Malaria in Pregnancy: Key Points for the Neonatologist

Article *in* NeoReviews · September 2023

DOI: 10.1542/neo.24-9-e539

5 authors, including:

Sharla Rent
Duke University
29 PUBLICATIONS **52** CITATIONS
SEE PROFILE

Melissa Bauserman
University of North Carolina at Chapel Hill
98 PUBLICATIONS **1,810** CITATIONS
SEE PROFILE

Jeremiah Laktabai
Moi University
60 PUBLICATIONS **577** CITATIONS
SEE PROFILE

Malaria in Pregnancy: Key Points for the Neonatologist

Sharla Rent, MD, MSc-GH,* Melissa Bauserman, MD, MPH,† Jeremiah Laktabai, MD,‡ Antoinette K. Tshefu, MD, PhD, MPH,§ Steve M. Taylor, MD, MPH¶

*Department of Pediatrics, Duke University School of Medicine, Durham, NC
†School of Medicine, University of North Carolina, Chapel Hill, NC
‡Moi University School of Medicine, Moi, Kenya
§Kinshasa School of Public Health, Kinshasa, Democratic Republic of the Congo
¶Department of Medicine, Duke University School of Medicine, Durham, NC

EDUCATION GAPS

1. Neonatologists should understand the role of malaria as a key contributor to global morbidity and mortality of pregnant persons and newborns.
2. There is a gap in knowledge about optimal testing and treatment of malaria during pregnancy, especially during the first trimester.

OBJECTIVES *After completing this article, readers should be able to:*

1. Describe the epidemiology of malaria in pregnancy and its global impact.
2. Explain the pathophysiology of malaria in pregnancy and the effect of malaria infection on the pregnant person, fetus, and newborn infant.
3. Describe current testing and treatment options for malaria infection during pregnancy.

ABSTRACT

In malaria-endemic regions, infection with the malaria parasite *Plasmodium* during pregnancy has been identified as a key modifiable factor in preterm birth, the delivery of low-birthweight infants, and stillbirth. Compared with their nonpregnant peers, pregnant persons are at higher risk for malaria infection. Malaria infection can occur at any time during pregnancy, with negative effects for the pregnant person and the fetus, depending on the trimester in which the infection is contracted. Pregnant patients who are younger, in their first or second pregnancy, and those coinfected with human immunodeficiency virus are at increased risk for malaria. Common infection prevention measures during pregnancy include the use of insecticide-treated bed nets and the use of intermittent preventive treatment with monthly doses of antimalarials, beginning in the second trimester in pregnant patients in endemic areas. In all trimesters, artemisinin-combination therapies are the first-line treatment for

AUTHOR DISCLOSURE Dr Bauserman has worked under grants from the National Institute of Allergy and Infectious Diseases and the National Institutes of Health and has been an invited speaker for a PAS panel on global health. Drs Rent, Laktabai, Tshefu, and Taylor have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

ABBREVIATIONS

ACTs	artemisinin-combination therapies
AL	artemether-lumefantrine
CSA	chondroitin sulfate A
DP	dihydroartemisinin-piperaquine
HIV	human immunodeficiency virus
IPTp	intermittent preventive treatment in pregnancy
IRS	indoor residual spraying
ISTp	intermittent screening and treatment during pregnancy
ITN	insecticide-treated bed net
IUGR	intrauterine growth restriction
LBW	low birthweight
RDT	rapid immune-chromatographic diagnostic test
SP	sulfadoxine-pyrimethamine

uncomplicated falciparum malaria, similar to treatment in nonpregnant adults. The World Health Organization recently revised its recommendations, now listing the specific medication artemether-lumefantrine as first-line treatment for uncomplicated malaria in the first trimester. While strong prevention and detection methods exist, use of these techniques remains below global targets. Ongoing work on approaches to treatment and prevention of malaria during pregnancy remains at the forefront of global maternal child health research.

INTRODUCTION

Improving the health of pregnant persons and children is a key global health priority. Although great improvements have been made in overall child mortality, advances in neonatal mortality have been slower. (1) As of 2017, neonatal deaths make up 47% of deaths before age 5 years, and most of these deaths occur in low- or middle-income countries. (2) In high mortality regions, such as sub-Saharan Africa, more than 80% of neonatal deaths occur in infants that are preterm or low birthweight (LBW). (3) Both preterm delivery and LBW are major consequences of antenatal infection with the malaria parasite *Plasmodium falciparum*, which threatens 125 million pregnancies in malaria-endemic areas each year. (4) In addition, in malaria-endemic regions of sub-Saharan Africa, where 1 in 3 pregnancies are exposed to *P falciparum*, (5) antenatal malaria may contribute to a quarter of all stillbirths, (6) making malaria one of the most important global modifiable causes of stillbirth. (7) It has been estimated that malaria accounts annually for over 10,000 and 200,000 deaths in pregnant persons and neonates, respectively. (8)

Malaria parasites are transmitted in over 80 countries. (5) Sub-Saharan Africa has the largest burden of cases of malaria, and over 90% of malaria-related deaths globally occur in this region. Of the over 247 million cases of malaria reported each year, children younger than 5 years account for 76% of all deaths. (5) These numbers represent progress, because globally, the incidence of malaria is declining: from 2010 to 2020, cases dropped from 71 to 59 per 1,000 people at risk. (5) These reductions are attributed to the scale-up of control activities, including the uptake and use of insecticide-treated bed nets (ITNs) and improved access to effective diagnosis and treatments. Despite these improvements, malaria kills approximately 2,000 people every day, most of them children. (9) Both the Millennium Development Goals and the Sustainable Development Goals highlight the importance of reducing childhood mortality, improving the health of pregnant persons, and promoting well-being in all ages. (10)(11)(12) It is therefore critical that the global community understand the impact of malaria infection on the fetus and newborn, successful prevention strategies, and treatments that currently exist to combat the negative perinatal effects of infection.

MALARIA

Microbiology and Epidemiology

Malaria is a mosquito-transmitted infection caused by 1 of 5 parasite *Plasmodium* species: *P vivax, P falciparum, P ovale, P malariae,* and *P knowlesi*. *P falciparum* is the most common and the deadliest, and is transmitted throughout the tropics, whereas *P vivax* circulates widely outside sub-Saharan Africa. Specifically in pregnancy, *P falciparum* is responsible for the majority of adverse outcomes in pregnant persons and fetuses infected with malaria, particularly in sub-Saharan Africa. In Southeast Asia and South America, similar pregnancy effects are seen due to infection with *P vivax,* which circulates more widely in those regions.

Malaria parasites are transmitted when an infected female *Anopheles* mosquito takes a human blood meal and releases *Plasmodium* into the bloodstream of another human host. (13) Parasites migrate to the liver and silently replicate within hepatocytes for 7 to 10 days before they are released back into the bloodstream. The parasites then invade the host red blood cells, progress through a 24- to 72-hour intraerythrocytic lifecycle, and then egress from the host cell to sequentially invade fresh cells. A small proportion of these blood-stage parasites develop into the sexual stage of the parasite that is then aspirated by a female anopheline mosquito during a blood meal to commence transmission to the next human host. (13)

Clinical Disease and Pathogenesis

Clinical symptoms typically appear 7 to 14 days after infection, though this interval and the severity of symptoms are heavily modified by the host's immunity. Mild or uncomplicated symptoms of malaria can include fever, headache, nausea, vomiting, and muscle aches. Severe malaria, most commonly caused by *P falciparum,* can manifest with respiratory distress, severe anemia, and cerebral malaria. These symptoms are mediated in part by the parasite's ability to export parasite proteins to the erythrocyte surface and thereby adhere to extracellular ligands. Adherence in

the microvascular endothelium activates this endothelium and widely promotes end organ damage owing to hemorrhage or infarct. (9)

Clinical and epidemiologic observations demonstrate that repeated infection with *Plasmodium* species promotes the acquisition of immunity to some aspects of clinical disease. (14) In highly endemic areas, the result is that severe infections are a disease of the young, and surviving these episodes attenuates the severity of school-age and adult infections. In contrast, in mesoendemic regions where exposure to malaria parasites is episodic rather than continuous, severe cases can develop across all ages. (14)(15) Consistent with these observations, people who are malaria naïve and therefore lack immune responses that attenuate disease are more likely to experience severe disease.

