Malaria

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Epidemiology

More than 100 million pregnant women acquire malaria annually [1]. Pregnant women—particularly primigravidas—are at higher risk of both infection and poor pregnancy outcomes. These include spontaneous abortion, stillbirths, and growth restriction [2]. Malaria in pregnancy contributes to approximately 200,000 infant deaths annually in addition to an unknown number of early pregnancy losses. The majority of pregnant women who acquire malaria reside and deliver in endemic areas, but an increasing number of pregnant women who reside in areas without malaria are acquiring travel-related malaria during their pregnancy and returning home to deliver (Fig. 1) [3–11].

Pathogenesis

Protection against malaria is conferred largely by antibody [12]. Pregnant women who have never been exposed to malaria (i.e., travelers from non-endemic regions) are at the highest risk. For women living in endemic regions, increasing age and increasing parity are associated with protective antibody levels and decreased risk for clinically apparent malaria [13, 14]. Therefore, young women and primigravidas are at higher risk for malaria in pregnancy [15].

The transmission of malaria to the fetus is shown in Fig. 2. Within 30 min of a mosquito bite, sporozoite forms of *Plasmodium sp.* are injected into the blood and spread to the liver, where they mature into schizonts. Each schizont contains

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J. B. Cantey (ed.), *Neonatal Infections*, https://doi.org/10.1007/978-3-319-90038-4_16

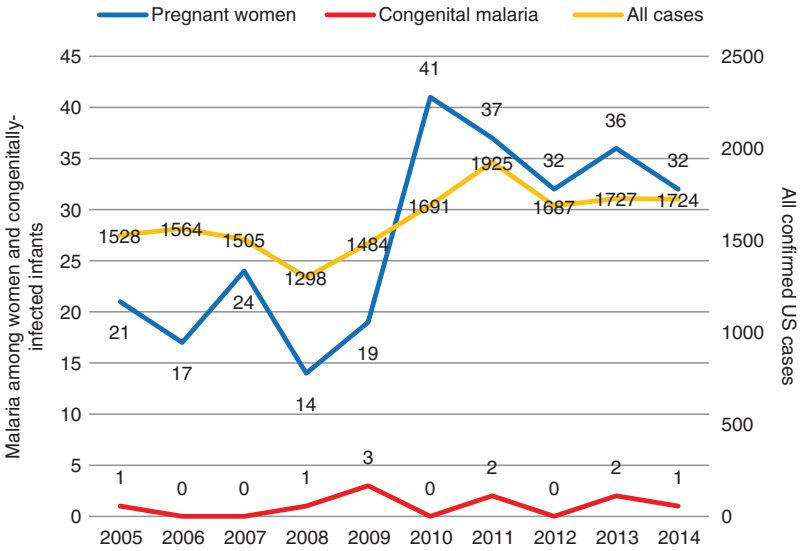

Fig. 1 US surveillance data from the CDC during the 10-year period from 2005 to 2014 [3–11]. Despite increasing incidence of malaria overall (yellow line) and among pregnant women (blue line), congenital malaria remains rare (red line). However, the outcome of the pregnancy was not known in many cases, and therefore congenital malaria rates may be underrecognized

