

CLINICAL INQUIRIES

From the
Family Physicians
Inquiries Network

What is the most effective and safe malaria prophylaxis during pregnancy?

Evidence-based answer

Chloroquine and mefloquine have superior safety profiles in pregnancy, though all antimalarials are effective for prophylaxis. Antimalarials will decrease the severity of maternal malaria infection and malaria-associated anemia, while decreasing the incidence of low birth weight and perinatal death in women having their first or second baby (strength of recommendation

[SOR]: **A**, based on systematic review of consistent, good-quality patient-oriented evidence).

You can determine malaria risk and sensitivity of *Plasmodium* species by country at wwwn.cdc.gov/travel/destinationList.aspx.¹ Urge women to delay travel until after pregnancy if possible² (SOR: **C**, based on patient-oriented expert opinion).

Clinical commentary

Don't forget to discuss mosquito netting and insect repellent

Adverse outcomes associated with malaria during pregnancy include restricted fetal growth, low birth weight, preterm delivery, congenital infection, spontaneous abortion, and perinatal death. You should counsel travelers to avoid travel to areas where malaria is endemic during pregnancy.

For those who are unable to avoid travel, or who reside in malaria-endemic areas during pregnancy, physicians should focus not only on chemoprophylaxis, but

provide verbal and written counsel regarding malaria personal protection measures.

Because mosquitoes usually feed at night, travelers should remain within screened areas after dusk, use permethrin-treated bed nets, wear protective clothing, and apply insect repellent. Advise patients who travel to malaria-endemic areas to quickly report febrile illnesses and to disclose their travel histories to healthcare providers.

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FAST TRACK

Urge women to delay travel to malaria-endemic areas until after pregnancy

Evidence summary

Malaria is a parasitic infection that causes significant morbidity and mortality worldwide, with more than 500 million people becoming severely ill every year.² For pregnant women, malarial infection can be severe, with high fevers, chills, and anemia lead-

ing to increased risk of poor maternal and fetal outcomes—including death. Pregnant women are also more likely to become infected and to develop more severe disease—they attract twice as many mosquitoes as nonpregnant women and have a relative immunosuppression.³

CONTINUED

TABLE

Antimalarials for prophylaxis: Chloroquine, mefloquine are best choices during pregnancy

DRUG	EFFICACY	SAFETY	PREGNANCY CLASS*	AVAILABILITY
Chloroquine	Good	Excellent	C	Worldwide
Chloroquine/proguanil	Good	Excellent	C	Worldwide
Mefloquine	Excellent	Good	C	Worldwide
Quinine	Excellent	Good	C†	Worldwide
Atovaquone/proguanil	Excellent	Good	C (poorly studied)	Worldwide
Artesunate	Excellent	Good	N/A	Asia, Africa, limited in UK, not in US
Primaquine	Good	Fair	C‡	Worldwide
Doxycycline	Excellent	Fair	D (teratogenic)	Worldwide
Sulfadoxine/pyrimethamine	Fair	Poor	C	Worldwide, but restricted in US

Note: Prescribers and patients are urged to refer to the CDC reference about pregnancy in malaria (wwwn.cdc.gov/travel/content/MalariaPregnantPublic.aspx) and to specific country information regarding sensitivities of malaria (wwwn.cdc.gov/travel/destinationList.aspx).

* **Pregnancy class C:** Animal reproduction studies have shown an adverse effect on the fetus and there are no adequate and well-controlled studies in humans, but potential benefits may warrant use of the drug in pregnant women, despite potential risks.

* **Pregnancy class D:** There is positive evidence of human fetal risk based on adverse reaction data from investigational or marketing experience or studies in humans, but potential benefits may warrant use of the drug in pregnant women, despite potential risks.

† Monitor patients for maternal hypoglycemia.

‡ There is no evidence of teratogenicity, but primaquine is associated with fetal intravascular hemolysis.