IMPACT OF MALARIA ON THE HEALTH OF THE PREGNANT PERSON, FETUS, AND NEONATE

Maternal Effects during Pregnancy

For nearly 100 years, it has been observed that pregnant persons are at higher risk of *P falciparum* infection compared to their nonpregnant peers, (16) and this risk has been correlated with observations of parasites sequestered in the intervillous spaces of placentae, (17) defining the syndrome of placental malaria. Furthermore, these elevated risks of parasitization and of placental malaria were observed to be highest among women in the first and second pregnancy and diminished with increasing gravidity. (18) This early work also revealed that the appearance of *P falciparum* parasites had consequences consistently for neonates who were born with lower birthweights if the placenta was infected with parasites. (18)

These observations were explained in part by the recognition that *P falciparum* harbors the capacity to bind to chondroitin sulfate A (CSA) in the syncytiotrophoblast, and that serum samples from multigravidae in endemic areas could interrupt this interaction. (19) Subsequent work established that *P falciparum* encodes a specific highly conserved protein called *VAR2CSA*, which is exported to the red blood cell surface and mediates adherence to CSA. (20) Anti-VAR2CSA antibodies are acquired in a gravidity-dependent manner and protect from placental malaria in subsequent pregnancies. (20) Thus, the *P falciparum*–specific syndrome of placental malaria is caused by a specific conserved parasite protein to which effective immune responses are eventually mounted in endemic areas. This phenomenon is generally less evident in regions with low or episodic malaria transmission. (21)

As noted earlier, sub-Saharan Africa has the highest burden of malaria, which includes a high burden of malaria among pregnant persons. (5) Each year, approximately 25 million pregnant persons in sub-Saharan Africa are at risk for *P falciparum* infection, and 25% of pregnant patients have evidence of placental infection at the time of delivery. (14) However, prevalence estimates might underrepresent the number of true cases of malaria in pregnancy due to diagnostic challenges. For example, prevalence estimates using placental infection at delivery likely underestimate the total number of pregnant persons with malaria because partially immune pregnant persons in endemic areas are able to clear parasites efficiently and therefore, might not have appreciable placental parasitic levels at delivery. Diagnostic tests using peripheral blood may also miss cases with lower levels of parasitemia, as peripheral parasite counts often underestimate the total number of parasites in the body. (9) As noted previously, the most common strain of *Plasmodium* in sub-Saharan Africa, *P falciparum*, can cause both placental and peripheral parasitemia. *P vivax*, common in Asia and the Americas, does not cytoadhere to the placenta yet still causes anemia in pregnant persons and LBW in infants. (14)

Malaria in Pregnancy: Effects on the Fetus

Malaria infection can occur anytime during pregnancy and negatively affect both the pregnant person and the developing fetus. The effect that a malarial infection has on the fetus, as well as currently available approaches to manage the infection, vary, based on trimester of infection and on whether the pregnant person receives appropriate medical treatment. In high-transmission regions, over 50% of pregnant persons can be infected with *P falciparum* at the time that they present to antenatal care. (22)(23) Younger patients, persons in their first or second pregnancy, and those who are malnourished or living with human immunodeficiency virus (HIV) have further increased risk of acquiring malaria parasites during pregnancy. (14)(24) Sub-Saharan Africa has the highest prevalence of women coinfected with malaria and HIV, an important concern for the region because, if untreated, coinfection leads to worse birth outcomes and worse overall morbidity and mortality for each disease. (25) In antenatal care practice, this biological interaction has been mitigated since the mid-2000s with the routine continuation of cotrimoxazole during pregnancy by HIV-infected women. (26) This can be an effective regimen to prevent antenatal malaria infections. (27) Figure 1 shows more information about HIV and malaria coinfection during pregnancy.

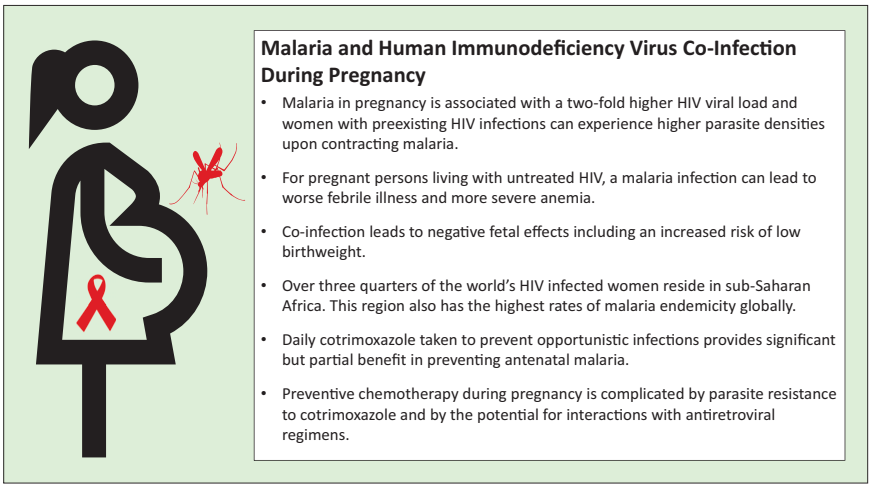

Figure 1. Malaria and human immunodeficiency (HIV) coinfection key points.

Malaria infections during the first trimester of pregnancy are common, with estimates that 20% to 65% of pregnant persons are infected during this period, (14)(28)(29) with increased prevalence observed in primigravidae. (30) These infections can result from either the persistence of parasites from the prenatal period or the acquisition of parasites during the first trimester. (31)

Malaria is associated with LBW infants, which can result from intrauterine growth restriction (IUGR), preterm birth, or a combination of both. The relative impact of malaria on IUGR versus preterm birth as drivers for LBW is best assessed by looking at high prevalence regions. In these settings, malaria is thought to contribute to up to 70% of IUGR cases but only 36% of preterm births. (32) Importantly, the risk for preterm birth was greater in women infected before 24 weeks' gestation. (33)

In malaria-endemic areas, malaria is estimated to cause 70% of IUGR cases. (34) These effects result from infections at any time during pregnancy. Early *P falciparum* infection restricts fetal growth by mid-pregnancy (35) and can increase the risk of IUGR by over 5-fold. (36) Placental malaria, which can result from infections at any gestational week following placentation, is associated with more than twice the risk of LBW compared with infants whose mothers were not infected with malaria in pregnancy. (34)(37) Given that LBW is consistently associated with both malaria in pregnancy and with an increased risk of infant mortality, (38)(39)(40) the prevention of LBW, both from IUGR and preterm birth, is a key indicator of the efficacy of malaria prevention strategies during pregnancy.

