



Illinois Teratogen Information Service
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Malaria Prevention & Pregnancy

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Malaria infection during pregnancy poses significant health risks to both the pregnant mother and her fetus. Since no method of malaria prevention is 100% effective, it is best to avoid travel to malarious regions during pregnancy. As this is not always possible, the Centers for Disease Control and Prevention (CDC) have developed guidelines and recommendations for pregnant women traveling to malarious regions. The purpose of this newsletter is to summarize the current guidelines and recommendations for preventing malaria during pregnancy.

Facts About Malaria

Malaria is a serious and potentially fatal disease transmitted by an infected female *Anopheles* mosquito. There are four *Plasmodium* species that cause malaria in humans: *P. falciparum*, *P. vivax*, *P. ovale*, and *P. malariae*. Classic symptoms of malaria include high fever with chills, rigor, sweats, and headache. The onset of symptoms typically occurs between 10 days to four weeks following infection, but can range anywhere from eight days to one year. Malaria is endemic in large regions of Central and South America, Haiti, and the Dominican Republic, Africa, the Indian sub-continent, Southeast Asia, the Middle East, and Oceania. Malaria affects 300-500 million people worldwide annually, and results in 1.1-2.7 million deaths per year (MMWR, 1990). In the United States, there are approximately 1000 cases of malaria per year that result from imported infection (Hulbert, 1992). Pregnancy can make a woman more susceptible to malaria, or increase the level of parasite in the blood.

Risks associated with malaria infection during pregnancy

Maternal Risks

Malaria tends to run a more severe course in pregnant women than in non-pregnant women.

Symptomatic pregnant women may experience anemia, hypoglycemia, pulmonary edema, fever and headache. Atypical manifestations of malaria are particularly more common in the second half of pregnancy. Generalized immunosuppression, reduction in gammaglobulin synthesis, inhibition of the reticulo-endothelial system, and decreased levels of anti-malarial antibodies during pregnancy are thought to cause an increased susceptibility to infection. Factors that increase the risk for more severe malarial infection include non-immunity and primigravida (Nosten et al, 1991).

Placental Changes

When a pregnant woman is infected with malaria, there is a chance that the placenta will become infected as well. The placenta is actually the preferred site of sequestration and development of the malaria parasite.

Intervillous spaces become filled with parasites and macrophages, and thus interfere with oxygen and nutrient transport to the fetus. Infected primigravida have approximately a 30-40% risk for placental infection, whereas multigravidae have an approximate 15-20% risk.

The difference in risk is possibly due to formation of anti-adhesion antibodies during previous pregnancies (www.geocities.com/HotSprings/resort/5403/pregnancy.htm).

Fetal Risks

Malaria during pregnancy poses significant risks to the fetus. Studies have shown that maternal infection is significantly correlated with low birth weight (Nyirjesy et al, 1993). Pregnancy loss, premature birth, stillbirth, placental insufficiency, and intrauterine growth retardation have all been observed in developing fetuses of non-immune infected mothers.

Complications during pregnancy that can adversely affect the fetus include maternal high grade fever, placental insufficiency, hypoglycemia and anemia (Ibhanesebhor, 1995). Although rare, transplacental spread of malaria parasites can lead to congenital malaria in the newborn (Nyirjesy et al, 1993).

Congenital Malaria

Congenital malaria occurs in up to 7.4% of non-immune mothers, and results most often in patients with *P. falciparum* infection. The predominant clinical features include fever, respiratory distress, pallor, anemia, hepatomegaly, jaundice and diarrhea (Covell, 1950).

Preventing malaria in pregnancy

The following guidelines and recommendations have been taken from the Centers for Disease Control and Prevention website: www.cdc.gov/travel/mal_preg_pub.htm.

Due to the increased morbidity and mortality associated with malaria during pregnancy, pregnant women should avoid traveling to malarious regions if possible. Antimalarial agents may be necessary during pregnancy for the prevention or treatment of malaria. Quinine derivatives are the classical drugs used for malaria, of which the most useful is chloroquine. Chloroquine is the drug of choice for the prophylaxis and treatment of malaria during pregnancy due to the substantial amount of literature on its "safety" during pregnancy.

I. Pregnant women traveling to malaria-risk areas in Mexico, Haiti, the Dominican Republic, and

certain countries in Central America, the Middle East, and Eastern Europe should take either chloroquine or hydroxychloroquine sulfate as their antimalarial.

a.

Chloroquine (500 mg/week) (or chloroquine derivative Hydroxychloroquine sulfate at 400mg/week):

- Should be taken 1 week before arrival
- Then, once per week, on the same day each week, while in the malarious region.
- Then, once per week for 4 weeks after leaving the region.

Possible side effects: (rare) nausea, vomiting, headache, dizziness, blurred vision and itching.

II. Due to chloroquine-resistance, pregnant women traveling to malaria-risk areas in South America, Africa, the Indian subcontinent, Asia, and the South Pacific should take mefloquine as their antimalarial drug.

a. Mefloquine (250 mg/week):

- First dose 1 week before arrival in malarious region.
- Then, once per week, on the same day of the week, while in region.
- Then, once per week for 4 weeks after leaving the region.

