprehensive metabolic panels were checked every 6 hours and electrolytes replaced accordingly. A G6PD level was within normal limits. The patient was started on D5NS. Cardiology was consulted for the possibility of QTc prolongation. The threshold for red blood cell transfusion was hemoglobin below 8 g/dL or a hematocrit below 24%. Given her thrombocytopenia, an abdominal ultrasound was performed to evaluate for hepatosplenomegaly. The liver was normal in size and echogenicity, while the spleen had echogenicity but was enlarged in size measuring 15.2 cm x 5.15 cm (Figure 2). A study performed in Nigeria measuring splenic dimensions in 109 females between 20 and 60 years of age (mean age 29.7 years ± 9.0 years standard deviation) found that the mean splenic length and width were 10.1 cm (± 0.7 cm standard deviation) by 4.0 cm (± 0.4 cm standard deviation) [3]. At that time, a high risk obstetric ultrasound was performed which showed a male fetus in vertex presentation with an anterior placenta. Estimated fetal weight was 44th percentile for 34 and 2/7 weeks gestational age. There was no evidence of fetal hydrops and umbilical artery and middle cerebral artery dopplers were both normal.

While in the MICU, the patient continued to hemolyze with her hemoglobin and hematocrit levels dropping as low as 6.7 g/dL and 20.2%. She ultimately required 3 units of packed red blood cells (PRBCs). Her platelets dropped as low as 24K/mm³, but a decision was made not to transfuse platelets unless levels dropped to less than 10K/mm³ or active bleeding developed, in order to decrease the risk of pulmonary edema. Repeat peripheral blood smear showed suspected *P. falciparum* species which was confirmed by plasmodium DNA real-time PCR.

Two days after transfer, the parasitemia load had dropped to less than 1% and she was switched to a PO regimen for five days to complete a seven day course. Telemetry and regular blood glucose finger-sticks were discontinued. Thrombocytopenia improved to 37K/mm³ as the parasitemia load decreased. Given the patient’s clinical improvement, she was transferred to our antepartum service. Cardiology recommended an echocardiogram for further evaluation of previous atrial fibrillation.

While on the antepartum service the echocardiogram demonstrated a left ventricular ejection fraction greater than 55% but suggesting the presence of an ascending aortic aneurysm. A chest CT confirmed an ascending aortic aneurysm measuring 4.5 cm x 4.9 cm at the level of the pulmonary arteries, tapering following the origins of the great vessels to 2.1 cm distally. Cardiac surgery consultation confirmed no relationship between the malarial infection and aortic aneurysm and no acute intervention was required other than keeping systolic blood pressures under 150 mmHg. Additionally, they recommended avoiding vaginal delivery for fear of dissection with valsala. On HD#5 during daily NST, the patient had a 5 minute prolonged deceleration with a nadir of 90 beats/min. Continuous monitoring was started. Over the next 22 hours she had a total of 6 more prolonged decelerations with moderate variability and accelerations between these decelerations. The decelerations ranged in length from three to nine minutes with nadirs from 40 to 90 beats/min. One such
deceleration is depicted in Figure 3. Consequently on HD#6, the patient underwent an uncomplicated primary cesarean section for fetal indications resulting in a live male infant with weight 2490 grams and APGARS of 8 and 9. Estimated blood loss was 800 mL. Parasite count at the time of cesarean section was less than 0.5%.

Pathologic evaluation of the placenta revealed evidence of chronic maternal malarial infection. Specific findings included:

1) Mild intervillous histiocytosis with hemozoin pigment

2) Mildly increased perivillous fibrin with hemozoin pigment associated with punctate foci of erosion and necrosis of villous syncytiotrophoblasts (<10% of villi affected) (Figure 4)

3) Mild patchy foci of villous stromal karyorrhexis and fibrosis (<5% of villi) (Figure 4)

4) Bridging intervillous fibrin containing hemozoin laden macrophages

5) Decidual arteries with a focus of fibrinoid necrosis and fibrin thrombus (Figure 5)

Further it was noted that while histologic review of the maternal red blood cells in the placental tissue did not demonstrate definitive parasites, the presence of perivillous macrophages with hemozoin pigment is considered to be evidence of a chronic infection.