The IUGR that occurs in pregnancies complicated by *P falciparum* infection is the result of placental dysfunction and altered vasculature. During normal placentation before 20 weeks' gestation, placental extravillous trophoblasts invade the uterus, transform the spiral arteries, and establish blood supply to the placenta. (41) Malaria in pregnancy hinders uterine blood flow, (42)(43) and interferes with trophoblast invasion and migration. (44) This impaired trophoblast invasion and poor uterine vascularization are associated with IUGR. (41) Although these placental effects have been primarily attributed to inflammation as a result of placental parasite sequestration, abnormal placental vascularization in pregnant persons who had first trimester malaria infection has been observed even in the absence of histologic evidence of placental infection. (45) Altered placental angiogenesis contributes directly to poor nutrient transport, (46) owing to altered villous architecture (47) and decreased surface area for nutrient exchange. Fetal growth is further impaired because inflammation in the placenta has been linked to impaired transport of glucose (48) and interference with the insulin-like growth hormone axis. (49)

Stillbirth is a more recently recognized consequence of malaria in pregnancy. In a meta-analysis of clinical studies, *P falciparum* infection of either the placenta or blood of the pregnant person at delivery doubled the risk of stillbirth; a population-level projection estimated that, in malaria-endemic settings of sub-Saharan Africa, malaria infections during pregnancy contribute to nearly a fifth of all stillbirths. (6) The pathogenesis of malaria-associated stillbirth is poorly understood and may result from the malaria-specific placental dysfunction reviewed previously or as a more general response to acute infections. Because malaria infection can be reduced via appropriate prevention

and treatment strategies, malaria infection is among the most important modifiable causes of stillbirth in sub-Saharan Africa. (7)

Malaria in Pregnancy: Effects on the Pregnant Person

Malaria in pregnancy also negatively affects the health of the pregnant person with a wide spectrum of severity. Severity is generally mediated by the intensity of prior exposure to malaria parasites, which shapes adaptive immunity to the parasite. Although some pregnant patients infected with malaria do not experience any clinical symptoms, others suffer from severe anemia, fever, and even death. Estimates of the contribution of malaria to maternal mortality vary widely, ranging from 0.6% to 12.5% in low-transmission areas to 0.5% to 25% in malaria-endemic regions. (50) In regions with lower, or sporadic, transmission, pregnant persons acquire limited immunity to the effects of antenatal malaria, and though infection rates are lower, if these pregnant patients become infected, they are more likely to experience more severe complications such as cerebral malaria, renal failure, and pulmonary edema. (51)

Among milder sequelae that are the most prevalent in areas with moderate to high transmission, anemia is a consistent consequence for pregnant persons with malaria infection. Although anemia during pregnancy is undoubtedly multifactorial, it is estimated that in endemic regions of sub-Saharan Africa, up to 25% of anemia during pregnancy is attributable to malaria parasites. (14) Anemia, normally the result of a combination of hemolysis, increased splenic clearance of erythrocytes, and decreased red blood cell production, may be exacerbated in pregnancy by the additional sequestration of erythrocytes in the placenta, often leading to more severe anemia in pregnant persons. The contribution of malaria to anemia during pregnancy in endemic regions is underscored by the observation that the successful prevention of malaria reduces the risk of severe anemia during pregnancy by up to 38%. (50)

During the Newborn Period

Clinical symptoms of malaria are uncommon during infancy, and when present in the first 6 months of age, *P falciparum* infection tends to have minimal to no symptoms and be associated with lower parasite density than infections in older children. (52) The protection against malaria infection in young infants is believed to result from the transplacental passage of antibodies from the pregnant person as well as the expression in infant red blood cells of hemoglobin F, which creates an insalubrious intraerythrocytic environment for parasites. (53)(54) Both mechanisms confer protection that wanes with time, (52)(53) but significantly reduce parasite density in children younger than 6 months compared with children 1 to 9 years of age. (55) However, estimates of malaria prevalence in infants younger than 6 months vary by local transmission intensities, with some high transmission areas reporting rates over 20%. (56) In young children living in regions with high rates of transmission, recurrent infections during the newborn and early childhood period can lead to chronic anemia and splenomegaly, (9) thus affecting their overall health. Globally, more work is needed to explore rates and presentations of malaria in young infants and the varied effects of malarial infection on infant health.

Malaria infection in the pregnant person can have effects on the infant after birth. In malaria-endemic areas of sub-Saharan Africa, 80% of neonatal deaths occur in infants who are preterm or LBW. (3) As described previously, *P falciparum* infection is a common cause of preterm birth and IUGR (15) and thus, rates of malaria infection are a critical target to improve birth outcomes. Globally, placental malaria infection has been associated with increased mortality (57) and decreased weight and length gain during the first year after birth. (58)(59) In addition, the prevalence of anemia at birth is high in malaria-endemic regions, with higher rates seen in infants born to mothers with high levels of parasitemia at delivery. (60) Malaria in pregnancy also leads to an increased risk of anemia during infancy. (61) Lastly, data suggest that there may be an association between malaria in pregnancy and offspring with neurodevelopmental delay. (62) This finding suggests that, independent of birthweight or preterm delivery, fetal exposure to malaria infection may be a modifiable risk factor for neurodevelopmental outcomes.

Congenital malaria is defined as "the presence of asexual *P falciparum* parasites in the cord blood or in the peripheral blood during the first week of life." (63) Burden estimates vary widely owing to discrepancies in parasite detection methods and the potential for molecular testing to detect vertically transmitted parasite nucleic acid rather than viable parasites. When present, clinical symptoms of congenital malaria include fever, hepatosplenomegaly, hemolysis, anemia, thrombocytopenia, and poor feeding. (64) Congenital malaria is often confused with other, more common neonatal conditions that can delay diagnosis and treatment. (65) Severe cases can have rapid progression of symptoms and be fatal. (50)

Emerging evidence suggests that the exposure to malaria parasites in utero may modulate a newborn's risk of various infections in early childhood. Prenatal malaria exposure is associated with an increased risk of malaria infection during the first year of age. (63) Malaria infection during pregnancy interferes with the passage of nonmalaria antibodies from the pregnant person to the fetus, (52) thus compromising immunity of the newborn and making them more vulnerable to early infection. Malaria during pregnancy has also been linked to increased newborn susceptibility to nonmalarial infections, such as measles, (66)(67) *Streptococcus pneumoniae*, (67) and tetanus. (68) Similarly, infection with malaria may reduce an infant's response to routine childhood immunization. (69) These findings suggest broad negative effects on infant immunity due to impaired antibody passage across the placenta or other cryptic mechanisms. (70)

PREVENTION AND MANAGEMENT OF MALARIA DURING PREGNANCY

The management of malaria during pregnancy requires tailored approaches to prevention, diagnosis, and treatment of pregnant patients. Although the global burden of malaria is predominantly in sub-Saharan Africa, understanding how to prevent, detect, and treat malaria is important for clinicians in the United States who have patients traveling to endemic regions or are treating patients who recently emigrated from countries where malaria is transmitted. Figure 2 provides guidance about malaria treatment and prevention for clinicians in the United States.