FAST TRACK

Give pregnant women verbal and written counsel on avoiding exposure by using permethrin-treated netting and insect repellent

Chemoprophylaxis lowers rates of maternal infection

Although prophylaxis for pregnant patients traveling to malarial regions is a public concern, data for decision-making must be extrapolated from the available evidence, which is based primarily on women living in endemic areas. In a Cochrane systematic review, antimalarials were found to decrease the incidence of maternal infections (relative risk [RR]=0.27; 95% confidence interval [CI], 0.17–0.44) and reduce maternal anemia (RR=0.62; 95% CI, 0.50–0.78) in low-parity women—ie, during a first or second pregnancy.³

In low-parity women, these drugs were also found to decrease perinatal death (RR=0.73; 95% CI, 0.53–0.99) and low birth weight (RR=0.57; 95% CI, 0.46–0.72) associated with ma-

larial infection. When used in all parity groups, antimalarials were somewhat less effective, yet still reduced maternal infections (RR=0.53; 95% CI, 0.33–0.86); the effects were similar with all antimalarials tested.^{3,4}

Chloroquine, mefloquine are safe in pregnancy, doxycycline is not

While chemoprophylaxis in pregnancy appears efficacious, a major question remains—which agents are safest for both the woman and fetus? Some drugs routinely used in nonpregnant individuals should not be offered to pregnant women because of known direct effects on the fetus. **Doxycycline** is teratogenic, and **primaquine** poses a significant risk of fetal intravascular hemolysis in G6PD-deficient fetuses.⁵ Other drugs, such as **atovaquone/proguanil** and **artesunate**, are

not well studied in pregnancy, and therefore are not recommended for use unless other options are not available.^{2,6}

Among drugs that are well studied and without known direct fetal-damaging effects, adverse drug reaction profiles can guide use based on disease prevalence and drug-resistance patterns.

- **Chloroquine** is widely used because it is inexpensive and well tolerated, with only pruritus, mouth ulcers, and gastrointestinal upset as the most common adverse effects.

- **Mefloquine** is usually well tolerated, but can cause dose-related neuropsychiatric effects; it is contraindicated in those with a history of epilepsy or psychiatric disease.

- **Sulfadoxine** and **pyrimethamine** are not normally used as prophylaxis for any patient, due to the risk of toxic epidermal necrolysis and Stevens-Johnson syndrome, and the possible risk of jaundice and kernicterus if used in the third trimester of pregnancy.

- **Quinine**, which can be used for treatment or prophylaxis, may cause hypoglycemia, an effect that is more pronounced during pregnancy and requires close monitoring of blood glucose levels.^{5,7}

Given these reaction profiles, chloroquine or mefloquine are usually the best choice with their superior safety and efficacy.

Recommendations from others

The World Health Organization (WHO) recommends pregnant women avoid travel to malarial regions. If travel is required, WHO recommends chloroquine as first-line prophylaxis in pregnancy (plus proguanil if the region exhibits emerging chloroquine resistance). In areas with proven chloroquine resistance, mefloquine is the drug of choice. Other antimalarials—such as quinine, pyrimethamine, sulfadoxine, and artesunate—should not be withheld if the preferred drugs are not available, or if the infection is life-threatening.²

The Centers for Disease Control

FIGURE

Best protection: Avoidance



Chloroquine and mefloquine are the safest antimalarials for use in pregnant women, but personal protection measures are also critical. Above, an *Anopheles stephensi* mosquito expelling a droplet of blood from its abdomen after having engorged itself on its human host's blood. (Source: CDC.)

and Prevention (CDC) also recommends avoiding travel to malaria-endemic regions during pregnancy, but if travel is necessary, the CDC advises use of chloroquine (or mefloquine in regions with chloroquine resistance). The CDC discourages the use of atovaquone/proguanil, doxycycline, and primaquine, due to known adverse fetal effects or inadequate experience in pregnancy.⁶ ■

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FAST TRACK

The World Health Organization recommends chloroquine as first-line prophylaxis in pregnancy