Malaria during Pregnancy

WHEC Practice Bulletin and Clinical Management Guidelines for healthcare providers. Educational grant provided by Women's Health and Education Center (WHEC).

Malaria during pregnancy is a severe disease. It increases the risk of adverse pregnancy outcomes, including low birth weight, pregnancy loss, and preterm birth. The prevention and prompt diagnosis and treatment are essential. Diagnosis can be challenging during pregnancy among persons with partial immunity because placental sequestration of parasite-infected red blood cells can result in in lower in lower parasite levels in peripheral blood. Recent identification of mosquito-borne transmission of malaria in the United States (U.S.), in Florida, Texas and Maryland and increasing travel to malaria-endemic countries raise the likelihood of that U.S. obstetricians might encounter a pregnant patient with malaria. Although malaria was previously endemic in the southeastern U.S., it has been considered to be eliminated through a variety of public health measures since 1951.[1] Approximately, 2,000 imported cases of malaria are reported each year in the U.S., with cases in all states. Despite recommendations that pregnant persons do not travel to malaria-endemic countries, imported cases are often seen in pregnant persons.[2] Mosquito surveillance and control measures have been put in place in the affected areas. Although the risk is low to U.S. pregnant persons who are not traveling internationally, avoiding mosquito bites is important, especially for pregnant persons residing in or visiting areas with recent local mosquito-borne transmission.

The purpose of this document is to review diagnosis, treatment, management and prevention of malaria during pregnancy. The advisory emphasizes the importance of considering malaria in the differential diagnosis of fever of unknown origin, even in patients without a history of travel to countries with known transmission. The advisory highlighted the importance of early diagnosis and treatment to avoid the development of severe malaria, a potentially fatal condition, and to reducing ongoing transmission to local mosquitos. The release of this advisory prompts a review of malaria for obstetricians and other healthcare professionals focusing on the effects of malaria on the pregnant patients, the fetus, and the newborns and recommendations for prevention and treatment of malaria during pregnancy.

Introduction and Prevalence

Malaria is a major public health burden globally, with an estimated 247 million cases and 619,000 deaths in 2023 malaria-endemic countries.[3] Two billion people risk contracting malaria annually, including those in 90 endemic countries and 125 million travelers and 1.5 to 2.7 million people dies in a year.[4] The *Plasmodium* parasite has a multistage lifecycle, which leads to characteristic cyclical fevers. With timely treatment, most people experience rapid resolution of symptoms; however, significant complications may occur, including cerebral malaria, severe malarial anemia, coma, or death. Preferred antimalarial therapeutic and chemoprophylactic regimens get dictated by species, geography, susceptibility, and patient demographics. Latent or reactivating infections may be reported years following exposure. Malaria is primarily found in

tropical and sub-tropical regions, with the highest number of cases in sub-Saharan Africa, where more than 95% of cases occur.

Etiology

Five species of the parasite genus *Plasmodium* (*P falciparum, P vivax, P malariae, P ovale,* and *P knowlesi*) possess the ability to infect humans. The incubation period, and therefore time to symptom development, varies by species: 8 to 11 days for *P. falciparum;* 8 to 10 days for *P. vivax;* 10 to 17 days for *P. ovale;*18 to 40 days for *P. malariae* (though possibly up to several years); and 9 to 12 days for *P. knowlesi.*[4]

