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Malaria in the pregnant traveler

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Abstract

Pregnant travelers face numerous risks, notably increased susceptibility to or severity of multiple infections, including malaria. Because pregnant women residing in areas non-endemic for malaria are unlikely to have protective immunity, travel to endemic areas poses risk of severe illness and pregnancy complications, such as low birthweight and fetal loss. If travel to malaria-endemic areas cannot be avoided, preventive measures are critical. However, malaria chemoprophylaxis in pregnancy can be challenging, since commonly used regimens have varying levels of safety data and national guidelines differ. Furthermore, although chloroquine and mefloquine have wide acceptance for use in pregnancy, regional malaria resistance and non-pregnancy contraindications limit their use. Mosquito repellents, including *N,N*-diethyl-m-toluamide (DEET) and permethrin treatment of clothing, are considered safe in pregnancy and important to prevent malaria as well as other arthropod-borne infections such as Zika virus infection. Pregnant travelers at risk for malaria exposure should be advised to seek medical attention immediately if any symptoms of illness, particularly fever, develop.

Keywords

Insect repellent; Malarone; atovaquone-proguanil; tafenoquine; doxycycline; mefloquine; primaquine

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All authors contributed to the literature review for the manuscript. K.L.M. drafted the manuscript, and all authors contributed to the final version.

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Conflict of Interest

The authors have declared no conflicts of interest.

Introduction

Malaria, a protozoan parasite infection transmitted by the bite of *Anopheles* mosquitoes, remains endemic in 91 countries and territories, putting half the world's population at risk.[1] According to the World Health Organization (WHO), in 2018 there were an estimated 228 million clinical episodes and 405 000 deaths.[2] In malaria-endemic areas, the most vulnerable populations are young children and pregnant women.[2] Globally, it is estimated that 125 million pregnant women are at risk for malaria infection annually.[3] Compared to disease in non-pregnant individuals, malaria in pregnancy (MIP) is often more severe, with increased risk of complications, including risks to the fetus.[4] Maternal malaria infection at delivery is associated with a nearly doubled odds of stillbirth, and 20% of stillbirths in endemic areas of sub-Saharan Africa are estimated to result from *Plasmodium falciparum* infection.[5]

Given the risks of malaria, pregnant women living in non-endemic areas should avoid travel to malaria-endemic areas when possible. Malaria is a common cause of febrile illness in travelers, and those residing in areas with little or no malaria transmission typically lack immunity to prevent severe disease.[6] If travel cannot be avoided, counseling of travelers on effective malaria chemoprophylaxis and mosquito avoidance measures is critical. Among travelers presenting to Global TravEpiNet (GTEN) consortium clinics in the USA from 2009 to 2014, 1.5% of 21 000 female travelers of childbearing age were either pregnant or breastfeeding, and almost all were planning travel to countries holoendemic for malaria.[7] However, only half were prescribed chemoprophylaxis.[7] A review of imported malaria cases in pregnant women in Europe, the USA and Japan found that among cases with chemoprophylaxis data from 1991 to 2014, 85.6% did not use any, and nearly half of those who reported use used an incorrect or incomplete regimen.[8] A major challenge for malaria prevention in pregnant travelers is the limited number of chemoprophylaxis regimens approved for use in pregnancy. Unfamiliarity about malaria prophylaxis among primary care and obstetric providers can also be a barrier to prescription of recommended prophylaxis. In this article we review issues related to malaria in pregnant and breastfeeding women traveling from non-endemic malaria areas to endemic areas, with a focus on prevention.