The patient’s postpartum course was uncomplicated. She finished her 7 day course of PO quinine and clindamycin and on hospital day number 10 she was discharged home. Post-partum cardiology recommended a magnetic resonance angiography which she agreed to as an out-patient. The patient’s thrombocytopenia was resolved on the day of discharge, she showed marked clinical improvement, and she went home on prn tylenol.

The neonate had an uncomplicated hospital course. Cord blood
was negative for *Plasmodium* on Giemsa Stain, and Polymerase Chain Reaction was also negative for *Plasmodium falciparum*, *malariae*, ovale, and vivax. He remained afebrile, showed no signs of infection, and had an uneventful hospital course and was consequently discharged on day four of life.

**Discussion**

World-wide malaria kills more than 1 million people annually, 90% of which are in sub-Saharan Africa [2]. Fortunately, the incidence in the United States is significantly less.

For instance, in a malaria surveillance study released by the CDC in 2012, it was reported that 1,691 reported cases of malaria occurred in the United States in 2010 [1]. Of these, 608 reported cases were in women with only 41 cases reported in pregnant women [1]. Of these 41 cases reported, eight were considered “severe”. Of these severe cases there was no available information on the patients’ birth outcomes [1]. Criteria for a severe malarial infection include at least one of the following criteria: neurological symptoms, renal failure, severe anemia (defined by hemoglobin less than 7 g/dL), acute respiratory distress syndrome, jaundice, or ≥5% parasitemia [1]. This analysis also noted that patients without any of the following, but who required artesunate, quinidine, or exchange blood transfusions were also considered severe [1]. Our patient thus qualified as having a severe malarial infection by multiple criteria, including hemoglobin less than 7 g/dL, jaundice, parasitemia ≥5%, and quinidine therapy. Further, while there was no available information on the birth outcomes in previous reports, our patient delivered a healthy neonate during her stay and was monitored and discharged healthy from our institution. One month after birth the newborn was reported to be healthy with no specific concerns of congenital malaria (fever, anemia, splenomegaly) which are reported to occur in approximately two infants in the United States annually [4].

This case is interesting for many reasons. First, in endemic areas, increasing gravidity usually has a protective effect on *Plasmodium* infection. For instance, one study in an endemic area found that 64% of primiparous, 29% of women in second and third pregnancies, and only 21% with four or more pregnancies had parasitemia [5]. Our patient had three previous pregnancies without complications before the current pregnancy and had lived in the same geographic location for all four pregnancies, a small village in Nigeria. The reason why she became infected and so critically ill in her fourth pregnancy remains unclear.

Unfortunately, *P. falciparum* is the most common species found in pregnant women accounting for 100% of malarial infections recorded in pregnant women in the United States in 2010 [1]. Contrastingly, *P. falciparum* accounted for only 58.1% of all malaria infected individuals over the same time [1]. *P. falciparum* is the most deadly, and the increased virulence is thought to be due to several factors [2]. First, it can infect red blood cells at all stages of the cells’ life cycles increasing parasite load and the potential for significant parasitemia [1]. Secondly, cytokine production is enhanced in *P. falciparum* compared to other plasmodium species resulting in more significant fever and red blood cell sequestration [2]. But perhaps most critically, *P. falciparum* facilitates red blood cells to adhere to one another (rosetting) as well as to endothelial cells in blood vessels which can result in significantly impeded blood flow [2]. *P. falciparum* synthesizes a distinct virulence factor called PfEMP1 (*P. falciparum* erythrocyte membrane protein-1) inside host red blood cells, which moves to the red blood cell membrane and facilitates adhesion to endothelial cells in the blood vessel wall [6]. It is the opinion of the authors that this red blood cell adherence both to each other, as well as to the walls of the placental micro-vascular, was the main contributor to the significantly compromised placental perfusion displayed by the numerous prolonged decelerations observed (Figure 3).