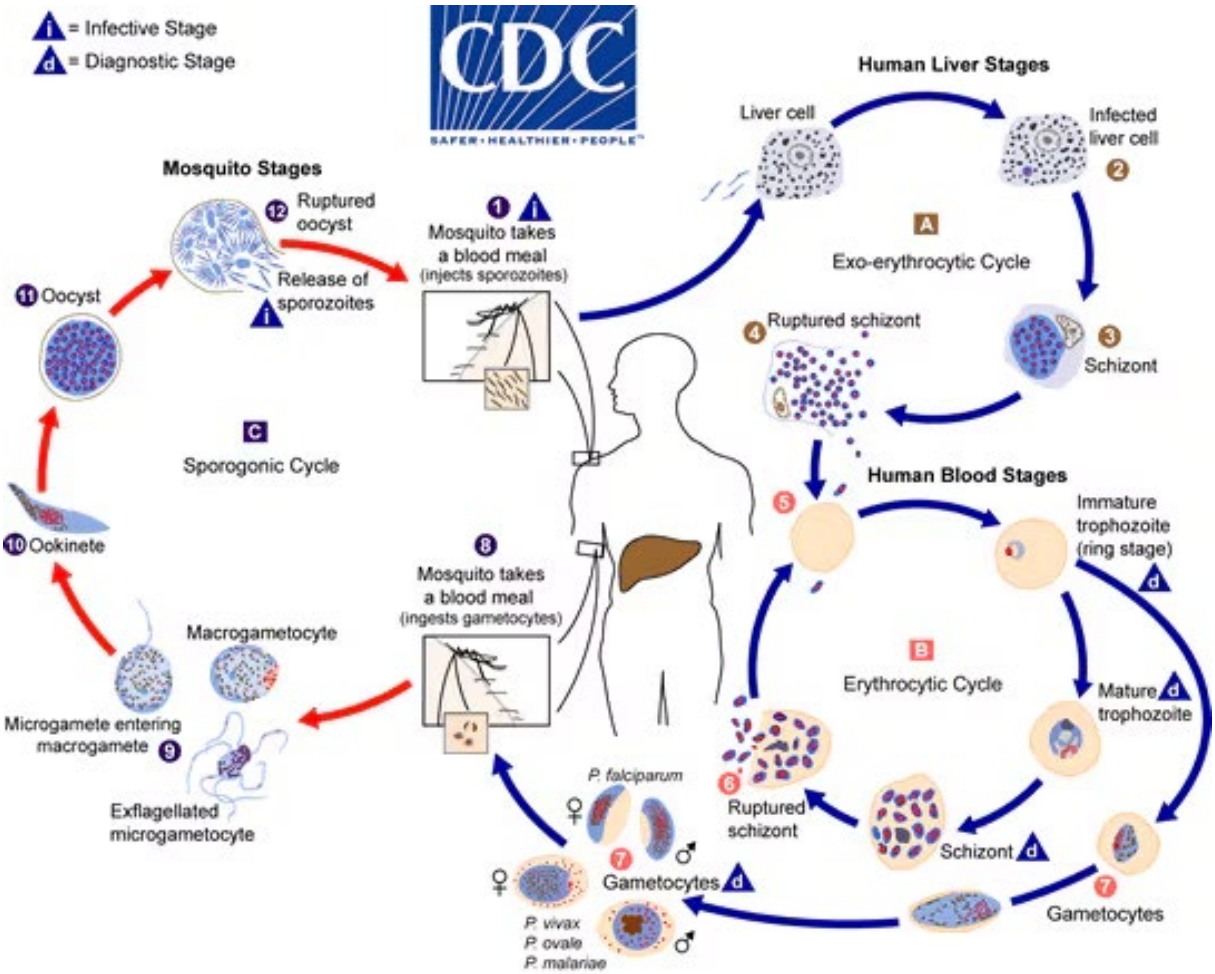

Figure 1. The malaria parasite life cycle involves two hosts. During blood meal, a malaria-infected female *Anopheles* mosquito inoculates sporozoites into the human host. Sporozoites infect liver cells and mature into schizonts, which rupture and release merozoites. After this initial replication in the liver, the parasites undergo asexual multiplication in the erythrocytes (erythrocytic schizogony). Merozoites infect red blood cells. The ring state trophozoites mature into schizonts, which rupture releasing merozoites. Some parasites differentiate into sexual erythrocytic stages (gametocytes). Blood stage parasites are responsible for the clinical manipulation of the disease.

The female *Anopheles* mosquito ingests gametes during a blood meal, which form sporozoites that replicated in the gut. During subsequent blood meals, saliva containing sporozoites gets released into human host's blood stream. Within 60 minutes, sporozoites reach the liver, invade

hepatocytes, and then rapidly divide, forming merozoites. Within erythrocytes, *Plasmodia* consume hemoglobin and develop from immature trophozoites (ring stage) to either mature trophozoites or gametocytes. Mature trophozoites replicate, forming schizonts, disrupting erythrocyte cell membrane integrity, and leading to capillary endothelial adherence and cell lysis.[5] Free heme is released into the peripheral blood, which stimulates endothelial activation. Untreated malaria lasts 2 to 24 months. *P. vivax* and *P. ovale* infections may display "dormant schizogony" where inactive intrahepatic parasites (hynozoites) remain until reactivation months to years in the future.

Pathophysiology

Pathogenesis stems from toxin-induced IFN-gamma and TNF-alpha secretion.[6] The innate immune response is dominated by monocyte and macrophage phagocytosis within the splenic red pulp. The liver and spleen enlarge, causing massive splenomegaly. Low arginine, low nitric oxide, and elevated arginase activity have been observed in severe malaria in peripheral blood. Studies have shown that the parasite's arginase enzyme may contribute to low arginine in severely ill patients, thus reducing nitric oxide production. Low nitric may lead to subsequent pulmonary hypertension and myocardial wall stress in children. Therefore, peripheral arginine or inhaled nitric oxide are possible treatment options.[7] Parasitemia dictates symptom onset and severity: symptoms typically develop with 0.002% parasitemia in naïve patients and 0.2% parasitemia in previously exposed patients. Severe infections usually exhibits parasitemia of 5%.[4]

Histopathology

Intracellular digestion of hemoglobin by parasites forms hemozoin and makes the membrane less deformable, which results in hemolysis or splenic clearance.