Epidemiology of Malaria in Travelers

Among travelers globally, most imported malaria cases are caused by *P. falciparum* (most often acquired in sub-Saharan Africa), followed by *P. vivax* (more commonly acquired in Asia and Latin America).[9] Notably, from 2008 to 2018, yearly growth in tourism to Africa and Asia averaged 4.5 and 6.5%, respectively.[10] Travelers visiting friends and relatives (VFR) are often at highest risk for acquiring malaria and other travelrelated infections, due to higher risk itineraries outside of popular destinations, lower-end accommodations compared to tourist and business travelers and lower uptake of preventive measures.[11] Furthermore, since immunity to malaria wanes without repeated exposure, immigrants and migrants originally from endemic areas quickly lose protective immunity while residing in non-endemic areas, yet these individuals often incorrectly assume they are immune.[11] Among US travelers, most cases of malaria occur among those traveling to sub-Saharan Africa, particularly West Africa.[12] In 2016, among 795 cases of malaria diagnosed in

women in the USA, 50 (6.3%) were pregnant.[12] Among the pregnant women with known reasons for travel, 47.4% were VFR travelers, and 36.8% were refugee or immigrants.[12]

Pathophysiology of Malaria in Pregnancy

Although incompletely understood, immunologic changes during pregnancy result in increased susceptibility to and/or severity of several infectious diseases, including influenza, hepatitis E, herpes simplex virus, listeriosis and malaria.[13] For *P. falciparum* infections, pregnancy appears to increase susceptibility and severity of infection, particularly in primigravidae[14]; pregnant women have a 3-fold higher risk of severe malaria than non-pregnant women.[15] This risk appears to persist into the immediate postpartum period as well.[16,17] The mechanism of severe intra-partum *P. falciparum* infections and associated adverse pregnancy outcomes appear to be mediated by VAR2CSA, a variant of the *P. falciparum* erythrocyte membrane protein 1 (PfEMP1) family of proteins that are exported to the surfaces of infected erythrocytes.[18] Variant PfEMP1 proteins bind to specific host receptors, facilitating sequestration of parasitized erythrocytes in host tissues. VAR2CSA binds to chondroitin sulphate A (CSA), a glycosaminoglycan attached to syndecan-1 in placental tissue, resulting in placental sequestration of *P. falciparum*-infected erythrocytes.[19] Placental infection results in inflammatory changes which are associated with impaired transplacental nutrient transport and uteroplacental blood flow.[14,20]

Maternal antibodies against VAR2CSA are protective against *P. falciparum* infection during pregnancy, and in areas of high transmission, primigravidae who become infected develop pregnancy-specific immunity that confers partial protection in subsequent pregnancies.[14] In areas of lower malaria transmission, less frequent infection during pregnancy is observed. However, illness is often more severe compared to illness in women in high transmission areas, as pregnant women tend not to have pre-existing malaria immunity.[18] Furthermore, unlike those in high transmission areas, multigravida women in low transmission areas are less likely to have the protective antibodies against VAR2CSA that results from previous infections during pregnancy.[18]

Plasmodium vivax infection in pregnancy has also been associated with placental changes and stillbirth,[5,14] although the pathogenesis of adverse pregnancy outcomes with *P. vivax* infection is less understood.

Presentation and Complications of Malaria Infection in Pregnancy

The severity of *P. falciparum* infection depends largely on immunity, and pregnant women residing in areas of low or unstable transmission have less pre-existing antimalarial immunity and thus are typically symptomatic and progress to complications if untreated.[13] The incubation period can vary from 7 days to months (depending on immunity and use of prophylaxis medications) after an infectious mosquito bite (usually 7–30 days), and patients typically present with a non-specific febrile syndrome, with chills, headache, myalgia and malaise.[1] The World Health Organization (WHO) defines severe *P. falciparum* malaria as parasitemia with evidence of end-organ dysfunction, including severe anemia (hemoglobin <7 g/dl), hypoglycemia, pulmonary oedema, acute respiratory distress syndrome (ARDS),

renal failure and cerebral malaria.[15] Compared to malaria in non-pregnant women, MIP is associated with higher rates of severe complications, including anemia, cerebral malaria, hypoglycemia, ARDS and hyperparasitemia.[15] In 2016, 74% of pregnant malaria cases reported in the USA resulted from infection with *P. falciparum*, and one-third of all cases among pregnant women were severe.[12] Although none of the 50 US malaria cases in pregnant women in 2016 resulted in death, reported casefatality rates for MIP in endemic areas range, widely, from 0.5 to 39%.[13,14] Although numerous factors, including access to routine care and nutritional state, can also contribute to the morbidity in endemic areas, pregnant women with malaria and HIV co-infection have a higher risk of severe malaria and worse birth outcomes compared to those who are HIV-negative.[21]

