Prophylactic use of antimalarials during pregnancy

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Abstract

Question Some of my pregnant patients wish to travel to malaria-endemic regions. Are there medications that can be used safely during pregnancy for malaria prophylaxis?

Answer Pregnant women should avoid travel to malaria-endemic areas if possible. However, if travel cannot be avoided, measures to prevent mosquito bites, along with an effective chemoprophylaxis regimen, should be implemented. Chloroquine or hydroxychloroquine are considered safe to use in all trimesters of pregnancy. Mefloquine is the agent of choice for chloroquine-resistant areas, and evidence suggests it is not associated with an increased risk to the fetus. Although the atovaquone-proguanil drug combination is not currently recommended for use during pregnancy, limited data suggest that it is not harmful to the fetus. Doxycycline and primaquine are not recommended during pregnancy.

Utilisation prophylactique d'antipaludéens durant la grossesse

Résumé

Question Certaines de mes patientes enceintes souhaitent voyager dans des pays où le paludisme est endémique. Y a-t-il des médicaments qui peuvent être utilisés en toute sécurité durant la grossesse en tant que mesure prophylactique contre la malaria?

Réponse Si possible, les femmes enceintes devraient éviter de voyager dans les régions où le paludisme est endémique. Cependant, s'il est impossible d'éviter ce voyage, il faut prendre des mesures pour éviter les piqûres de moustiques, et entreprendre un régime chimioprophylactique efficace. L'utilisation de la chloroquine ou de l'hydroxychloroquine est considérée sécuritaire durant tous les trimestres de la grossesse. La méfloquine est l'agent de première intention dans les régions où la malaria est résistante à la chloroquine et, selon des données probantes, elle ne serait pas associée à des risques accrus pour le fœtus. Même si la combinaison de l'atovaquone et du proguanil n'est actuellement pas recommandée durant la grossesse, selon des données limitées, elle ne serait pas dommageable pour le fœtus. La doxycycline et la primaquine ne sont pas recommandées durant la grossesse.

Malaria is caused by *Plasmodium* parasites. Of the various species, *Plasmodium falciparum* and *Plasmodium vivax* are the most common.[1] Malaria is transmitted to humans by the bite of *Anopheles* mosquitoes, and during pregnancy it can be congenitally transmitted from mother to fetus.[2] Pregnant women are twice as likely to be bitten by mosquitoes.[3] Malaria-endemic areas include Central and South America, parts of the Caribbean, Africa, Asia, Eastern Europe, and the South Pacific,[2] although most malaria cases occur in sub-Saharan Africa.[1] Malaria presents with fever and influenza-like symptoms such as chills, headache, and myalgia, and can progress to a more severe presentation involving multiple organ systems, sometimes leading to death. Severe illness is most commonly caused by *P falciparum*.[1,2] In nonimmune pregnant women, malaria carries an additional risk of miscarriage (up to 60% in *P falciparum* infection),[1] neonatal death,[3] stillbirth,[3] low birth weight,[4] and high maternal death rates (10% to 50%).[1] For these reasons, and because no prophylactic regimen provides complete protection, it is recommended that pregnant women avoid traveling to malaria-endemic areas.[2] However, it might not always be possible for pregnant women to avoid travel, and thus an effective chemoprophylaxis regimen should be selected and appropriate mosquito-avoidance measures should be encouraged (**Box 1**[2,3]). The chemoprophylactic regimen that is selected will depend on many factors, including the travel itinerary and antimalarial drug resistance reported in that location. The available evidence for the safety of each antimalarial drug during pregnancy is summarized below. **Table 1**[2-4] summarizes Motherisk recommendations for malaria chemoprophylaxis during pregnancy.

Chloroquine or hydroxychloroquine

No harmful effects on the fetus have been observed when chloroquine or hydroxychloroquine are used in the recommended doses for malaria prophylaxis.[2] Observational data[5,6] (amounting to more than

1000 exposures) and 1 double-blind randomized-controlled trial[7] (N=951) have evaluated the use of chloroquine at various stages of pregnancy for the prevention of malaria and have not identified any teratogenicity or other adverse events. As a result, this agent is considered safe for use in all trimesters of pregnancy.

Doxycycline

There is no evidence for human teratogenicity with doxycycline use during pregnancy.[8] Despite this, the main concern with doxycycline, like tetracycline, is the risk to the fetus of inhibition of bone growth and discoloration and dysplasia of the teeth,[3] which can occur during the period of calcification beyond the fourth month of gestational age.[4] Because of the potential harm, doxycycline is not recommended during pregnancy. However, keeping in mind that treatment is continued for 4 weeks after leaving the malaria-endemic area,[9] doxycycline can be considered as long as treatment is completed by the fourth month of pregnancy.