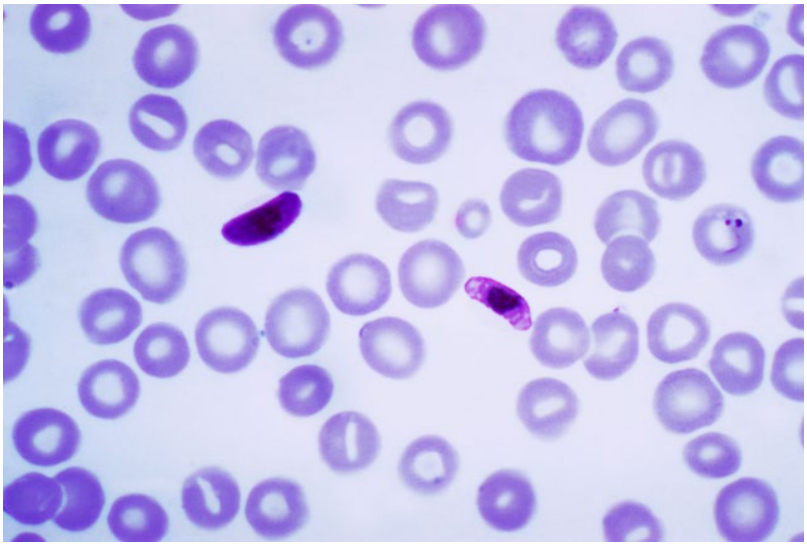

Figure 2. *Plasmodium falciparum* – it is a unicellular protozoan parasite of humans, and the deadliest species of *Plasmodium* that causes in malaria. Macrogametocyte (left) and Microgametocyte (right)

Microscopic examination of a blood film reveals only early (ring form) trophozoites and gametocytes that are in peripheral blood. Mature trophozoites and schizonts in peripheral blood smears, as these are usually sequestered in the tissues. On occasion, faint, comma-shaped, red

dots are seen on the erythrocyte surface. These dots are Maurer' cleft and are secretory organelles that produce proteins and enzymes essential for nutrient uptake immune evasion processes.[8]

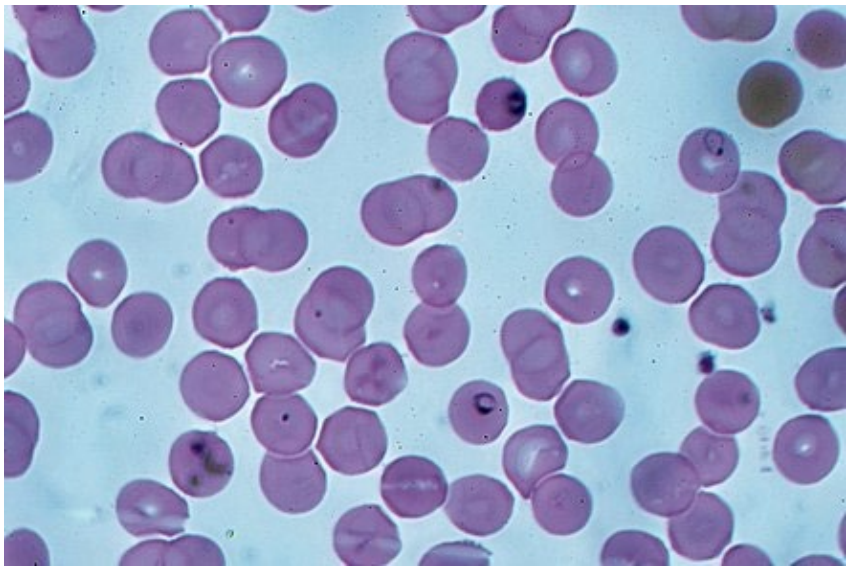

Figure 3. Ring forms in red blood cells. Positive blood smear for malaria.

Signs and symptoms

Malaria symptoms are non-specific and include fevers, shaking chills, myalgias, headache, cough and diarrhea. The traditional description of paroxysmal fevers is rarely seen early in the course of the disease and should not be relied on for diagnostic purposes. Laboratory abnormalities of uncomplicated malaria include anemia, thrombocytopenia, hyperbilirubinemia, and elevated transaminases. Prompt diagnosis and treatment are necessary to avoid the development of severe malaria. *Severe malaria,* most commonly caused by *P falciparum*, is defined by the World Health Organization (WHO) as clinical or laboratory evidence of vital organ dysfunction.[9] findings include impaired consciousness including seizures and coma, hemoglobin less than 7 g/dL, acute kidney injury, acute respiratory distress syndrome, circulatory collapse or shock, acidosis, disseminated intravascular coagulation, and parasite density of 5% or greater. Severe complication are related to sequestration of parasite-containing erythrocytes in small- and medium-sized vessels.[10] In *P vivax* and *P ovale*, the infection can become dormant in the liver, with relapses occurring months or years after the initial infection.