Fetal complications of *P. falciparum* infection include miscarriage, low birthweight (<2500 g) due to intrauterine growth restriction and pre-term (<37 weeks) delivery.[4] In a recent meta-analysis of 59 studies of MIP, *P. falciparum* infection detected at delivery was associated with stillbirth [odds ratio (OR) 1.8; 95% confidence interval (95CI) 1.4–2.3].[5] This association persisted, though at a lower magnitude, in those who were diagnosed and treated for malaria (OR 1.5; 95CI 1.1–1.9).[5] Maternal peripheral parasitemia is also associated with adverse infant outcomes including anemia, mortality (neonatal and infant) and congenital malaria.[4] Congenital transmission of malaria is defined as passage of asexual parasites from the mother to her infant either transplacentally or during delivery; as compared to autochthonous cases, there is no liver stage. In endemic settings, it can be difficult to distinguish true congenital cases from autochthonous cases; thus a time frame of 7 days has been used to limit the possibility or misclassification of autochthonous cases as congenital. In non-endemic settings, where there is no possibility of post-natal exposure, the definition is not restricted to the first 7 days of life. Asymptomatic parasitemia detected at delivery frequently clears spontaneously.[23] And, if the mother is adequately educated about the possibility of congenital malaria and follow-up is assured, it is not clear whether treatment is indicated. Symptomatic congenital malaria has been reported to occur in up to 10% of malaria cases in non-immune mothers; symptoms generally appear between 10 and 30 days of life but have been documented to occur as late as 15 months, with fever, hepatosplenomegaly, hemolytic anemia, thrombocytopenia and feeding intolerance.[22,23]

Risk Assessment in the Pregnant Traveler

Assessment of infectious and environmental risks specific to a travelers' itinerary is a routine part of pre-travel consultations, and providers seeing pregnant travelers should emphasize the risks of malaria and other infections that are particularly dangerous in pregnancy, such as Zika virus infection.[24] Given that approved malaria chemoprophylaxis medications and mosquito avoidance measures are not 100% effective, pregnant women are advised to avoid travel to malaria-endemic areas whenever possible. Furthermore, due to the limited safety data on antimalarial use in pregnancy, chemoprophylaxis options approved by drug regulatory authorities for use in pregnancy are limited, particularly for areas with drug resistance (see below). For example, in the USA there is currently no US Food and Drug Administration (FDA)-approved chemoprophylaxis option for pregnant women traveling to areas of Southeast Asia where chloroquine and mefloquine resistance are present[1] (Table 1). Comorbid conditions, such as neuropsychiatric conditions that preclude mefloquine use, can

further limit the options available for the pregnant traveler. Some guidelines, including those from Germany and Switzerland, recommend that travelers to areas with lower malaria risk carry standby emergency treatment rather than taking chemoprophylaxis; however, pregnant travelers are advised to take chemoprophylaxis rather than standby treatment.[25,26]

Although some absolute medical contraindications to travel during pregnancy are well-established,[27,28] the decision whether or not to travel is usually made in a shared decision-making model between the provider and traveler, considering the itinerary, infectious and environmental risks, pregnancy status (trimester, presence of complications, etc.), urgency of travel and the risk tolerance of the traveler. To promote decisions that are appropriate and prudent for travelers, it is critical that providers ensure that pregnant travelers understand the risks of malaria and available preventative measures. Availability and quality of local obstetric care for emergencies are also important considerations, particularly for longer-term travel or travel later in pregnancy.