Prevention

Prevention of malaria during pregnancy is critical to mitigate the adverse consequences detailed previously and is one of the pillars of management. Successful prevention of malaria is associated with significant reductions in LBW and neonatal mortality. (71)

The use of ITNs during pregnancy is a cornerstone of prevention. ITNs, like any bed net, offer some protection against malaria as they serve as a physical barrier and are also impregnated with insecticide to repel and kill mosquitos. (72) The widespread use of ITNs in sub-Saharan Africa averted more cases of malaria than any other control measure between 2000 and 2015. (73) Similarly, in pregnant women, ITN use is credited with reductions of 33% in miscarriages and stillbirths and 23% in LBW at delivery (74) as well as a specific decrease in the rate of placental malaria. (72) As of 2021, 47% of all people, and 53% of pregnant women, in sub-Saharan Africa reported sleeping under an ITN. (5) Given the potential to increase use of this valuable intervention, ITN distribution at antenatal clinics is considered a core component of high-quality antenatal care in malaria-endemic settings. An additional vector control intervention, indoor residual spraying (IRS) of insecticide to the interior of houses, is a highly effective method to reduce community parasite transmission. Although IRS has theoretical benefits to pregnant people and their offspring, (75)(76) it is currently unclear if IRS has an added benefit in communities using ITNs. (77) In addition, there is some concern about widespread use, given evidence that pesticides used for IRS are vertically transmitted to neonates and produce phenotypic effects. (78)

In moderate- and high-transmission settings, in which exposure to malaria parasites is frequent, chemoprevention strategies are commonly used to mitigate the consequences of infections during pregnancy, for both the pregnant person and offspring. Intermittent preventive treatment in pregnancy (IPTp) is a strategy whereby monthly doses of antimalarials are administered to a pregnant person beginning in the second trimester. Sulfadoxine-pyrimethamine (SP) is currently the only medication used for IPTp, and when taken monthly for at least 2 months, is associated with a risk reduction of 40% for moderate to severe anemia and 27% for LBW. (79) IPTp with SP is administered throughout most of malaria-

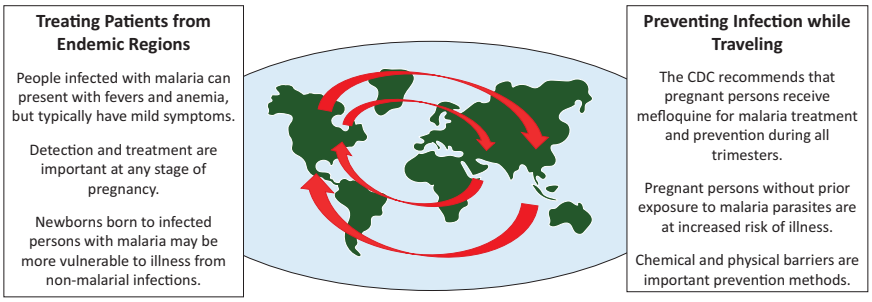

Figure 2. Malaria treatment and prevention guidance for clinicians in the United States.

endemic sub-Saharan Africa, where each successive dose of SP reduces the risk of LBW by 21% to 27%. (80) Multiple alternatives to SP as IPTp have been tested, including mefloquine, (81) chloroquine, (82) azithromycin-chloroquine, (83) and dihydroartemisinin-piperaquine (DP), (23)(84)(85) but none have proven superior to SP as an IPTp strategy for the prevention of LBW.

As an alternative to IPTp, a strategy of intermittent screening and treatment during pregnancy (ISTp) has been tested, wherein women are screened with a rapid diagnostic test at each visit, and if positive, treated with artemisinin-combination therapies (ACTs). ISTp with either artemether-lumefantrine (AL) (86) or DP (22)(85) has not been superior to IPTp-SP with regard to birth outcomes, and ISTp implementation is limited. A more promising alternative to IPTp-SP is IPTp with DP, also starting in the second trimester; in studies in Uganda (23)(84) and Kenya, (85) IPTp-DP was not shown to improve birth outcomes but was superior at preventing infections in the pregnant person and placenta. Current studies are exploring alternate DP administration strategies to enhance the efficacy of IPTp alternatives, including the pairing of DP with SP. (87)

Detection

The principal approaches to parasite detection for the diagnosis of malaria are light microscopy and rapid immunechromatographic diagnostic tests (RDTs). Other techniques, like molecular detection using polymerase chain reaction or loop-mediated isothermal amplification, are highly sensitive approaches that are generally reserved for research studies owing to resource availability and longer turnaround time. (15) To diagnose placental malaria, placental histopathology is the reference standard, but is not used in clinical settings for routine placental analysis.

Both RDTs and light microscopy are routinely used for diagnosis of malaria in pregnant and nonpregnant populations. Microscopy has been the traditional reference method, though the requirements for specialized equipment and a trained microscopist limit its efficacy and widespread use. In many settings, microscopy has been supplanted by routine RDTs, in which parasite antigens are detected using a lateral-flow cartridge with a visual readout, which requires little specialized training. Compared with a very sensitive polymerase chain reaction assay of parasites as the reference method, the sensitivity of conventional RDTs for detecting malaria parasites is 65% to 90% in primigravidae and 40% to 80% in secundigravidae. (22)(85)(86) Newer, high-sensitivity malaria RDTs are able to detect infection at a 10-fold lower limit compared with conventional RDTs and have shown increased clinical sensitivity, (88)(89) including during the first trimester, though they have not widely entered clinical practice. (29) Despite imperfect sensitivity, it is generally accepted that conventional RDTs effectively diagnose clinically significant cases of malaria in both pregnant and nonpregnant persons. What is heretofore unknown is the effect on pregnancy outcomes of low-density infections that are undetected with RDTs in pregnant patients, which may be clarified by an ongoing meta-analysis. (90)

Treatment

Malaria during pregnancy should be treated promptly to avoid potential complications for the pregnant person and her fetus. (91) Treatment of uncomplicated malaria involves balancing potential adverse fetal effects from drug toxicity and improved clinical outcomes of the pregnant person and newborn.

In all trimesters, ACTs are the first-line treatment for uncomplicated falciparum malaria, similar to treatment in nonpregnant adults. ACTs involve treating with a short-acting artemisinin component alongside a longer-acting "partner" drug, such as piperaquine, lumefantrine, or mefloquine. (92) Artemisinin acts to quickly reduce the number of circulating parasites, whereas the partner drug eliminates the remaining parasites and provides a post-treatment prophylactic effect.

In the second and third trimester, several ACTs are safe and effective. Specifically, ACT regimens have led to cure rates as high as 99.2% in uncomplicated malaria in pregnancy (93) and, relative to quinine, demonstrate improved birth outcomes. (94) The PregACT study from 2010–2013 randomized over 3,000 African women in the second and third trimesters to 1 of 4 ACTs for treatment. (93) All ACTs were highly effective as treatment, and though AL had the fewest side effects, it provided the shortest post-treatment period of prophylaxis of just 11 to 14 days. (95) In contrast, DP, which was also tolerated well, conferred up to 6 weeks of post-treatment prophylaxis.

In the first trimester, the first-line treatment for uncomplicated falciparum malaria is AL. (96)(97) This represents a break from tradition, which has historically been a 7-day course of quinine with clindamycin, but this regimen suffers from poor adherence and efficacy, and alternatives were limited by widespread resistance to chloroquine, the poor tolerability of mefloquine in pregnancy, (76)(95) and teratogenicity of SP and doxycycline. (96) Up to now, the use of ACTs has been limited by risks from animal models, including fetal loss, cardiovascular malformations, and skeletal anomalies, (98) in the absence of toxicity to the