Effects of Malaria on Pregnant Patients

Pregnancy increases both the likelihood of contracting malaria and of severe disease among those infected. These adverse effects are believed to be related to an altered immune response during pregnancy and sequestration of the parasite in the placental intervillous space, decreasing the likelihood of clearance of infected protein. *P falciparum* parasites; VAR2CSA binds to chondroitin-sulfate A on syndecan-1, which is expressed by placental trophoblasts.[11] *P vivax* can also lead to placental changes, but placental sequestration has not been demonstrated.[11] Several older studies have shown a higher risk of becoming infected with malaria among pregnant

patients when compared with non-pregnant patients. In addition, to pregnant, other risk factors have been identified in more recent studies. For example, because of the development of antibodies to VAR2CSA protein, the risk for malaria in endemic areas is highest in the 1st and 2nd pregnancies, compared with subsequent pregnancies, in which immunity is likely to be protective. In low or epidemic transmission areas, this effect is lessened or absent.[12] Other independent risk factors for infection include young maternal age, malnutrition, and human immunodeficiency virus (HIV) infection.

In addition to the increased risk of developing malaria during pregnancy, pregnant persons infected with malaria are at increased risk of adverse maternal outcomes and of development of severe malaria. Although severe disease during pregnancy is most often seen with *P falciparum,* all species of malaria can cause severe disease during pregnancy. Anemia is a common adverse outcome among pregnant persons with malaria, due to reduced erythrocytes, and hemolysis of infected cells, and can increase the risk for maternal and fetal complications. *Placental malaria* (presence of the parasite or its pigment hemozoin in the placenta or placental blood) is associated with an increased risk for anemia and preeclampsia.[13,14] Further, pregnant patient are more likely to progress to severe malaria. In stable endemic areas, pregnant patients are at a 3-fold greater risk of severe malaria compared with non-pregnant patients. In recent studies, median mortality of severe malaria during pregnancy was 39%.[15] Pregnant patients living in areas with low transmission of malaria are more likely to develop serious complications given their lower likelihood of acquired immunity.

Effects of malaria on unborn and newborn children

Malaria during pregnancy also puts the unborn (fetus) and newborns at risk of adverse outcomes. Placental malaria can occur in up to 63% of pregnant persons in endemic regions.[16] It has shown negative consequences for the fetus and newborn due to placental inflammation, impaired transplacental transport of nutrients, and altered uteroplacental malaria include stillbirth, low-birthweight, small for gestational age, and preterm birth.[17]

Congenital malaria (infection identified in cord blood or in peripheral blood during the first week of life) can also occur among neonates born to individuals with malaria infection due to transmission shortly before and during the delivery. [18] Due to difficulty in distinguishing congenital from mosquito-borne transmission, rates of congenital malaria in endemic countries are not well established; however, congenital malaria has been rare in the United States, with reports of only 81 cases in 40 years in a report from 1966 to 2005.[19] Newborns with congenital malaria can present with fever, irritability, lethargy, and poor appetite, resembling neonatal sepsis. Additionally, effects of malaria infection during pregnancy can extend into child's later years. These effects include an increased risk of malaria and non-malaria infections during infancy, possibly, related to decreased placental transmission of maternal antibodies and effects on the development of the fetal and infant immune system.[20] Some children born after infection with malaria early in pregnancy might develop immune tolerance to malaria antigens, with could put them at increased risk for malaria infection during childhood; in others, prenatal exposure appears to respond more efficiently. Malaria in pregnancy is also associated with lower hemoglobin concentrations in infancy.

Evaluation

It is essential that obstetricians consider malaria when evaluating pregnant patients with febrile illness of unknown origin, because prompt diagnosis and treatment can reduce the risk of adverse outcomes. Taking a travel history is essential: travel history to countries with active malaria transmission in the previous year, especially among patients who did not receive adequate chemoprophylaxis, should raise suspicion for malaria as a diagnosis.[21] For pregnant patients, refugees, or other migrants from malaria-endemic countries, obstetricians should have a high index suspicion to perform testing for malaria. Given the recent cases of mosquito-borne transmission of malaria in the United States, malaria should be considered even in the absence of an international travel history to areas with live in or have traveled to areas with recent locally acquired malaria infections.

Initial evaluation of undifferentiated fever in stable patients with possible malaria exposure includes a complete blood count, comprehensive metabolic panel, coagulation panel, blood culture, urinalysis, chest radiograph, and thick and thin blood smears. In patients with altered mental status, when cerebral malaria is suspected, a lactate level, arterial blood gas, and lumbar puncture may also be indicated.[22]

In patients with malaria, complete blood count reveals thrombocytopenia in 60-70% of all cases and varying degrees of anemia in 29% adults, and 78% of children.[22] Anemia is more severe in *P falciparum* due to invasion of all aged erythrocytes and capillary and splenic erythrocyte sequestration secondary to decreased flexibility and cytoadherence. Anemia is typically moderated with *P vivax and P malariae* due to preferential invasion of reticulocytes and older erythrocytes, respectively. A comprehensive panel may reveal hepatocellular injury secondary to parasitic invasion, indirect hyperbilirubinemia due to hemolysis, electrolyte abnormalities secondary to the release of intracellular contents, concomitant dehydration, and kidney injury secondary to glomerular damage. The coagulation panel may reveal coagulopathy concerning bleeding risk in patients with severe thrombocytopenia or liver dysfunction.[23] Urinalysis may show proteinuria indicative of nephrotic syndrome.