Malaria Chemoprophylaxis for Pregnant and Breastfeeding Travelers

Although malaria chemoprophylaxis recommendations for pregnant travelers vary somewhat among experts and guidelines,[29] chloroquine and mefloquine are the most accepted agents for use in pregnancy, particularly after the first trimester (Table 1). Most guidelines do not recommend atovaquone–proguanil or doxycycline chemoprophylaxis during pregnancy, although some are permissive for use of doxycycline during certain periods of gestation in cases where the benefit is thought to outweigh the risks (Table 1).[29]

Chloroquine has a long history of use in pregnancy and remains useful in areas without documented resistance.[1] Studies on chloroquine for prevention and treatment of malaria in pregnant women in endemic areas have not demonstrated increased rates of adverse pregnancy outcomes, though studies vary in regimens, quality of study design and outcomes measured.[30–32] Notably, in a randomized, double-blind, placebo-controlled trial of chloroquine prophylaxis for *P. vivax* prevention in Thai pregnant women (500 women in each treatment arm), chloroquine (given as 1000 mg chloroquine phosphate followed by weekly doses of 500 mg) was well-tolerated, and no differences in birthweight, gestational age, stillbirths, development of newborns or visual acuity in infants at 1 year of age were observed.[33] Data on chloroquine for chemoprophylaxis in pregnant travelers or expatriates are limited. In a study of births among US staff at US embassies and consulates, a cohort of 169 births to women exposed to chloroquine throughout pregnancy did not experience birth defects at a rate significantly different than those in unexposed pregnancies, though the limited numbers could only exclude a strong teratogenic effect.[34] A recent analysis of data from a US military pregnancy and birth surveillance system for exposures to malaria chemoprophylaxis identified 131 women exposed to chloroquine in a cohort of 198 164 pregnancies over an 11-year period and found no increased risk of adverse birth outcomes with a decreased risk of fetal loss.[35] Hydroxychloroquine is structurally very similar to chloroquine and is also recommended by Centers for Disease Control and Prevention (CDC) for malaria prophylaxis in pregnancy for travel to areas without chloroquine resistance.[1] Hydroxychloroquine is most commonly used in rheumatologic diseases, and its safety

during pregnancy is supported by multiple studies of pregnant women taking amounts much higher than that used in chemoprophylaxis (i.e. 200–400 mg daily).[36–38]

Acceptance of mefloquine for chemoprophylaxis and treatment in pregnant women (used alone or in combination with other medications) has increased as more studies supporting its safety have been published. A meta-analysis of 18 studies of pregnant women exposed to mefloquine did not demonstrate any increased risk of adverse pregnancy outcomes.[39] A more recent Cochrane review of six randomized or quasi-randomized trials including mefloquine for prevention of malaria (8192 women included) concluded that mefloquine reduced maternal anemia and malaria and was not associated with adverse pregnancy outcomes, prematurity or low birthweight.[40] A drug safety database analysis of reported mefloquine exposure during pregnancy and the pre-natal period in France, the UK, Germany and the USA showed that rates of fetal loss and birth defects in exposed women were comparable to levels in the general population.[41] In this study, most reported mefloquine exposures occurred before conception and/or during the first trimester of pregnancy. This data resulted in the FDA recategorizing mefloquine to a lower risk category in pregnancy.[42] Similar to its findings for chloroquine, the US military data analysis referenced above did not find increased rates of adverse birth outcomes among 156 pregnant women exposed to mefloquine.[35] Although mefloquine can be used for prophylaxis in areas with chloroquine-resistant *P. falciparum*, mefloquine resistance is present in certain areas of Southeast Asia,[1] and in these areas there is no universally approved malaria chemoprophylaxis regimen for pregnant women. Other limitations of mefloquine include contraindications in the setting of seizure disorder and psychiatric conditions, as well as limited utility for last-minute travelers, since dosing should be started 2 weeks prior to entering malarious areas.[1,43]