*P. falciparum* parasites can also be sequestered in the placental bed [7]. In fact, one study in a malaria endemic area in Nigeria found a 65.2% prevalence of *falciparum* placental malaria in asymptomatic women [7]. This same study showed that there were cases with identifiable placental parasitemia even in the absence of parasitemia in both peripheral and cord blood samples [7]. While the pathology slides in our case did not demonstrate placental parasitemia at the time of delivery, the significant reduction in the peripheral parasitemia load from greater than 7.5% to less than 0.5% could certainly have been the reason for this lack of visualization. While there is little evidence in the literature regarding placental manipulation and peripheral parasitemia load, it is possible that placental aggravation may cause a peripheral parasitemia spike and potential maternal decompensation. This possibility, although theoretical, may both further underscore the immense importance of early maternal stabilization in a fully equipped unit, as well as delaying delivery until stabilization has occurred and parasitemia load is better controlled.

The importance of early maternal stabilization in the acutely ill patient with malaria cannot be over-emphasized. Based on gestational age, subsequent fetal monitoring may or may not be indicated. Potential signs or symptoms of labor may lead to a premature admission to labor and delivery before the patient is adequately stabilized. First priority should be maternal stabilization, and this patient was appropriately sent to the level of care she needed in the MICU. Since the patient was complaining of some abdominal cramping, likely from her vomiting, immediately sending a patient to labor and delivery instead of the MICU could be a critical error with potential fatality.

Malaria in pregnancy is indeed a rare diagnosis in the United States, but the diagnosis needs to be considered in order not to be missed. Taking a thorough travel history is absolutely paramount in considering the diagnosis, and is emphasized in other case reports [8]. Travelers or residents of an endemic area who are pregnant and clinically ill should be screened for malaria (either by peripheral blood smear, antigen rapid diagnostic tests, or PCR for parasitic nucleic acids). Further, United States citizens usually have a weaker immune response to malaria than do individuals who live in endemic areas. One study of 185 fatal cases between 1963 and 2001 in United States travelers, found that among U.S. travelers diagnosed with malaria one in one hundred died [9]. People native to or who have recently traveled to Nigeria, India, Haiti, or Ghana are at high risk. In our case, if a proper complete history was not taken the diagnosis may have been missed and she could have decompensated before transfer to a facility that could provide a higher level of care.

Finally, due to the rarity of severe malaria in pregnant women in the United States a multidisciplinary approach is critical to
optimize patient outcome. All diagnosed malaria cases in the United States are reported to local and state health departments [1].

Conclusions
Any residents or travelers to malaria endemic areas who present with signs suspicious for malarial infection should be a cause for a low threshold for malaria testing. Pregnant women, especially primiparous women are at increased risk for heightened morbidity and mortality from malaria, but multiparous women can also decompensate quickly, especially if the diagnosis is delayed. The initial priority is maternal stabilization. Finally, severe malaria in pregnant women in the United States is exceedingly rare, but when it occurs, a multidisciplinary approach is paramount to optimize patient care.

Consent
Written informed consent was obtained from the patient for publication of this case report and any accompanying images. A copy of the written consent is available for review by the Editor of this Journal.

Authors’ Contributions
NAK: Major contributor in writing, reviewing, and editing manuscript
MB: Major contributor in writing and reviewing manuscript
KCK: Major contributor in reviewing manuscript
OV: Major contributor in pathology evaluation and interpretation
LF: Major contributor in pathology evaluation and interpretation

Acknowledgements
The authors would like to acknowledge the Medical Intensive Care Unit at Albany Medical Center for providing a high level of care to this patient.

References