The gold standard for malaria diagnosis is a microscopic evaluation of Giemsa-stained thick and thin smears of a free-flowing venipuncture blood specimen. Examination with oil immersion mut be completed at 100-times and 1000 times magnification to avoid missing low-level parasitemia or “delicate ring forms.” The extent of parasitemia is estimated by the number of organisms per high-power field.

An initial negative smear does not rule out malaria, as infected erythrocytes may become intravenously sequestrated; if clinical suspicion of malaria is high, smears require repetition in 12 to 24 hours. The malarial pigment in monocytes and neutrophils may also manifest on the blood smear, particularly in patients with cerebral malaria.[23] Other diagnostic modalities include rapid diagnostic testing (RDT), microhematocrit centrifugation, and polymerase chain reaction (PCR).[24] Microhematocrit centrifugation isolates infected erythrocytes, then binds to acridine in the collection tube, causing the fluorescence of parasites. PCR is useful in low-level parasitemia detection and speciation.

Treatment / Management

Treatment should be initiated urgently in pregnant patients diagnosed with malaria to avoid serious complications to the mother and fetus. Presumptive treatment (without laboratory confirmation) is not recommended because clinical diagnosis, even in endemic areas, is unreliable. (Source: CDC)[25]

Species and Drug Susceptibility (based on where Acquired)	**Recommended Adult Regimens**
Uncomplicated malaria Chloroquine sensitive: *P. falciparum* (Central America west of Panama Canal, Haiti, and Dominican Republic) *P. vivax or P. ovale* (All malaria-endemic regions except Papua New Guinea and Indonesia) *P. malariae or P. knowlesi* Chloroquine resistant: *P. falciparum* (all malaria-endemic regions except Central America west of Panama Canal, Haiti and Dominic Republic) *P. vivax or P. ovale* (Papua New Guinea and Indonesia)	Chloroquine phosphate or Hydroxychloroquine. If *P. vivax or P. ovale*: add chloroquine for remainder of pregnancy for relapse and prevention. Artemether-lumefantrine (Coartem®) or quinine sulfate plus clindamycin, or mefloquine (only if there are no other options available). If *P. vivax or P. ovale*: add chloroquine for remainder of pregnancy for relapse prevention.
Uncomplicated or Severe Malaria due to *P. vivax* or *P. ovale* infections – relapse prevention	Prevention of relapse due to dormant parasite in liver is needed. Recommended medications: Primaquine phosphate (for 14 days) or tafenoquine (Krintafel) – single dose.
Patients with G6PD deficiency [Glucose-6-phosphate-dehydrogenase] deficiency	Primaquine phosphate and tafenoquine should be avoided in patients with G6PD deficiency, because can cause hemolytic anemia. Should be avoided during pregnancy because of unknown G6PD unknown status of fetus. Chloroquine chemoprophylaxis for the remainder of pregnancy is recommended
Postpartum and Breastfeeding	Primaquine phosphate or tafenoquine can be given postpartum in patients with normal G6PD activity, NOT breastfeeding.† Breastfeeding mothers: primaquine phosphate can be given if infant has normal G6PD activity.*

Table 1. †The CDC does not recommend tafenoquine for breastfeeding mothers because data on its use during lactation are lacking; https://www.cdc.gov/malaria/resources/pdf/malaria_treatment_table_202306.pdf
*for postpartum patients who are unable to take primaquine phosphate or tafenoquine, weekly chloroquine therapy for 1 year after the acute malaria diagnosis is recommended.[26]

Criteria for Severe Malaria

Progression to severe malaria occurs when infections are complicated by serious organ failures or abnormalities in the patient's blood or metabolism, usually following delays in diagnosis and treatment. Criteria for severe malaria may differ slightly on the country where you are practicing. [27] For healthcare providers practicing in the U.S. the criteria for severe malaria include any one or more of the following: High percent parasitemia (>5%); Impaired consciousness; Seizures; Circulatory collapse/shock; Pulmonary edema or acute respiratory distress syndrome (ARDS); Acidosis; Acute kidney injury; Abnormal bleeding or disseminated intravascular coagulation (DIC); Jaundice (must be accompanied by at least one other sign); Severe anemia (Hb <7g/dL).

Treatment of Severe Malaria – Recommended Adult Regimens.