At this time, atovaquone–proguanil is not recommended for use in pregnancy in the USA and in many other countries (Table 1). While data exist on the safety of proguanil monotherapy in pregnancy, there is a paucity of human studies to assess teratogenicity of atovaquone–proguanil and thus FDA cautions against its use in pregnancy.[44] A systematic literature review documenting infant outcomes following exposure to atovaquone–proguanil, atovaquone and proguanil in pregnancy (including studies of populations in malaria-endemic areas and travelers) identified 16 studies with 1557 women exposed to atovaquone–proguanil or proguanil (alone or in other combinations).[44] The rates of miscarriage, stillbirth, early neonatal death or congenital anomaly were not higher than expected in similar populations. However, only 446 of the pregnancies were exposed to atovaquone–proguanil, and only 5 studies were randomized clinical trials comparing atovaquone–proguanil (1 study) or proguanil (alone or in combination, 4 studies) with a comparator group.[44] The analysis of US military data referenced above identified 50 women exposed to atovaquone–proguanil.[35] Among those exposed to atovaquone–proguanil, there were non-statistically significant increases in the risk of fetal loss and adverse live birth outcomes (pre-term birth, low birthweight or small for gestational age). Limitations of this study include the small number of atovaquone–proguanil-exposed women and reliance on administrative medical claim data to determine outcomes.[35] Based on this limited data, further safety data are needed before atovaquone–proguanil can be recommended for use in pregnancy. Most chemoprophylaxis guidelines advise against the use of doxycycline in pregnancy (Table 1). Caution against its use in pregnancy is mostly extrapolated from other tetracycline class

drugs, which have been associated with fetal and maternal risks, including bone growth inhibition, tooth discoloration and fatal maternal hepatitis.[45,46] The risk of tetracycline-associated fetal tooth discoloration and bone growth inhibition is considered highest during the second and third trimesters when tooth calcification and extensive fetal growth occur.[45–47] A case–control study also suggests that oxytetracycline can be teratogenic when given in the first trimester.[48] In contrast, animal and human data on doxycycline use in pregnancy largely support its safety when used at typical treatment or chemoprophylaxis doses.[45,47,49,50] No published data have demonstrated that fetal exposure to doxycycline results in discoloration of teeth,[47,50] possibly because of doxycycline's reduced ability to chelate calcium.[45] Although there were 17 cases of congenital abnormalities associated with doxycycline exposure early in pregnancy reported to the WHO Collaborating Centre for International Drug Monitoring from 1965 to 1994,[49] more recent studies on the teratogenicity of doxycycline have mostly been reassuring. A Hungarian case–control study of 18 515 cases of congenital abnormalities compared to 32 804 controls demonstrated an association with doxycycline exposure (OR 1.6, 95CI 1.1–2.3); however, analysis restricted to exposures occurring during the second and third months of gestation (during organogenesis) did not show a statistically significant association.[51] A subsequent study of data from the same registry demonstrated no intrauterine growth restriction when pregnant women were treated with doxycycline, except for mild growth retardation when exposure was between the 31st and 34th week of gestation.[52] Other cohort studies have not demonstrated an association with congenital abnormalities, including a small study of mothers exposed during treatment for *Ureaplasma*,[53] Tennessee Medicaid recipients (1843 exposed pregnancies) [54] and a Swedish register of 1809 pregnant women exposed to tetracyclines (mostly doxycycline).[55] These reassuring studies should be interpreted in light of their retrospective designs and the relatively small numbers of exposures which limit their statistical power to detect small risks. Given that the data are insufficient to conclude there is no risk,[47,50] most malaria experts and chemoprophylaxis recommendations advise against its use in pregnancy, although some guidelines are permissive for use early in pregnancy when no other options are available (Table 1).[43,55]