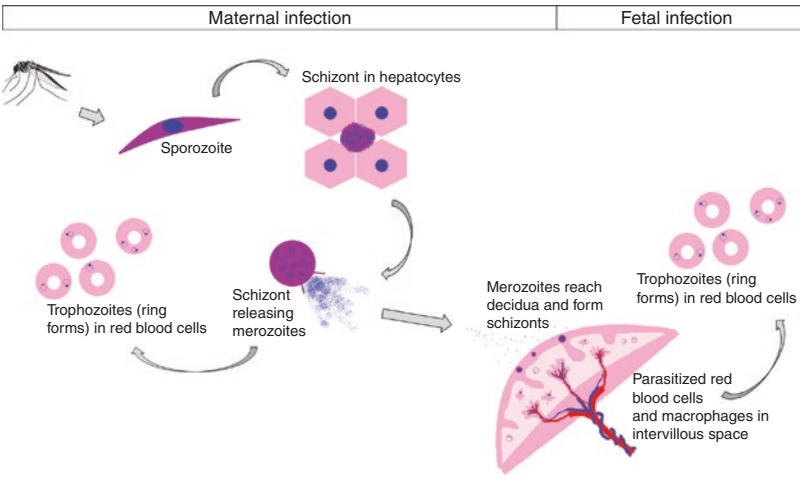

Fig. 2 The stages of maternal-fetal malaria infection are shown here. Mosquitos inject sporozoites into maternal circulation during a blood meal. Sporozoites infect hepatocytes and mature into schizonts, which release merozoites into maternal circulation. Merozoites that infect maternal red blood cells become trophozoites (the characteristic "ring forms" of malaria) or gametocytes (not shown, allow reproduction inside the mosquito when gametocytes are ingested during a subsequent blood meal). Merozoites that reach the maternal side of the placenta (decidua) will infect endometrial cells and mature into schizonts. Malaria reaches the intervillous space either by translocation of the parasite directly via antigen/antibody complexes, infected red blood cells, or within macrophages. In 95% of the cases, the placenta is able to prevent transmission to the fetus. In the remaining 5%, parasites reach the fetus and can lead to true congenital malaria

thousands of merozoites, which are released into the blood. Merozoites then infect red blood cells and become trophozoites (ring forms). The trophozoite within each cell then matures into a schizont and ruptures, causing marked hemolysis and inflammation. The newly released merozoites are capable of infecting new red blood cells in turn, leading to cycles of hemolysis and fever [16].

When merozoites reach the maternal side of the placenta (the decidua), they can infect both endometrial cells as well as the decidual macrophages. The intervillous space becomes crowded with parasite-infected macrophages, decreasing nutrition and oxygen exchange and contributing to fetal growth restriction [17].

In rare cases, *Plasmodium sp*. can reach fetal circulation either by maternal-fetal hemorrhage or active transport of antibody-*Plasmodium* complexes. However, the placenta is an effective barrier to fetal transmission; only approximately 5% of infants with infected placentas will have parasitemia [15].

To complicate matters, sporozoite forms of *P. vivax* and *P. ovale* are capable of forming hypnozoites ("sleeping animals" in Greek) that can remain latent within hepatocytes for prolonged periods before reactivating. Since hypnozoites are not susceptible to all anti-parasitic therapies, maternal treatment of *P. vivax* and *P. ovale* requires the addition of primaquine. However, sporozoites are not transmitted to the fetus in congenital malaria, so treatment of newborns with primaquine is not necessary (see Treatment, below).

Clinical Findings

Growth Restriction and Prematurity

The most common findings (Box 1) among infants born to mothers with malaria during pregnancy include lower birth weight than matched controls at similar gestational ages, with an average decrease of approximately 200–300 g [18]. Preterm

Box 1 Clinical Findings Among Infants Born to Mothers with Malaria During Pregnancy

- Intrauterine growth restriction (+++)
- Prematurity (++)
- Congenital malaria (+)
- Fever (+)
- Anemia (+)
- Splenomegaly (+)
- Jaundice *
- Hepatomegaly *

+++Most common, ++common, +least common, *rare

delivery is also more common but more difficult to quantify in low-resource settings where pregnancy dates may be uncertain [19]. As a correlate, regional malaria control efforts have been associated with decreased rates of preterm delivery and low birth weight [20, 21].

Congenital Malaria

A small fraction of infants will develop congenital malaria (i.e., parasitemia). The average age at presentation for infants with congenital malaria is approximately 2–4 weeks (95% confidence interval, 1–8 weeks) [22, 23]. However, symptomatic infants have been identified within the first 24 h after delivery when parasite burden is very high [24]. The most common presentation for infants with congenital malaria includes fever, anemia, and splenomegaly. The fever usually does not achieve the cyclical pattern seen in older patients with malaria. The anemia may be striking and can be associated with hyperbilirubinemia and reticulocytosis. Hepatomegaly may also be present but is less common and less severe than splenomegaly [23].