Table. Ongoing Research and Gaps

Topic	Key Points
Treatment in the First Trimester	Infections can result from either the persistence of parasites from the prenatal period or the acquisition of parasites during the first trimester. (31) Artemether-lumefantrine is now the first-line treatment for uncomplicated malaria in the 1st trimester. (96)(97) Ongoing work is examining how to best implement malaria treatment programs in the 1st trimester.
Malaria Vaccine	The RTS,S/ASO1 vaccine is now recommended for children in regions with high rates of malaria transmission. (101) However, it is not under consideration for use in adults, including pregnant persons. Pregnancy-specific vaccines designed to prevent placental malaria by disrupting the ability of infected erythrocytes to sequester in the placenta are being developed. (102) Several other malaria vaccines are under various phases of development, with researchers hoping to achieve even higher rates of infection reduction.
Interaction between Aspirin in Pregnancy and Malaria Infection	Low-dose aspirin (LDA) is an effective strategy to reduce preterm birth. A multisite study in sub-Saharan Africa showed that LDA initiated between 6 and 13 weeks' gestation reduced preterm delivery and perinatal mortality. (103) Subanalysis of this study focused on pregnant women with malaria in early pregnancy and showed that malaria did not modify the effects of LDA on preterm birth, but was associated with less efficacy of LDA to reduce perinatal mortality. (104) As LDA becomes integrated into antenatal care globally, the effects of this intervention in malaria endemic locations should be monitored.
Maternal Iron Supplements and Malaria in Infants	Research from Burkina Faso explored whether infants of mothers who received weekly iron supplementation were at increased risk for malaria. Results showed that periconceptional iron supplementation did not alter the body iron stores of their children. Higher body iron stores increased the risk for childhood parasitemia. (105) A related study on the impact of long-term weekly iron supplementation in nulliparous women showed that this regimen was associated with a higher risk of preterm birth. (106)

pregnant animal. (99) However, in a recent meta-analysis of over 30,000 human pregnancies with over 500 exposures to ACTs in the first trimester, exposure to artemisinins in the first trimester was not associated with an increase in miscarriage, stillbirth, or congenital malformation. (100) These data led the World Health Organization to revise its treatment guidelines in 2022 to recommend AL as first-line treatment for uncomplicated falciparum malaria in the first trimester, (96) with the Centers for Disease Control and Prevention following suit. (97) Severe first-trimester cases of malaria are treated with the artemisinin derivative artesunate in parenteral form.

ONGOING RESEARCH AND GAPS

As malaria remains a key global health issue, there is ongoing research into prevention, treatment, and management of malaria infection. The Table highlights some key findings and remaining questions in the dynamic field of malarial research.

CONCLUSION

The global burden of malaria in pregnancy is significant. Infection with malaria during pregnancy can have deleterious effects on the developing fetus, including preterm delivery, LBW, and stillbirth. Affected infants are at increased risk for anemia, childhood infection with malaria or other infectious agents, and poor growth that continues into early childhood. While strong prevention and detection methods exist, coverage of these techniques in endemic areas remains below global targets. Ongoing work into improved treatment and prevention approaches remains at the forefront of global maternal child health research.

American Board of Pediatrics Neonatal-Perinatal Content Specification

- Know the clinical manifestations, diagnostic features, management, and complications of neonatal malaria.
- Know the effects on the fetus and/or newborn infant of other maternal infections (eg, malaria) and their management.

References

1. World Health Organization. *World Health Statistics Data Visualizations Dashboard*. Geneva, Switzerland: World Health

Organization; 2017, Available at: http://apps.who.int/gho/data/view.sdg.3-2-data-reg?lang=. Accessed June 10, 2023

2. Hug L, Alexander M, You D, Alkema L; UN Inter-agency Group for Child Mortality Estimation. National, regional, and global levels and trends in neonatal mortality between 1990 and 2017, with scenario-based projections to 2030: a systematic analysis. *Lancet Glob Health*. 2019;7(6):e710–e720
3. Lawn JE, Blencowe H, Oza S, et al; Lancet Every Newborn Study Group. Every newborn: progress, priorities, and potential beyond survival. *Lancet*. 2014;384(9938):189–205
4. Dellicour S, Tatem AJ, Guerra CA, Snow RW, ter Kuile FO. Quantifying the number of pregnancies at risk of malaria in 2007: a demographic study. *PLoS Med*. 2010;7(1):e1000221
5. World Health Organization. World Malaria Report 2022. Geneva, Switzerland: World Health Organization; 2022. Available at: https://www.who.int/teams/global-malaria-programme/reports/world-malaria-report-2022. Accessed June 10, 2023
6. Moore KA, Simpson JA, Scoullar MJL, McGready R, Fowkes FJI. Quantification of the association between malaria in pregnancy and stillbirth: a systematic review and meta-analysis. *Lancet Glob Health*. 2017;5(11):e1101–e1112
7. Lawn JE, Blencowe H, Waiswa P, et al; Lancet Ending Preventable Stillbirths Series study group; Lancet Stillbirth Epidemiology investigator group. Stillbirths: rates, risk factors, and acceleration towards 2030. *Lancet*. 2016;387(10018):587–603
8. Schantz-Dunn J, Nour NM. Malaria and pregnancy: a global health perspective. *Rev Obstet Gynecol*. 2009;2(3):186–192
9. White NJ, Pukrittayakamee S, Hien TT, Faiz MA, Mokuolu OA, Dondorp AM. Malaria. *Lancet*. 2014;383(9918):723–735
10. Paul J. Millenium development goals: world health and population. *World Health Popul*. 2008;10(2):3–4
11. Liu L, Oza S, Hogan D, et al. Global, regional, and national causes of under-5 mortality in 2000-15: an updated systematic analysis with implications for the Sustainable Development Goals. *Lancet*. 2016;388(10063):3027–3035
12. Inter-Agency and Expert Group on MDG Indicators led by the Department of Economic and Social Affairs of the United Nations Secretariat. The Millennium Development Goals Report 2015. New York, NY: United Nations; 2016 Available at: https://www.un.org/millenniumgoals/2015_MDG_Report/pdf/MDG%202015%20rev%20(July%201).pdf. Accessed June 10, 2023
13. Taylor SM, Molyneux ME, Simel DL, Meshnick SR, Juliano JJ. Does this patient have malaria? *JAMA*. 2010;304(18):2048–2056
14. Desai M, ter Kuile FO, Nosten F, et al. Epidemiology and burden of malaria in pregnancy. *Lancet Infect Dis*. 2007;7(2):93–104
15. Rogerson SJ, Desai M, Mayor A, Sicuri E, Taylor SM, van Eijk AM. Burden, pathology, and costs of malaria in pregnancy: new developments for an old problem. *Lancet Infect Dis*. 2018;18(4):e107–e118
16. Wickramasuriya GAW. Some observations on malaria occurring in association with pregnancy. with special reference to the transplacental passage of parasites from the maternal to the foetal circulation. *J Obstet Gynaecol Br Emp*. 1935;42(5):816–834
17. McGregor IA. Epidemiology, malaria and pregnancy. *Am J Trop Med Hyg*. 1984;33(4):517–525
18. Brabin BJ. An analysis of malaria in pregnancy in Africa. *Bull World Health Organ*. 1983;61(6):1005–1016
19. Ayres Pereira M, Mandel Clausen T, Pehrson C, et al. Placental sequestration of plasmodium falciparum malaria parasites Is mediated by the interaction between VAR2CSA and chondroitin sulfate A on syndecan-1. *PLoS Pathog*. 2016;12(8):e1005831
20. Moore KA, Fowkes FJI, Wiladphaingern J, et al. Mediation of the effect of malaria in pregnancy on stillbirth and neonatal death in an area of low transmission: observational data analysis. *BMC Med*. 2017;15(1):98
21. Newman RD, Hailemariam A, Jimma D, et al. Burden of malaria during pregnancy in areas of stable and unstable transmission in Ethiopia during a nonepidemic year. *J Infect Dis*. 2003;187(11):1765–1772
22. Madanitsa M, Kalilani L, Mwapasa V, et al. Scheduled intermittent screening with rapid diagnostic tests and treatment with dihydroartemisinin-piperaquine versus intermittent preventive therapy with sulfadoxine-pyrimethamine for malaria in pregnancy in Malawi: an open-label randomized controlled trial. *PLoS Med*. 2016;13(9):e1002124
23. Kakuru A, Jagannathan P, Muhindo MK, et al. Dihydroartemisinin-piperaquine for the prevention of malaria in pregnancy. *N Engl J Med*. 2016;374(10):928–939
24. Ataíde R, Mayor A, Rogerson SJ. Malaria, primigravidae, and antibodies: knowledge gained and future perspectives. *Trends Parasitol*. 2014;30(2):85–94
25. ter Kuile FO, Parise ME, Verhoeff FH, et al. The burden of co-infection with human immunodeficiency virus type 1 and malaria in pregnant women in sub-saharan Africa. *Am J Trop Med Hyg*. 2004;71(2 Suppl):41–54
26. World Health Organization. *Guidelines on Co-trimoxazole Prophylaxis for HIV-related Infections among Children, Adolescents and Adults in Resource-limited Settings: Recommendations for a Public Health Approach*. Geneva, Switzerland: World Health Organization; 2006
27. Kapito-Tembo A, Meshnick SR, van Hensbroek MB, Phiri K, Fitzgerald M, Mwapasa V. Marked reduction in prevalence of malaria parasitemia and anemia in HIV-infected pregnant women taking cotrimoxazole with or without sulfadoxine-pyrimethamine intermittent preventive therapy during pregnancy in Malawi. *J Infect Dis*. 2011;203(4):464–472
28. Tuikue Ndam N, Tornyigah B, Dossou AY, et al. Persistent *Plasmodium falciparum* infection in women with an intent to become pregnant as a risk factor for pregnancy-associated malaria. *Clin Infect Dis*. 2018;67(12):1890–1896
29. Briand V, Cottrell G, Tuike Ndam N, et al. Prevalence and clinical impact of malaria infections detected with a highly sensitive HRP2 rapid diagnostic test in Beninese pregnant women. *Malar J*. 2020;19(1):188
30. Hounkonnou CPA, Briand V, Fievet N, et al. Dynamics of submicroscopic *Plasmodium falciparum* infections throughout pregnancy: a preconception cohort study in Benin. *Clin Infect Dis*. 2020;71(1):166–174
31. Jafari-Guemouri S, Courtois L, Mama A, et al. A genotyping study in Benin comparing the carriage of *Plasmodium falciparum* infections before pregnancy and in early pregnancy: story of a persistent infection. *Clin Infect Dis*. 2021;73(2):e355–e361
32. Steketee RW, Nahlen BL, Parise ME, Menendez C. The burden of malaria in pregnancy in malaria-endemic areas. *Am J Trop Med Hyg*. 2001;64(1-2 suppl):28–35
33. Elphinstone RE, Weckman AM, McDonald CR, et al. Early malaria infection, dysregulation of angiogenesis, metabolism and inflammation across pregnancy, and risk of preterm birth in Malawi: a cohort study. *PLoS Med*. 2019;16(10):e1002914