The 8-aminoquinoline drugs, primaquine and tafenoquine, are used for presumptive anti-relapse therapy and chemoprophylaxis; however their use is contraindicated in individuals with G6PD deficiency due to the risk of hemolysis.[1] This precludes their use in pregnancy due to concern that fetal hemolytic anemia could occur *in utero* if the drugs are transplacentally passed to a G6PD-deficient fetus.[1] Animal data have demonstrated dose-related abortions when tafenoquine was given to pregnant rabbits during the period of organogenesis.[56]

Although very small amounts of antimalarial medications are excreted in breastmilk, the amount is insufficient for infant protection, and breastfed infants must have chemoprophylaxis administered directly according to pediatric chemoprophylaxis guidelines.[1] However, because breastmilk exposure occurs, chemoprophylaxis regimens used by breastfeeding women are limited to those considered safe for the infants, including chloroquine, mefloquine and atovaquone–proguanil (latter for infants weighing >5 kg).[1] Although safety data are limited, most experts consider short-term doxycycline use acceptable in breastfeeding mothers.[57] Primaquine and tafenoquine can be used by

breastfeeding mothers for prophylaxis only if the infant is confirmed to have a normal G6PD level.[57,58]

Evaluation and Treatment

Although complications from malaria can develop quickly, the presenting symptoms of malaria are non-specific and resemble other common causes of fever in travelers, including dengue, typhoid and influenza.[6] Pregnant travelers to endemic areas should be educated on malaria symptoms and advised to seek urgent medical attention if they develop them during or after travel, regardless of chemoprophylaxis use or history of mosquito bites. Since physicians who practice in non-endemic areas might not immediately consider malaria and other travelrelated infections, travelers should be advised to report any travel history in the previous year when seeking care for illness. Likewise, clinicians caring for febrile pregnant women should always inquire about travel history. Suspected or confirmed cases of malaria should be treated as a medical emergency. Providers taking care of ill travelers should be familiar with diagnostic testing options for malaria, primarily microscopy and rapid diagnostic tests.[6,14]

Treatment of malaria in the pregnant traveler should be started immediately after laboratory confirmation; in women with severe symptoms, if timely diagnosis is not feasible, treatment should be started immediately while waiting for laboratory confirmation. As with non-pregnant malaria cases, the species of *Plasmodium* and severity of malaria (i.e. uncomplicated vs complicated illness) determine the treatment regimen. Due to varying amounts of safety data available for different drugs, antimalarials fall into various categories of approval, often dependent on the stage of pregnancy. Some are unapproved in pregnancy (e.g. atovaquone–proguanil, doxycycline), while some others (e.g. chloroquine, quinine, clindamycin) are considered safe in all trimesters.[14,59] Artemisinin-based therapies, including artemether–lumefantrine and artesunate, have been shown to be safe in the second and third trimesters.[15,60] The CDC and WHO recommend that use of oral artemisinins during first trimester should be reserved for situations without other options,[59,61] though accumulating safety data have led some experts to recommend oral artemisinin-based therapies a treatment option that is equivalent to quinine during the first trimester.[15,60] While the CDC considers mefloquine treatment safe in pregnancy during all trimesters, as a single-drug treatment, it is not first-line due to side effects associated with treatment doses.[59] Other guidelines, including the WHO, recommend mefloquine in pregnancy as a part of artemisinin-based combination therapy after the first trimester.[61,62] In the case of severe malaria where the benefits of treatment far outweigh the risk, intravenous artesunate should be used in all trimesters.[59] Quinine, in combination with clindamycin, is considered safe in all trimesters of pregnancy. The WHO recommends treatment with quinine and clindamycin for 7 days,[61] while the CDC recommends 3 days of quinine treatment combined with a 7-day course of clindamycin, unless the infection was acquired in Southeast Asia for which a course of both drugs for 7 days is recommended.[59] However, patients treated with the recommended 7-day course of quinine will likely experience cinchonism,[63] which can manifest with tinnitus, slight deafness, photophobia, headache and nausea and which resolves upon withdrawal of the drug.