Box 1. Mosquito-avoidance measures Mosquito-avoidance measures include the following:

- Remain in well-screened areas, especially between dusk and dawn
- Use mosquito bed nets (preferably insecticide-treated nets)
- Use a pyrethroid-containing flying-insect spray in living and sleeping areas during evening and nighttime hours
- Consider wearing clothing that is impregnated with insecticide (permethrin)
- Wear clothes that cover most of the body; also, tuck shirts into pants, and tuck pants into socks or footwear
- Dress in light-coloured clothing
- Use an effective mosquito repellent that contains DEET (diethyltoluamide) in concentrations of 30% or less; apply to clothing and the exposed parts of the skin

Data from the Centers for Disease Control and Prevention[2] and the Committee to Advise on Tropical Medicine and Travel.[3]

Atovaquone-proguanil

Proguanil has been used as a malarial prophylactic agent for decades, with no known toxic effects on the fetus.[10] Four small 3-day treatment studies with the atovaquone-proguanil combination in the second and third trimesters of pregnancy did not identify any adverse effects in the fetuses or newborns.[11-14] In a recent retrospective cohort study of the Danish Medical Birth Register, based on a limited number of exposed pregnancies (N=149), there was no significant association between atovaquone-proguanil use during the first trimester and major birth defects. Most of the exposed mothers were likely travelers receiving atovaquone-proguanil for prophylaxis, as mothers diagnosed with malaria were excluded from the cohort to avoid potential confounding from other therapies.[15]

Although the available data are reassuring, the evidence for its use during pregnancy remains limited, and thus it is not currently recommended for the prevention of malaria in pregnant women.[2] However, it might be considered if the expected benefit for the mother outweighs any potential risk to the fetus.

Mefloquine

Observational data[6] and a placebo-controlled trial[16] evaluating mefloquine use in the second half of pregnancy have found no effect on the rate of stillbirths, birth defects, or other adverse fetal or pregnancy outcomes. Mefloquine registries and surveillance data have

Table 1. Summary of Motherisk recommendations for malaria chemoprophylaxis during pregnancy

ANTIMALARIAL DRUG	EVIDENCE OF TERATOGENICITY	TIMING OF EXPOSURE	LEVEL OF EXPERIENCE	RECOMMENDATIONS FOR USE DURING PREGNANCY
Chloroquine or hydroxychloroquine	No	All trimesters	Substantial data available	Drug of choice in chloroquine-sensitive areas[3]
Doxycycline	No	First 4 mo of pregnancy	Limited data available	Not recommended owing to adverse effects on the fetus with the use of tetracyclines when used after the fourth month of pregnancy, including discoloration and dysplasia of the teeth, and inhibition of bone growth[3,4]
Atovaquone-proguanil combination	No	All trimesters	Limited data available	Might be considered after careful discussion of the benefits and risks in women who cannot avoid travel to mefloquine-resistant areas
Mefloquine	No	All trimesters	Substantial data available	Recommended for use anytime during pregnancy in chloroquine-resistant areas
Primaquine	No data available	No data available	No data available	Not recommended, as the G6PD status of the fetus cannot be established and the drug can be passed transplacentally[2]

G6PD—glucose-6-phosphate dehydrogenase.

recorded thousands of exposures mainly in the first trimester of pregnancy with no increased rate of malformations or spontaneous abortions.[17,18] Based on the available evidence, malaria prophylaxis with mefloquine does not appear to be associated with risks to the fetus, even when used in the first trimester.

Primaquine

There are no data on the use of primaquine during pregnancy. Primaquine causes acute hemolysis in those with a glucose-6-phosphate dehydrogenase deficiency.[19] Therefore, because the glucose-6-phosphate dehydrogenase status of the fetus cannot be established, primaquine is not recommended for use during pregnancy.[2]

Conclusion

Current data suggest that chloroquine, hydroxychloroquine, mefloquine, and the proguanil-atovaquone combination do not pose any safety concerns for pregnant women. However, experience with the proguanil-atovaquone combination in the first trimester is limited. Primaquine and doxycycline are not recommended during pregnancy, although, theoretically, doxycycline could be considered for use in the first trimester of pregnancy.

Competing interests
None declared

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