Possible side effects: (rare) nausea, dizziness, difficulty sleeping, and vivid dreams. Very rare symptoms include seizures, hallucinations, and severe anxiety.

Malaria medications

Chloroquine

Several research studies have analyzed the effects of chloroquine use during pregnancy (Anonymous, 1983; White, 1996; Wolfe and Cordero, 1985). Wolfe and Cordero (1985) reported on the outcome of 169 births in which doses (average 300mg) of chloroquine were ingested once per week during pregnancy. In this study, two infants were born with anomalies including Tetralogy of Fallot and congenital hypothyroidism. This study showed that the rate of birth defects with use of chloroquine during pregnancy is not significantly higher than the background rate of birth defects of 3-5%.

Chloroquine is often the medication of choice for malaria treatment during pregnancy. Chloroquine should not be used if the woman has a history of liver disease or glucose-6-phosphate dehydrogenase deficiency.

Small amounts of chloroquine are transferred into breast milk. However, because the exposure to nursing infants is low, harmful effects are considered unlikely (Committee on Drugs, American Academy of Pediatrics, 1994).

Mefloquine

Mefloquine use during pregnancy has not been shown to be associated with an increased risk for pregnancy loss, or other adverse effects during the second and third trimesters (Steketee et al, 1996). One study evaluated over 500 pregnancies that included first trimester exposure to Mefloquine and did not find a significantly increased risk for birth defects (Phillips-Howard et al, 1998). This study did show an apparent increased risk for pregnancy loss. The authors concluded that the rate of pregnancy

loss was not increased when compared to the high background rate of the population studied (Phillips-Howard et al, 1998).

Additional studies evaluating 167 women and 218 women, respectively, did not find an increased risk for a congenital malformation or miscarriage (Harinasuta, 1990; Elefant, 1991).

Small amounts of Mefloquine are excreted into breast milk. However, adverse effects from exposure to nursing infants are not expected because the amount ingested would be very small (Edstein et al, 1988).

Doxycycline

While doxycycline has been used for the treatment of malaria, pregnant women should avoid taking doxycycline for malaria prevention during pregnancy. Doxycycline is a tetracycline derivative that is assumed to cause similar effects of tetracycline exposure during pregnancy including staining of the teeth in the fetus and depressed fetal bone growth (Rendle-Short, 1962).

Malarone

Malarone is a combination of atovaquone and proguanil HCl used in the prophylactic treatment of malaria. There are no adequate or well-controlled studies of Malarone use or its individual components in pregnancy. Proguanil has been used for in Europe with no reported complications or increased incidence of malformations. This agent has been found to reduce folate levels; however, neural tube defects have not been reported to date (GlaxoSmithKline, July 2001). If a patient requires proguanil therapy, it is recommended that she receive additional folic acid.

Over the past few years, atovaquone in conjunction with proguanil has been prescribed as an anti-malarial therapy. Atovaquone is highly lipophilic and highly protein bound. There is currently no human reproduction data available regarding this agent. Personal European and American physician experiences have not documented an increased risk for a congenital anomaly or other adverse effects (personal communication, London School of Tropical Medicine, John Hopkins Tropical Medicine Department, 2001).

In summary, to date there is no indication that Malarone or its individual components are teratogenic. However, clearly well-controlled studies are required to firmly establish an accurate risk assessment. If a person is inadvertently exposed to Malarone early in the first trimester, there is no data to suggest the pregnancy is at an increased risk for complications. If a patient requires an anti-malaria medication for use during pregnancy, a better suited agent such as mefloquine would be recommended.

Summary

Malaria infection during pregnancy is serious and increases the risk for maternal complications and fetal loss. If there has been a previous exposure, there is thought to be some level of immunity established. However, pregnancy may actually increase susceptibility, as this is a time in which cell-mediated immunity is decreased. If maternal infection occurs during pregnancy, the concern is that the infection will affect the placenta. It has been found that the intensity of the infection in the placenta is directly related to the severity of the effect on the fetus. The most common effect of a placental infection is low birth weight, as less blood and nutrients are available to the fetus. There is increased risk for miscarriage, premature delivery, stillbirth, jaundice, liver enlargement, and anemia. If a pregnant woman is traveling to an area where malaria is prevalent, prophylactic treatment is recommended.

Current Research Studies

ITIS is currently enrolling and following up on pregnancies as part of the following studies. If you have a patient who would like to participate in one of the studies, please contact ITIS at (800) 252-4847.

Asthma Medications in Pregnancy Project

Rheumatoid Arthritis in Pregnancy Study

Ondansetron in Pregnancy Study

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CDC

website: Malarone for Malaria Treatment and Prophylaxis.

www.cdc.gov/travel/diseases/malaria/malarone.htm

CDC:

Preventing Malaria in the Pregnant Woman - www.cdc.gov/travel/mal_preg_pub.htm

CDC: Pregnancy, Breast Feeding, and Travel - www.cdc.gov/travel/pregnant.htm

Committee on Drugs, American Academy of Pediatrics. The transfer of drugs and other chemicals into human breast milk. Pediatrics (1994) 93:137-150.

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