Severe Malaria All species, drug susceptibility not relevant for acute treatment of severe malaria	IV artesunate (3 total doses at 0, 12 and 24 h) Plus follow-on treatment (based on parasite density measured at least 4 – h after 3rd dose) If IV artesunate is not readily available, give oral antimalarials until IV artesunate is obtained. Artemether-lumefantrine (Coartem®) preferred; or Quinine sulfate; or Atovaquone-proguanil (Malarone™); or Mefloquine (only if there are no other options available).
	If oral therapy is not tolerated, oral medications can be given by nasogastric tube or after and antiemetic. If parasite density is <1% and patient is able to tolerate oral medications: Give a complete follow-up oral regimen. Options include Artemether-lumefantrine (Coartem®) – preferred; or Quinine plus clindamycin; or Mefloquine (only if no other options available).
	If parasite density is >1% continue IV artesunate, for a total of 7 days until parasite density <1%, give complete follow-up oral regimen.
	If parasite density is <1% but patient is unable to tolerate oral medication: Continue IV artesunate for a total 7days until patient is able to tolerate oral therapy.
	If *P. vivax or P. ovale:* add chloroquine for remainder of pregnancy for relapse prevention.

Table 2. Modified from CDC Treatment tables. For doses *see*https://www.cdc.gov/malaria/hcp/clinical-guidance/treatment-of-severe-malaria.html Abbreviations: IV – intravenous; h – hour.

Malaria Relapse

In *P. vivax* and *P. ovale* infections, patients having recovered from the first episode of illness may suffer several additional attacks ("relapses") after months or even years without symptoms. Relapses occur because *P. vivax* and *P. ovale* have dormant liver stage parasites (hypnozoites) that may reactivate, infect peripheral erythrocytes, and begin a new symptomatic episode of malaria. Treatment to reduce the chance of such relapses is available and should follow treatment of the first attack.

Complications of Malaria

The significant complications of malaria are: 1) Cerebral Malaria, 2) Severe Malarial Anemia; and 3) Nephrotic syndrome (NS).

Cerebral Malaria: it accounts for 80% of fatal malaria cases, most often occurring with *P. falciparum* infection.[28] it presents as slow-onset altered mental status, violent behavior, headache, and extremely high fever (up to 42 degrees C), followed by coma, metabolic acidosis, hypoglycemia, and possibly seizures and death. It most commonly affects children under age 5, with a case fatality rate of 18%. Pathogenesis involves malarial rosettes (one infected erythrocyte surrounded by three uninfected erythrocyte, causing cerebral sequestration and vasodilation, as well as excessive oxygen free radicals, IFN-gamma, and TNF-alpha leading to an extreme inflammatory response.[29] This leads to congestion, decreased perfusion, endothelial activation, impairment of the blood-brain barrier, and cerebral edema, which increases brain volume.

Increased brain volume is the major contributor to mortality in cerebral malaria. In a 2015 study of Malawian children with cerebral malaria, 84% of those who died had severely increased brain volume on MRI; children who survived showed lower initial brain volume or downtrend over time.[28]

Severe Malarial Anemia: It stems from TNF-alpha-mediated mechanism involving both increased destruction and decreased production of erythrocytes, including cell lysis as parasites replicate and exit erythrocytes, splenic removal and autoimmune lysis of immune-marked erythrocytes, poor iron incorporation into new heme molecules, and bone marrow suppression during server infection leading to decreased production.[29] Blackwater fever is severe anemia with hemoglobinuria and renal failure in the context of "massive intravascular hemolysis" in the setting of repeat *P. falciparum* infections treated with chronic quinine; it is rare and thought to be associated with G6PD deficiency.[30]

Nephrotic Syndrome: It occurs secondary to glomerular antigen-antibody complex deposition and presents similarly to membrano-proliferative glomerulonephritis with proteinuria and decreased renal function, which may lead to renal failure. Nephrotic syndrome is common in *P. malariae* and *P. knowlesi,* possible in *P. vivax,* and rare in *P. falciparum* and *P. ovale* infections.[4]

Additional complications include:

- Bilious remittent fever with abdominal pain and persistent vomiting that may lead to severe dehydration, jaundice, and dark urine.

- Algid malaria is an adrenal insufficiency due to parasitic congestion and subsequent necrosis of the adrenal glands.
- Acute respiratory distress syndrome, circulatory collapse, disseminated intravascular coagulation, pulmonary edema, coma, and death.
- Malaria infection during pregnancy may result in low-birth-weight or fetal death.

Prevention

Given the serious consequences of malaria in pregnancy, priority needs to be given to malaria prevention among pregnant people. To prevent malaria infection in pregnancy for persons born and raised in areas of moderate to high malaria transmission, the WHO recommends a three-pronged approach:[31]

1. Insecticide-treated bed nets;
2. Intermittent preventive treatment with sulfadoxine-pyrimethamine starting in the second trimester of pregnancy with a goal of at least three doses at least 1 month apart; and
3. Prompt diagnosis and initiation of effective treatment of malarial illness.