34. Guyatt HL, Snow RW. Impact of malaria during pregnancy on low birth weight in sub-Saharan Africa. *Clin Microbiol Rev*. 2004;17(4):760–769

35. Rijken MJ, Papageorghiou AT, Thiptharakun S, et al. Ultrasound evidence of early fetal growth restriction after maternal malaria infection. *PLoS One*. 2012;7(2):e31411

36. Griffin JB, Lokomba V, Landis SH, et al. *Plasmodium falciparum* parasitaemia in the first half of pregnancy, uterine and umbilical artery blood flow, and foetal growth: a longitudinal Doppler ultrasound study. *Malar J*. 2012;11:319

37. Ofori M, Ansah E, Agyepong I, Ofori-Adjei D, Hviid L, Akanmori B. Pregnancy-associated malaria in a rural community of ghana. *Ghana Med J*. 2009;43(1):13–18

38. Umbers AJ, Aitken EH, Rogerson SJ. Malaria in pregnancy: small babies, big problem. *Trends Parasitol*. 2011;27(4):168–175

39. Vilanova CS, Hirakata VN, de Souza Buriol VC, Nunes M, Goldani MZ, da Silva CH. The relationship between the different low birth weight strata of newborns with infant mortality and the influence of the main health determinants in the extreme south of Brazil. *Popul Health Metr*. 2019;17(1):15

40. Macdorman MF, Mathews TJ. Recent trends in infant mortality in the United States. *NCHS Data Brief*. 2008;9:1–8

41. Kaufmann P, Black S, Huppertz B. Endovascular trophoblast invasion: implications for the pathogenesis of intrauterine growth retardation and preeclampsia. *Biol Reprod*. 2003;69(1):1–7

42. Dorman EK, Shulman CE, Kingdom J, et al. Impaired uteroplacental blood flow in pregnancies complicated by falciparum malaria. *Ultrasound Obstet Gynecol*. 2002;19(2):165–170

43. Chua CLL, Khoo SKM, Ong JLE, Ramireddi GK, Yeo TW, Teo A. Malaria in pregnancy: from placental infection to its abnormal development and damage. *Front Microbiol*. 2021;12:777343

44. Umbers AJ, Stanisic DI, Ome M, et al. Does malaria affect placental development? Evidence from in vitro models. *PLoS One*. 2013;8(1):e55269

45. Moeller SL, Nyengaard JR, Larsen LG, et al. Malaria in early pregnancy and the development of the placental vasculature. *J Infect Dis*. 2019;220(9):1425–1434

46. Conroy AL, Silver KL, Zhong K, et al. Complement activation and the resulting placental vascular insufficiency drives fetal growth restriction associated with placental malaria. *Cell Host Microbe*. 2013;13(2):215–226

47. Chaikitgosiyakul S, Rijken MJ, Muehlenbachs A, et al. A morphometric and histological study of placental malaria shows significant changes to villous architecture in both *Plasmodium falciparum* and *Plasmodium vivax* infection. *Malar J*. 2014;13:4

48. Chandrasiri UP, Chua CL, Umbers AJ, et al. Insight into the pathogenesis of fetal growth restriction in placental malaria: decreased placental glucose transporter isoform 1 expression. *J Infect Dis*. 2014;209(10):1663–1667

49. Umbers AJ, Boeuf P, Clapham C, et al. Placental malaria-associated inflammation disturbs the insulin-like growth factor axis of fetal growth regulation. *J Infect Dis*. 2011;203(4):561–569

50. Garner P, Gülmezoglu AM. Drugs for preventing malaria in pregnant women. *Cochrane Database Syst Rev*. 2006; (4):CD000169

51. Menendez C. Malaria during pregnancy. *Curr Mol Med*. 2006;6(2):269–273

52. McLean ARD, Stanisic D, McGready R, et al. *P. falciparum* infection and maternofetal antibody transfer in malaria-endemic settings of varying transmission. *PLoS One*. 2017;12(10):e0186577

53. Dobbs KR, Dent AE. Plasmodium malaria and antimalarial antibodies in the first year of life. *Parasitology*. 2016;143(2):129–138

54. Amaratunga C, Lopera-Mesa TM, Brittain NJ, et al. A role for fetal hemoglobin and maternal immune IgG in infant resistance to *Plasmodium falciparum* malaria. *PLoS One*. 2011;6(4):e14798

55. Mormina M, Pinder S. A conceptual framework for training of trainers (ToT) interventions in global health. *Global Health*. 2018;14(1):100

56. Ceesay SJ, Koivogui L, Nahum A, et al. Malaria prevalence among young infants in different transmission settings, Africa. *Emerg Infect Dis*. 2015;21(7):1114–1121

57. Verhoeff FH, Le Cessie S, Kalanda BF, Kazembe PN, Broadhead RL, Brabin BJ. Post-neonatal infant mortality in Malawi: the importance of maternal health. *Ann Trop Paediatr*. 2004;24(2):161–169

58. Walther B, Miles DJ, Crozier S, et al. Placental malaria is associated with reduced early life weight development of affected children independent of low birth weight. *Malar J*. 2010;9:16

59. De Beaudrap P, Turyakira E, Nabasumba C, et al. Timing of malaria in pregnancy and impact on infant growth and morbidity: a cohort study in Uganda. *Malar J*. 2016;15:92