Postnatal Malaria

Mosquito-acquired malaria presents similarly to congenital malaria. Because many infants at risk for congenital malaria are delivered and raised in malaria-endemic areas, it may be difficult to differentiate postnatal malaria from congenital infection. In the United States and other malaria-free areas, infants are assumed to be congenitally infected unless they have traveled to a malaria-endemic region postnatally [25]. Notably, fetal exposure to malaria has been clearly linked to earlier and more frequent episodes of mosquito-acquired malaria in the first few years of life. It is hypothesized that the fetus is forced to develop a decreased immune response (tolerance) in order to survive, which predisposes the infant to postnatal infections [26, 27].

Diagnosis

The diagnosis of congenital malaria can be made via several modalities (Table 1), but thick and thin smears of peripheral blood are the gold standard [28].

Thick and Thin Smears

When performed by an experienced provider, microscopic examination of serial thick and thin smears of the peripheral blood obtained via heel stick has excellent sensitivity and specificity and is the gold standard for diagnosis. When congenital malaria is suspected, a minimum of three sets of thick and thin smears should be obtained every 12–24 h until malaria has been confirmed or excluded.

Table 1 Diagnostic tests for congenital malaria

Test	Advantages	Disadvantages
Thick smear	• Excellent sensitivity for parasite detection	• Does not allow speciation
Thin smear	• Allows speciation by parasite morphology	• Less sensitive than thick smears
Rapid antigen test	• Portable and inexpensive	• Less sensitive • Not all kits provide species information • Not recommended in the United States
Nucleic acid detection	• Extremely sensitive	• Expensive • Relatively slow compared to smears • Not widely available
Serology	• Used for screening blood donors	• Neither sensitive nor specific for congenital malaria • Does not preclude need for thick and thin smears when malaria suspected

Thick smears have good sensitivity and allow quantification of parasitemia, usually expressed as percentage of red blood cells infected. Thin smears allow speciation of the *Plasmodium* species based on the morphology, which in turn will inform treatment. Before peripheral smears are obtained, nursery providers should coordinate with the microbiology lab and infectious diseases service in order to ensure that the smears can be properly fixed, stained, and read. The Centers for Disease Control and Prevention (CDC) have a telemedicine service that allows fast and accurate identification if parasitology is not locally available (http://www.cdc.gov/dpdx/contact.html) [29].

Microscopic examination of the placenta is very sensitive for congenital malaria, as placental malaria is a prerequisite for fetal infection. However, the placenta is an effective barrier to malaria transmission, and the majority of infants born to mothers with placental malaria do not have congenital malaria (see Pathophysiology, above) [15, 30].

Rapid Antigen Detection

A variety of antigen detection tests are available for malaria and are widely used in low-resource settings. Although inexpensive and easily portable, these tests have lower sensitivity than peripheral blood smears and are not recommended for use in high-resource settings [31].

Nucleic Acid Detection

Polymerase chain reaction (PCR) testing and other nucleic acid-based detection methods are increasingly used for research purposes but have not become widely available for clinical use. Unsurprisingly, nucleic acid-based tests have excellent sensitivity but are expensive and comparatively slow relative to peripheral blood smears and do not currently quantify parasitemia [32].

Serology

Serology is not indicated for the evaluation of congenital malaria. Since the majority of women of childbearing age living in a malaria-endemic region possess antibody, detection of antibody is not specific for congenital malaria. Since preexisting immunity is not sufficient for protection during pregnancy (see Epidemiology), infants with detectable levels of antimalarial immunoglobulin are still at risk for congenital malaria. However, maternal-fetal risk is greatest with primigravid, nonimmune mothers, whose infants may lack transplacental antibody. Therefore, serologic testing is of little clinical value when congenital malaria is suspected.

Treatment

Treatment of congenital malaria should be provided in coordination with pediatric infectious diseases and with the local health department. Up-to-date treatment guidelines are available on the CDC website (https://www.cdc.gov/malaria/diagnosis_treatment/treatment.html) [33].

For sensitive strains of *P. falciparum* and all *P. vivax*, *P. ovale*, and *P. malariae*, chloroquine is the recommended treatment (Table 2). Chloroquine can be given orally and is well tolerated. For infants who cannot receive oral therapy, intravenous quinidine can be substituted. Resistant strains of *P. falciparum* require combination therapy, usually with quinidine and clindamycin.