Primaquine and tafenoquine are contraindicated for anti-relapse therapy during pregnancy due to risk of hemolysis in G6PD-deficient fetuses, and relapse prevention following treatment of *P. vivax* and *P. ovale* infections is achieved with weekly chloroquine for the duration of the pregnancy.[59,61] National and international guidelines for malaria treatment in pregnancy can vary, as can specific drug availability in different countries. Therefore, providers treating MIP are encouraged to consult with local experts given the range of treatment options and high risk of severe disease and adverse pregnancy outcomes.

Mosquito Avoidance

In addition to chemoprophylaxis, prevention of malaria includes the use of mosquito avoidance measures such as mosquito repellents and barriers like long-sleeved clothing, window screens and bed nets.[64] This is particularly important given that pregnant women are more likely to be bitten by mosquitoes than non-pregnant women.[65,67] Although *Anopheles* mosquitoes typically bite between dusk to dawn, arthropod bite avoidance at all hours is important given the presence of other arthropod-borne infections. Notably, dengue and Zika viruses are transmitted via *Aedes* mosquito species which are typically more actively feeding during the day.

Mosquito repellents currently recommended by the CDC represent US Environmental Protection Agency (EPA)-registered products with sufficient scientific evidence for efficacy.[64] These include *N,N*-diethyl-m-toluamide (DEET), also known as *N,N*-diethyl-3-methylbenzamide, picaridin (KBR 3023), oil of lemon eucalyptus (OLE) or para-menthane-3,8-diol (PMD, the synthesized version of OLE), IR3535 and 2-undecanone. EPA-registered topical repellents have been evaluated for safety, and no additional precautions are recommended by the EPA for use with pregnant or breastfeeding women when applied according to instructions.[64] Some experts recommend using topical repellents at concentrations in the lower end of recommended ranges during pregnancy.[28] National guidelines vary somewhat in specifically approved mosquito repellents for the general public and pregnancy,[68,69] although DEET is commonly recommended. Despite this, surveys of pregnant women and other populations suggest that safety concerns about mosquito repellents including DEET are common.[70] Providers should emphasize to pregnant travelers that the well-established dangers of malaria and other arthropod-borne infections far outweigh any concern for adverse events related to the use of approved repellents.

Among approved repellents, DEET by far is the most studied. The concentration of DEET determines its duration of effectiveness, with the ideal concentration being 20–50% since efficacy plateaus at 50%[64]. An abundance of data on DEET toxicity in humans and animals is available,[71–73] and it remains the most widely used repellent, used by ~50–100 million persons in the USA each year.[74] While there are case reports of hypotension, seizure and coma resulting from DEET ingestion,[71] evidence has not supported a causative relationship between appropriate topical use of DEET and severe adverse events in adults or children.[71,73] Rare case reports, primarily in children, of encephalopathy and seizures temporally related to topical DEET usage have previously raised some concern;[74] however, given that seizures occur in 3–5% of children and DEET use is common, the rare reported seizures following DEET use may reflect a chance association.[71,72] Safety of DEET during

pregnancy has been studied in a randomized, double-blind trial of 897 pregnant women in their second and third trimester in Thailand.[75] Daily application of 20% DEET did not result in adverse effects for the women or fetus. Furthermore, survival, growth and neurologic development of infants born to mothers who used DEET did not differ from those who did not. Consistent with animal studies that indicate that DEET can cross the placenta, a subgroup sampling of umbilical cord blood in this study detected DEET in 8%. A US study of pesticide levels in paired maternal and cord blood specimens from 150 pregnancies also detected DEET in 100% of specimen,[76] although no significant associations were found between elevated DEET concentrations and birth indices, including birthweight, head circumference and abdominal circumference.