60. Brabin BJ, Kalanda BF, Verhoeff FH, Chimsuku LH, Broadhead RL. Risk factors for fetal anaemia in a malarious area of Malawi. *Ann Trop Paediatr*. 2004;24(4):311–321

61. Accrombessi M, Ouédraogo S, Agbota GC, et al. Malaria in pregnancy is a predictor of infant haemoglobin concentrations during the first year of life in Benin, West Africa. *PLoS One*. 2015;10(6):e0129510

62. Weckman AM, Conroy AL, Madanitsa M, et al. Neurocognitive outcomes in Malawian children exposed to malaria during pregnancy: An observational birth cohort study. *PLoS Med*. 2021;18(9):e1003701

63. Moya-Alvarez V, Abellana R, Cot M. Pregnancy-associated malaria and malaria in infants: an old problem with present consequences. *Malar J*. 2014;13:271

64. Menendez C, Mayor A. Congenital malaria: the least known consequence of malaria in pregnancy. *Semin Fetal Neonatal Med*. 2007;12(3):207–213

65. Nwaneli EI, Nri-Ezedi CA, Okeke KN, Edokwe ES, Echendu ST, Iloh KK. Congenital cerebral malaria: a masquerader in a neonate. *Malar J*. 2022;21(1):34

66. Owens S, Harper G, Amuasi J, Offei-Larbi G, Ordi J, Brabin BJ. Placental malaria and immunity to infant measles. *Arch Dis Child*. 2006;91(6):507–508

67. de Moraes-Pinto MI, Verhoeff F, Chimsuku L, et al. Placental antibody transfer: influence of maternal HIV infection and placental malaria. *Arch Dis Child Fetal Neonatal Ed*. 1998;79(3):F202–F205

68. Brair ME, Brabin BJ, Milligan P, Maxwell S, Hart CA. Reduced transfer of tetanus antibodies with placental malaria. *Lancet*. 1994;343(8891):208–209

69. Kizito D, Tweyongyere R, Namatovu A, et al. Factors affecting the infant antibody response to measles immunisation in Entebbe-Uganda. *BMC Public Health*. 2013;13:619

70. Rachas A, Le Port A, Cottrell G, et al. Placental malaria is associated with increased risk of nonmalaria infection during the first 18 months of life in a Beninese population. *Clin Infect Dis*. 2012;55(5):672–678

71. Eisele TP, Larsen DA, Anglewicz PA, et al. Malaria prevention in pregnancy, birthweight, and neonatal mortality: a meta-analysis of 32 national cross-sectional datasets in Africa. *Lancet Infect Dis*. 2012;12(12):942–949

72. Gamble C, Ekwaru JP, ter Kuile FO. Insecticide-treated nets for preventing malaria in pregnancy. *Cochrane Database Syst Rev*. 2006;2006(2):CD003755

73. Bhatt S, Weiss DJ, Cameron E, et al. The effect of malaria control on *Plasmodium falciparum* in Africa between 2000 and 2015. *Nature*. 2015;526(7572):207–211

74. Gamble C, Ekwaru PJ, Garner P, ter Kuile FO. Insecticide-treated nets for the prevention of malaria in pregnancy: a systematic review of randomised controlled trials. *PLoS Med*. 2007;4(3):e107

75. Roh ME, Shiboski S, Natureeba P, et al. Protective effect of indoor residual spraying of insecticide on preterm birth among pregnant women with HIV infection in Uganda: a secondary data analysis. *J Infect Dis*. 2017;216(12):1541–1549

76. Muhindo MK, Kakuru A, Natureeba P, et al. Reductions in malaria in pregnancy and adverse birth outcomes following indoor residual spraying of insecticide in Uganda. *Malar J*. 2016;15(1):437

77. Choi L, Pryce J, Garner P. Indoor residual spraying for preventing malaria in communities using insecticide-treated nets. *Cochrane Database Syst Rev*. 2019;5(5):CD012688

78. Prahl M, Odorizzi P, Gingrich D, et al. Exposure to pesticides in utero impacts the fetal immune system and response to vaccination in infancy. *Nat Commun*. 2021;12(1):132

79. Radeva-Petrova D, Kayentao K, ter Kuile FO, Sinclair D, Garner P. Drugs for preventing malaria in pregnant women in endemic areas: any drug regimen versus placebo or no treatment. *Cochrane Database Syst Rev*. 2014;2014(10):CD000169

80. van Eijk AM, Larsen DA, Kayentao K, et al. Effect of Plasmodium falciparum sulfadoxine-pyrimethamine resistance on the effectiveness of intermittent preventive therapy for malaria in pregnancy in Africa: a systematic review and meta-analysis. *Lancet Infect Dis*. 2019;19(5):546–556

81. González R, Mombo-Ngoma G, Ouédraogo S, et al. Intermittent preventive treatment of malaria in pregnancy with mefloquine in HIV-negative women: a multicentre randomized controlled trial. *PLoS Med*. 2014;11(9):e1001733

82. Divala TH, Mungwira RG, Mawindo PM, et al. Chloroquine as weekly chemoprophylaxis or intermittent treatment to prevent malaria in pregnancy in Malawi: a randomised controlled trial. *Lancet Infect Dis*. 2018;18(10):1097–1107

83. Kimani J, Phiri K, Kamiza S, et al. Efficacy and Safety of Azithromycin-Chloroquine versus Sulfadoxine-Pyrimethamine for Intermittent Preventive Treatment of *Plasmodium falciparum* malaria infection in pregnant women in Africa: an open-label, randomized trial. *PLoS One*. 2016;11(6):e0157045

84. Kajubi R, Ochieng T, Kakuru A, et al. Monthly sulfadoxine-pyrimethamine versus dihydroartemisinin-piperaquine for intermittent preventive treatment of malaria in pregnancy: a double-blind, randomised, controlled, superiority trial. *Lancet*. 2019;393(10179):1428–1439

85. Desai M, Gutman J, L'lanziva A, et al. Intermittent screening and treatment or intermittent preventive treatment with dihydroartemisinin-piperaquine versus intermittent preventive treatment with sulfadoxine-pyrimethamine for the control of malaria during pregnancy in western Kenya: an open-label, three-group, randomised controlled superiority trial. *Lancet*. 2015;386(10012):2507–2519

86. Tagbor H, Cairns M, Bojang K, et al. A non-inferiority, individually randomized trial of intermittent screening and treatment versus intermittent preventive treatment in the control of malaria in pregnancy. *PLoS One*. 2015;10(8):e0132247

87. National Institutes of Health. Sulfadoxine-pyrimethamine plus dihydroartemisinin-piperaquine for intermittent preventive treatment in pregnancy (NCT05426434). 2022 Available at: https://www.clinicaltrials.gov/ct2/show/NCT05426434 Accessed June 10, 2023

88. Das S, Jang IK, Barney B, et al. Performance of a high-sensitivity rapid diagnostic test for *Plasmodium falciparum* malaria in asymptomatic individuals from Uganda and Myanmar and naive human challenge infections. *Am J Trop Med Hyg*. 2017;97(5):1540–1550

89. Landier J, Haohankhunnatham W, Das S, et al. Operational performance of a *Plasmodium falciparum* ultrasensitive rapid diagnostic test for detection of asymptomatic infections in Eastern Myanmar. *J Clin Microbiol*. 2018;56(8):e00565-18

90. van Eijk AM, Rogerson S, Taylor S, et al; National Institute for Health and Care Research (PROSPERO). Protocol for a systematic review and meta-analysis of the relationship between subpatent malaria infection and pregnancy/pregnancy outcome. 2015 PROSPERO 2015 CRD42015027342. Available at: https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42015027342. Accessed June 10, 2023