Q & A on Malaria Eradication (WHO)
https://www.who.int/teams/global-malaria-programme/elimination/q-a-on-malaria-eradication

Pregnant Travelers

Pregnant travelers from the United States should avoid or delay travel to malaria-endemic areas. For travel that can not be avoided, a prophylactic regimen should be used. For destinations with chloroquine is recommended for prophylaxis; mefloquine is recommended for travelers to destinations with chloroquine resistance.[32] More information is available in the CDC's Yellow Book.[21] Prevention measures to avoid mosquito bites also should be implemented to include U.S. Environmental Protection Agency, registered insect repellants, protective clothing, and mosquito nets. When used as directed, these insect repellants are believed to be safe in pregnancy; given the adverse effects of mosquito-borne illnesses during pregnancy, the benefits greatly outweigh the potential risk. Pregnant travelers returning from malaria-endemic areas should seek medical attention promptly if they become ill and ensure that their obstetrician is aware of their travel.

Malaria Vaccines

Malaria vaccine is not just a scientific breakthrough, it is life-changing for families across Africa. It demonstrates the power of science and innovation for health. As of October 2023, WHO recommends the programmatic use of malaria vaccines for prevention of *P. falciparum* malaria in children living in malaria endemic areas, prioritizing areas of moderate and high transmission. This applies to both RTS,S/AS01 and R21/Matrix-M vaccines. The vaccine has reached nearly 2 million children in Ghana, Kenya and Malawi through the Malaria Vaccine Implementation Program.[33] These vaccine is safe and feasible to deliver, and that it substantially reduces deadly severe malaria. WHO guidance to countries as they consider whether and how to adopt RTS, S as an additional tool to reduce child illness and deaths from malaria. RTS,S is a first-generation vaccine that could be complemented in the future by other vaccines with similar or higher efficacy.[34]

Malaria vaccines (RTS,S and R21) Q & A
https://www.who.int/news-room/questions-and-answers/item/q-a-on-rts-s-malaria-vaccine

There are also new medicines in pipeline. Tafenoquine, single dose has been approved for use in adults by U.S. Federal Drug Administration and by drug regulatory bodies in other countries, including Brazil, Peru and Thailand. As a single dose, tafenoquine is expected to support patient adherence to treatment. The current standard of care requires a 7- or 14-day course of medication.

Summary

In recent years, progress in reducing malaria has ground to a standstill. Not only does malaria continue to directly endanger health and cost of lives, but it also perpetuates a vicious cycle of inequity. People living in the most vulnerable situations including pregnant women, infants, children under 5 years of age, refugees, migrants, internally displaced people, and Indigenous Peoples continue to be disproportionately impacted. Pregnancy reduces a woman's immunity to malaria, making her more susceptible to infection and increasing her risk of severe disease and death. Gender inequalities, discrimination and harmful gender norms heighten her risk of contracting the disease. If untreated, malaria in pregnancy can cause severe anemia, maternal death, stillbirth, premature delivery, and low-birth weight babies.

The *Global technical strategy for malaria 2016 – 2030* was adopted by the World Health Assembly in May 2015. It provides a comprehensive framework to guide countries in their efforts to accelerate progress towards malaria elimination. The strategy sets the target of reducing global malaria incidence and mortality rates by at least 90% by 2030. While the milestones and targets remain the same, the approaches to tackling the disease, in some areas, have evolved to keep pace with the changing malaria landscape.

Resources

1. World Health Organization (WHO)
   Malaria
   https://www.who.int/en/news-room/fact-sheets/detail/malaria
   World Malaria Report 2024
   https://www.who.int/teams/global-malaria-programme/reports/world-malaria-report-2024

2. The Center of Disease Control and Prevention (CDC)
   Malaria
   https://www.cdc.gov/malaria/

References

1. Centers for Disease Control and Prevention (CDC). Elimination of malaria in the United States (1947 – 1951). Available @ https://www.cdc.gov/malaria/ Last accessed on 23 Jan. 2025
2. Mace KE, Lucchi NW, Tan KR. Malaria surveillance-United States. 2018. *MMWR Serveill Summ* 2022;71:1-35.