Treatment of clothing and bed nets with permethrin for arthropod bite prevention is approved by the EPA and recommended by the CDC for use in pregnant women.[77] Permethrins are pesticides with low human toxicity[73] and commonly used topically as a treatment for scabies. Clothing and other items treated with permethrins kill and repel a wide range of disease vector and nuisance arthropods.[64] Treated materials typically retain their repellent activity after laundering, though pre-treated fabrics retain activity longer than consumer-applied treatments. Permethrins are the most commonly used agent for insecticidetreated bed nets (ITN), a widely used intervention in malaria control efforts in endemic areas shown to reduce placental malaria, low birthweight and fetal loss in Africa and Asia.[78] Increasing resistance of *Anopheles* mosquitoes to permethrins is of concern.[79] Though safety data in pregnant travelers is lacking, most experts consider permethrins safe in pregnant travelers based on safety data from its other indicated uses.[80] Recently some concern over the effect of permethrins and other pesticides on pre-natal neurodevelopment has been raised based on animal and human studies.[81–83] The human studies are observational and involve permethrin exposures resulting from agricultural and residential pesticide applications. These preliminary findings are difficult to extrapolate to permethrin use in clothing treatment and ITNs. On the other hand, well-established risks of malaria and other infections to pregnant travelers warrant continued recommendation of permethrin use by pregnant travelers.

Conclusion

Travel medicine providers play a critical role in risk assessment and providing preventive advice to pregnant travelers. Pregnant travelers face numerous unique risks, including increased susceptibility to or severity of numerous infections, including malaria. Because pregnant women residing in non-endemic areas are unlikely to have any protective antimalarial immunity, travel to malaria-endemic areas poses risk of severe illness and complications of pregnancy, including low birthweight and fetal loss. If travel to malarious areas cannot be delayed, chemoprophylaxis and mosquito avoidance measures are critical; however, available options for use in pregnancy, particularly during the first trimester, are limited. Further research on the safety of chemoprophylaxis drugs in pregnancy is needed. Because many travelers have limited understanding of malaria, providers must ensure that the traveler is educated to make prudent decisions, including taking chemoprophylaxis or even consideration of not traveling when appropriate. Due to the increased risk of severe

infection, pregnant travelers at risk for malaria exposure should be advised to seek medical attention immediately if any symptoms of malaria illness develop.

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Table 1.

International recommendations for malaria chemoprophylaxis in pregnant travelers

	Canada[84]	Germany[25]	Switzerland[26]	USA[1,58]	UK (Public Health England)[43]	WHO[85]
Atovaquone–Proguanil	N/R[a]	N/R[a]	N/R[a]	N/R[a]	N/R[a]	N/R[a]
Chloroquine[b]	Safe	N/A[c]	N/A[c]	Safe	Safe[d]	Safe
Doxycycline	N/R	N/R	N/R	N/R	N/R[e]	N/R
Mefloquine	Recommended with caution[f]	Safe	Safe	Safe	Recommended with caution[f]	Safe
Primaquine	N/R	N/A[c]	N/A[c]	N/R	N/A[c]	N/A[c]
Tafenoquine	N/A	N/A	N/A	N/R	N/A	N/A

Abbreviations: N/R not recommended or contraindicated; N/A not applicable or not available.

[a]Not recommended during pregnancy. However some authorities allow use of atovaquone–proguanil during pregnancy if no other options are available and after careful risk–benefit assessment. Recommendations from Canada and the UK specify that atovaquone–proguanil can only be considered after the first trimester.

[b]For travel to areas with chloroquine sensitive malaria.

[c]Regimen not included in prophylaxis recommendations for non-pregnant travelers.

[d]Use with proguanil and folic acid supplementation recommended.

[e]Contraindicated in pregnancy but might be considered under special circumstances before 15 weeks of gestation if no other options are available. The doxycycline course, including 4 weeks after travel, must be completed before 15 weeks of gestation.

[f]Can be used in all trimesters, but caution in first trimester is advised.