91. D'Alessandro U, Hill J, Tarning J, et al. Treatment of uncomplicated and severe malaria during pregnancy. *Lancet Infect Dis*. 2018;18(4):e133–e146

92. Tarning J. Treatment of malaria in pregnancy. *N Engl J Med*. 2016;374(10):981–982

93. Pekyi D, Ampromfi AA, Tinto H, et al; PREGACT Study Group. Four Artemisinin-based treatments in African pregnant women with Malaria. *N Engl J Med*. 2016;374(10):913–927

94. Burger RJ, van Eijk AM, Bussink M, Hill J, Ter Kuile FO. Artemisinin-based combination therapy versus quinine or other combinations for treatment of uncomplicated *Plasmodium falciparum* malaria in the second and third trimester of pregnancy: a systematic review and meta-analysis. *Open Forum Infect Dis*. 2015;3(1):ofv170

95. Bretscher MT, Dahal P, Griffin J, et al. The duration of chemoprophylaxis against malaria after treatment with artesunate-amodiaquine and artemether-lumefantrine and the effects of pfmdr1 86Y and pfcrt 76T: a meta-analysis of individual patient data. *BMC Med*. 2020;18(1):47

96. World Health Organization. WHO Guidelines for Malaria Geneva. 2022 Available at: https://www.who.int/publications/i/item/guidelines-for-malaria. Accessed June 10, 2023

97. Centers for Disease Control and Prevention. Malaria treatment (United States). 2023. Available from: https://www.cdc.gov/malaria/diagnosis_treatment/treatment.html. Accessed June 10, 2023

98. Clark RL, White TE, A Clode S, Gaunt I, Winstanley P, Ward SA. Developmental toxicity of artesunate and an artesunate combination in the rat and rabbit. *Birth Defects Res B Dev Reprod Toxicol*. 2004;71(6):380–394

99. Clark RL, Lerman SA, Cox EM, Gristwood WE, White TE. Developmental toxicity of artesunate in the rat: comparison to other artemisinins, comparison of embryotoxicity and kinetics by oral and intravenous routes, and relationship to maternal reticulocyte count. *Birth Defects Res B Dev Reprod Toxicol*. 2008;83(4):397–406

100. Dellicour S, Sevene E, McGready R, et al. First-trimester artemisinin derivatives and quinine treatments and the risk of adverse pregnancy outcomes in Africa and Asia: a meta-analysis of observational studies. *PLoS Med*. 2017;14(5):e1002290

101. World Health Organization. WHO recommends groundbreaking malaria vaccine for children at risk 2021. Available at: https://www.who.int/news/item/06-10-2021-who-recommends-

groundbreaking-malaria-vaccine-for-children-at-risk. Accessed June 10, 2023

102. Gamain B, Chêne A, Viebig NK, Tuikue Ndam N, Nielsen MA. Progress and insights toward an effective placental malaria vaccine. *Front Immunol*. 2021;12:634508

103. Hoffman MK, Goudar SS, Kodkany BS, et al; ASPIRIN Study Group. Low-dose aspirin for the prevention of preterm delivery in nulliparous women with a singleton pregnancy (ASPIRIN): a randomised, double-blind, placebo-controlled trial. *Lancet*. 2020;395(10220):285–293

104. Bauserman M, Leuba SI, Hemingway-Foday J, et al. The efficacy of low-dose aspirin in pregnancy among women in malaria-endemic countries. *BMC Pregnancy Childbirth*. 2022;22(1):303

105. Gies S, Roberts SA, Diallo S, Lompo OM, Tinto H, Brabin BJ. Risk of malaria in young children after periconceptional iron supplementation. *Matern Child Nutr*. 2021;17(2):e13106

106. Brabin B, Gies S, Roberts SA, et al. Excess risk of preterm birth with periconceptional iron supplementation in a malaria endemic area: analysis of secondary data on birth outcomes in a double blind randomized controlled safety trial in Burkina Faso. *Malar J*. 2019;18(1):161

NEO QUIZ

1. Malaria infection during pregnancy is associated with preterm birth, low birthweight and stillbirth. Which of the following malaria parasite is responsible for the majority of adverse outcomes during pregnancy?

   A. *P falciparum*.
   B. *P knowlesi*.
   C. *Plasmodium (P) ovale*.
   D. *P malariae*.
   E. *P vivax*.

2. The risk of *P falciparum* malaria infection is higher during pregnancy due to parasite sequestration in the intervillous spaces of the placenta. Which of the following statement regarding risk factors for malaria infection during pregnancy is correct?

   A. Advanced maternal age.
   B. Co-occurring iron-deficiency anemia.
   C. Gestational diabetes.
   D. Primiparity.
   E. Obesity.

3. Malaria infection can occur anytime during pregnancy and can negatively affect the fetus. Which of the following statement regarding the impact of malaria infection on the fetus is correct?

   A. In high endemic regions, malaria accounts for 30% of intrauterine growth restriction cases (IUGR).
   B. In high endemic regions, malaria accounts for 15% of preterm births.
   C. In malaria endemic settings, malaria infection contributes up to 40% of all stillbirths.
   D. The risk of IUGR is highest in infections caused by *P ovale*.
   E. The risk of preterm birth is increased when the infection occurs before 24 weeks of gestation.

4. Congenital malaria is defined as the identification of asexual *P falciparum* parasites in the cord blood or the newborn's peripheral blood during the first week after birth. Which of the following DOES NOT represent a typical presentation of congenital malaria?

   A. Anemia.
   B. Hepatosplenomegaly.
   C. Hemolysis.
   D. Hypothermia.
   E. Thrombocytopenia.

REQUIREMENTS: Learners can take *NeoReviews* quizzes and claim credit online only at: https://publications.aap.org/neoreviews.

To successfully complete 2023 *NeoReviews* articles for *AMA PRA Category 1 Credit*™, learners must demonstrate a minimum performance level of 60% or higher on this assessment. If you score less than 60% on the assessment, you will be given additional opportunities to answer questions until an overall 60% or greater score is achieved.

This journal-based CME activity is available through Dec. 31, 2025, however, credit will be recorded in the year in which the learner completes the quiz.

2023 *NeoReviews* is approved for a total of 30 Maintenance of Certification (MOC) Part 2 credits by the American Board of Pediatrics (ABP) through the AAP MOC Portfolio Program. *NeoReviews* subscribers can claim up to 30 ABP MOC Part 2 points upon passing 30 quizzes (and claiming full credit for each quiz) per year. Subscribers can start claiming MOC credits as early as October 2023. To learn how to claim MOC points, go to: https://publications.aap.org/journals/pages/moc-credit.

5. Prompt treatment of malaria infection during pregnancy is required to prevent complications for both the pregnant person and the fetus. When selecting a treatment regimen, it is critical to consider potential adverse fetal effects and pregnancy timing. Artemisin-combination therapies (ACTs) represent the first-line therapy in non-pregnant individuals. ACTs involve the use of a short-acting artemisinin component in combination with a longer acting drug such as piperaquine, lumefantrine or mefloquine. Which the following statement regarding treatment of malaria during pregnancy is correct?

   A. A 7-day course of quinine and clindamycin is the first-line treatment regimen for uncomplicated *P falciparum* infection during the first trimester of pregnancy.
   B. Cure rates with ACT regimens are lower in the second and third trimester compared with the first trimester of pregnancy.
   C. Chloroquine is the recommended regimen for uncomplicated malaria infection in the first trimester if adherence to treatment regimen is a concern.
   D. In a randomized controlled trial, treatment with artemether-lumefantrine was noted to have the least side effects.
   E. Treatment with artemether-lumefantrine confers post-treatment prophylaxis for up to 12 weeks.