Severe malaria (e.g., >5% parasitemia or end-organ dysfunction) should be treated with intravenous quinidine and clindamycin. Exchange transfusion should also be considered for very high levels of parasitemia, usually >10%.

Prevention

Nonimmune pregnant women traveling to malaria-endemic regions represent an extremely high-risk population. Eliminating exposure to mosquitos that may transmit malaria is the most effective strategy for prevention. Avoiding travel to

Table 2 Treatment of congenital malaria

Diagnosis	Treatment
P. falciparum, chloroquine-resistant	Quinine PO and clindamycin PO
P. falciparum, chloroquine-sensitive	Chloroquine PO
P. malariae, *vivax*, and *ovale*	Chloroquine PO
Severe malaria, any species (>5% parasitemia or signs of organ failure)	Quinidine IV and clindamycin IV Consider exchange transfusion if >10% load

Note: Up-to-date recommendations, including information regarding worldwide chloroquine resistance, can be found on the CDC website [33]. Treatment of congenital malaria should always be administered via coordination with the health department and pediatric infectious diseases

malaria-endemic areas during pregnancy is the most certain means of prevention. Use of long sleeves and pants to minimize skin exposure, mosquito repellants containing DEET, and mosquito netting around sleeping areas are critical.

In addition, chemoprophylaxis for pregnant women traveling to malaria-endemic areas is recommended. For chloroquine-sensitive areas, chloroquine or hydroxychloroquine can be taken safely during all trimesters. In chloroquine-resistant areas, mefloquine is recommended. Atovaquone has not been well studied but is sometimes used as a second agent in chloroquine-resistant areas for women who have hallucinations or other severe side effects from mefloquine. Doxycycline and primaquine are not recommended in pregnancy.

Finally, pregnant women who live in an endemic area should take intermittent preventive treatment (IPT). Historically, this was accomplished with sulfadoxine-pyrimethamine monthly beginning in the second trimester [34]. However, recent studies suggest that the combination of dihydroartemisinin-piperaquine has superior efficacy and a similar safety profile [35, 36]. IPT is associated with less maternal malaria, less placental malaria, longer pregnancies, and higher birth weights.

References

1. Conroy AL, McDonald CR, Kain KC. Malaria in pregnancy: diagnosing infection and identifying fetal risk. Expert Rev Anti-Infect Ther. 2012;10:1331–42.
2. Moore KA, Simpson JA, Scoullar MJL, et al. Quantification of the association between malaria in pregnancy and stillbirth: a systematic review and meta-analysis. Lancet Glob Health. 2017;5:e1101–12.
3. Mace KE, Arguin PM. Malaria surveillance—United States, 2014. MMWR Surveill Summ. 2017;66:1–24.
4. Cullen KA, Mace KE, Arguin PM. Malaria surveillance—United States, 2013. MMWR Surveill Summ. 2016;65:1–22.
5. Cullen KA, Arguin PM. Malaria surveillance—United States, 2012. MMWR Surveill Summ. 2014;63:1–22.
6. Cullen KA, Arguin PM. Malaria surveillance—United States, 2011. MMWR Surveill Summ. 2013;62:1–17.
7. Mali S, Kachur SP, Arguin PM. Malaria surveillance—United States, 2010. MMWR Surveill Summ. 2012;61:1–17.
8. Mali S, Tan KR, Arguin PM. Malaria surveillance—United States, 2009. MMWR Surveill Summ. 2011;60:1–15.
9. Mali S, Steele S, Slutsker L, Arguin PM. Malaria surveillance—United States, 2008. MMWR Surveill Summ. 2010;59:1–15.
10. Mali S, Steele S, Slutsker L, Arguin PM. Malaria surveillance—United States, 2006. MMWR Surveill Summ. 2008;57:24–39.
11. Thwing J, Skarbinski J, Newman RD, et al. Malaria surveillance—United States, 2005. MMWR Surveill Summ. 2007;56:23–40.
12. Teo A, Feng G, Brown GV, et al. Functional antibodies and protection against blood-stage malaria. Trends Parasitol. 2016;32:887–98.
13. Agomo CO, Oyibo WA. Factors associated with risk of malaria infection among pregnant women in Lagos, Nigeria. Infect Dis Poverty. 2013;2:19.
14. Beeson JG, Rogerson SJ, Elliott SR, Duffy MF. Targets of protective antibodies to malaria during pregnancy. J Infect Dis. 2005;192:1647–50.