3. World Health Organization. World Malaria report 2023. Available @ https://www.who.int/teams/global-malaria-programme/reports/world-malaria-report-2023
Last accessed 2 January 2025
4. Garcia LS. Malaria. *Clin Lab Med* 2010;30(1):93-129
5. Carlton JM. Malaria parasite evolution a test tube. *Science* 2018;12:359(6372):159-160
6. Ferreira A, Balla J, Jeney V, Balla G, Soares MP. A central role for free heme in the pathogenesis of severe malaria: the missing link? *J Mol Med* 2008;86(10):1097-1111
7. Bangirana P, Conroy AL, Opoka RO, Hawkes MT, et al. Inhaled nitric oxide and cognition in pediatric severe malaria: A randomized double-blind placebo controlled trial. *PLoS One* 2018;13(1):e0191550
8. Lanzer M, Wichert H, Krohne G, Vincensini L, et al. Maurer's clefts: A novel multifunctional organelle in the cytoplasm of *Plasmodium falciparum*-infected erythrocytes. *Int J. for Parasitology* 2006;36(0):23-36
9. World Health Organization. World malaria report 2023. Available @: https://www.who.int/teams/global-malaria-programme/reports/world-malaria-report-2023 Last accessed 5 January 2025
10. Ashley EA, Pyae Phyo A, Woodrow CJ. Malaria. *Lancet* 2018;391:1608-1621
11. Bauserman M, Conroy AL, North K, Patterson J, et al. An overview of malaria in pregnancy. *Semin Perinatol* 2019;43:282-290
12. Desai M, Ter Kuile FO, Nosten F, McGready R, Asamoa K, et al. Epidemiology and burden of malaria in pregnancy. *Lancet Infect Dis* 2007;7:93-104
13. Cardona-Arias JA, Higuita-Gutierrez LF, Carmona-Fonseca J. Clinical and parasitological profiles of gestational, placental, placental and congenital malaria in northwestern Colombia. *Trop Med Infect Dis* 2023;8:292
14. Felician EK, Ngoda OA, Jahanpour OF, Kahima J, Msuya SE, Lukambagire AH. Placental parasitic infections and pregnancy outcomes among women delivering at a tertiary hospital in northern Tanzania. *East Afr Health Res J* 2022;6:141-146
15. Rijken MJ, McGready R, Boel ME, Poespoprodjo R, Singh N, et al. Malaria in pregnancy in Asia-Pacific region. *Lancet Infect Dis* 2012;12:78-88
16. Zakama AK, Weeks T, Kajubi R, Kakuru A, et al. Generation of a malaria negative Ugandan birth weight standard for the diagnosis of small for gestational age. *PLoS one* 2020;15:e0240157
17. Lufele E, Umbers A, Ordi J, Ome-Kaius M, et al. Risk factors and pregnancy outcomes associated with placental malaria in a prospective cohort of Papa New Guinean women. *Malaria J* 2017;16:427
18. Moya-Alvarez V, Abellana R, Cot M. Prepregnancy-associated malaria and malaria in infants: an old problem with present consequences. *Malaria J* 2014;13:271
19. Lesko CR, Arguin PM, Newman RD. Congenital malaria in the United States: a review of cases from 1966 to 2005. *Arch Pediatr Adolesc Med* 2007;161:1062-1067
20. Harrinton WE, Kakuru A, Jagannathan P. Malaria in pregnancy shapes the development of fetal and infant immunity. *Parasite Immunol* 2019;41:e12573
21. Centers for Disease Control and Prevention (CDC). Malaria information and prophylaxis, by country. CDC Yellow Book 2024 for Malaria. Available @ https://wwwnc.cdc.gov/travel/yellowbook/2024/infections-diseases/malaria Last accessed on 3 January 2025
22. Fletcher TE, Beeching NJ, Malaria. *J R Army Med Corps* 2013;159(3):158-166
23. Buck E, Finnigan NA. Malaria. National Library of Medicine; *National Center for Biotechnology Information* Last updated July 31; 2023
24. Mathison BA, Pritt BS. Update on malaria diagnostics and test utilization. *J Clin Microbiology* 2017;55(7):2009-2017
25. Centers for Disease Control and Prevention (CDC). 2023; Malaria in the United States: Treatment Tables (modified) available @ and last accessed 15 March 2025
https://www.cdc.gov/malaria/resources/pdf/malaria_treatment_table_202306.pdf
26. Rasmussen SA, Arguin PM, Jamieson DJ. Malaria and pregnancy. *Obstet Gynecol* 2023;142:1303-1309
27. World Health Organization (WHO). 2024. WHO guidelines for malaria. Available @ https://www.who.int/publications/i/item/guidelines-for-malaria Last accessed 18 March 2025.
28. Seydel KB, Kampondeni SD, Valim C, Potchen MJ, Milner DA, et al. Brain swelling and death in children with cerebral malaria. *N Engl J Med* 2015;Mar 19;372(12):1126-1137
29. Carlton JM. Malaria parasite evolution in a test tube. *Science* 2018; Jan12;359(6372):159-160
30. Shanks GD. The Multifactorial Epidemiology of Blackwater Fever. *Am J Trop Med Hyg* 2017;Dec 97(6):1804-1807

31. World Health Organization. WHO guidelines for prevention and treatment of malaria in pregnancy. Last accessed 25 March 2025 https://iris.who.int/bitstream/handle/10665/379635/B09146-eng.pdf?sequence=1
32. Galang R, Caroll ID, Oduyebo T. Pregnant travelers. CDC Yellow Book 2024. https://wwwnc.cdc.gov/travel/yellowbook/2024/family/pregnant-travelers Last accessed 22 March 2025
33. World Health Organization (WHO). Malaria Vaccine Implementation Programme. 2024; available @ https://www.who.int/news/item/21-04-2022-over-1-million-african-children-protected-by-first-malaria-vaccine Last accessed 24 March 2025
34. World Health Organization. Malaria vaccine: WHO position paper – March 2022. *Weekly Epidemiol Rec* 2022;97:61-80