15. Okafor UH, Oguonu T, Onah HE. Risk factors associated with congenital malaria in Enugu, South Eastern Nigeria. J Obstet Gynaecol. 2006;26:612–6.
16. Cowman AF, Healer J, Marapana D, Marsh K. Malaria: biology and disease. Cell. 2016;167:610–24.
17. Brabin BJ, Romagosa C, Abdelgalil S, et al. The sick placenta—the role of malaria. Placenta. 2004;25:359–78.
18. 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;12:942–9.
19. Menendez C, Ordi J, Ismail MR, et al. The impact of placental malaria on gestational age and birth weight. J Infect Dis. 2000;181(5):1740.
20. Hershey CL, Florey LS, Ali D, et al. Malaria control interventions contributed to declines in malaria parasitemia, severe anemia, and all-cause mortality in children less than 5 years of age in Malawi, 2000-2010. Am J Trop Med Hyg. 2017;97:76–88.
21. Ramharter M, Schuster K, Bouyou-Akotet MK, et al. Malaria in pregnancy before and after the implantation of a national IPTp program in Gabon. Am J Trop Med Hyg. 2007;77:418–22.
22. Vottier G, Arsac M, Farnoux C, et al. Congenital malaria in neonates: two case reports and review of the literature. Acta Paediatr. 2008;97:505–8.
23. 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;161:1062–7.
24. Opare DA. Congenital malaria in newborn twins. Ghana Med J. 2010;44:76–8.
25. Hagmann S, Khanna K, Niazi M, Purswani M, Robins EB. Congenital malaria, an important differential diagnosis to consider when evaluating febrile infants of immigrant mothers. Pediatr Emerg Care. 2007;23:326–9.
26. Boudova S, Divala T, Mungwira R, et al. Placental but not peripheral Plasmodium falciparum infection during pregnancy is associated with increased risk of malaria in infancy. J Infect Dis. 2017;216:732–5.
27. Bardaji A, Sigauque B, Sanz S, et al. Impact of malaria at the end of pregnancy on infant mortality and morbidity. J Infect Dis. 2011;203:691–9.
28. Mathison BA, Pritt BS. Update on malaria diagnostics and test utilization. J Clin Microbiol. 2017;55:2009–17.
29. Centers for Disease Control and Prevention. DPDx—laboratory identification of parasitic diseases of public health concern. http://www.cdc.gov/dpdx/contact.html. Accessed 9 Jan 2018.
30. Fried M, Muehlenbachs A, Duffy PE. Diagnosing malaria in pregnancy: an update. Expert Rev Anti-Infect Ther. 2012;10:1177–87.
31. Boyce MR, O'Meara WP. Use of malaria RDTs in various health contexts across sub-Saharan Africa: a systematic review. BMC Public Health. 2017;17:470.
32. Zheng Z, Cheng Z. Advances in molecular diagnosis of malaria. Adv Clin Chem. 2017;80:155–92.
33. Centers for Disease Control and Prevention. Malaria: Malaria treatment (United States). https://www.cdc.gov/malaria/diagnosis_treatment/treatment.html. Accessed 9 Jan 2018.
34. World Health Organization. Malaria: intermittent preventive treatment in pregnancy (IPTp). Available at http://www.who.int/malaria/areas/preventive_therapies/pregnancy/en/. Accessed 9 Jan 2018.
35. 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, randomized controlled superiority trial. Lancet. 2015;386:2507–19.
36. Kakuru A, Jagannathan P, Muhindo MK, et al. Dihydroartemisinin-piperaquine for the prevention of malaria in pregnancy. N Engl J Med. 2016;374:928–39.