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Travel and Pregnancy

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It is not uncommon for a pregnant woman to plan international travel for business or recreation. Several issues relating to travel during pregnancy are clinically significant as the maintenance of maternal and fetal health may require specific considerations. This RISK//NEWSLETTER will address several of the concerns which frequently arise as a pregnant woman considers international travel, including airline flight, immunizations, malarial infection and antimalarial agents.

General Travel Concerns

The American College of Obstetricians and Gynecologists (ACOG) considers the second trimester the best time to travel (ACOG Technical Bulletin, 1994). During this period, a woman's body has adjusted to pregnancy, and movement is not yet limited. Also, the second trimester is considered safer because the risk for miscarriage is lower than during the first trimester. After the sixth month of pregnancy, there is an increased risk of premature labor and other complications.

There are several general medical concerns which should be addressed before a pregnant woman travels. First, a woman should have a thorough consultation with her obstetrician. Careful assessment of a woman's obstetrical and medical history should be performed so that both the physician and the patient are aware of potential complications (Rose, 1997). Tubal pregnancy, multifetal pregnancy and placental abnormalities should be ruled out. The quality and availability of medical and obstetric care in the regions on the itinerary should be assessed. United States embassies and consulates maintain lists of English-speaking physicians and can provide referrals. Also, the International Association for Medical Assistance to Travelers (IAMAT) can provide travelers with a listing of qualified English-speaking physicians overseas at (519) 836-0102. The specifics of travel health insurance policies can vary; travelers should compare policies and be familiar with their exclusions (e.g., miscarriage, delivery) prior to purchase (Rose, 1997).

Airline Travel

Domestic and foreign airlines restrict travel for pregnant women after 36 and 35 weeks gestation, respectively (Barry, 1989). When a pregnant woman prepares to board an airplane, initial concern may arise when the woman encounters a security metal detector at the airport. These devices generally produce a magnetic field through which a person passes (Barry, 1997). There is no evidence to suggest that magnetic fields are harmful to a fetus.

Most commercial jetliners maintain cabin pressures at those found 5000-8000 feet (1524-2438 meters) above sea level. This results in a decrease in oxygen intake from 20% to 15% oxygen (Scholten, 1976). The change in fetal oxygenation is less, because fetal hemoglobin maintains a greater degree of

oxygen saturation due to its oxygen-dissociation curve (Barry, 1989). Overall, the cabin pressures maintained in modern jet aircraft do not appear to be harmful to a fetus.

Cosmic radiation is increased during flight at altitudes maintained by modern commercial jets. Generally, radiation at levels lower than 5 rads during a pregnancy has not been associated with increased fetal risk. Since the monthly exposure limit for pregnant flight attendants is 50 millirads, it is unlikely that a traveler would exceed this limit (Rose, 1997). Therefore, the radiation exposure from commercial flying is unlikely to pose a risk to the fetus.

Pregnant women should also maintain hydration and frequent stretching and other activity to decrease the risk of dehydration and deep vein thrombosis while flying (Barry, 1989).

Immunizations

Many foreign countries do not have strict requirements for immunizations prior to entry. Vaccine recommendations are often obtained from consultation with travel-advisory groups. Ideally, a woman should receive immunizations prior to pregnancy. If immunization is indicated during pregnancy, the risk of exposure and risks to the mother and to the fetus from the disease must be weighed against potential risks of immunization (Barry, 1989).

It is important to consider the type of immunizing agent used for a particular vaccination. There are five types currently used: live vaccines, killed or inactivated vaccines, immune globulins, recombinant agents, and toxoids (ACOG, 1991). Overall, there is no evidence that vaccines in use today have harmful effects on the fetus. The concern regarding immunization during pregnancy involves the theoretical risk to the fetus of a live vaccine. Because live viral and bacterial vaccines are capable of replicating, there is concern that they could infect the mother, and therefore the fetus, potentially causing birth defects. Consequently, it is recommended that live viral or bacterial vaccines be avoided during pregnancy, especially during the first trimester during organogenesis. However, if a woman is at substantial risk of acquiring a particular infection, the risks and benefits of vaccination should be weighed. The ACOG Technical Bulletin Number 160 (October, 1991) serves as an excellent reference, as it presents the current recommendations of the Immunization Practices and Advisory Committee (ACIP) for immunization of pregnant women.

In the United States, most women of childbearing age are immune to measles, mumps, rubella, tetanus, diphtheria and poliomyelitis through vaccination or natural infection (ACOG, 1991). Travelers may need to consider other vaccinations depending on their destination. Yellow fever, typhoid fever, cholera, meningococcal meningitis and/or hepatitis A vaccines may be recommended.

Yellow fever vaccine is a live virus vaccine, so there is a theoretical risk associated with its use during pregnancy. In one study, out of 41 infants born to women who had been immunized with this vaccine during the first trimester, one infant had serological evidence of intrauterine infection but did not show any adverse fetal effects (Tsai et al., 1993). In addition, a large study of yellow fever vaccination in women of childbearing age did not suggest any increased risk for adverse fetal outcome (Nasidi et al., 1993). In general, if travel is unavoidable to regions where yellow fever is endemic, the vaccination is not contraindicated because of the significant morbidity and mortality associated with yellow fever infection.

Cholera, typhoid, and meningococcus are all killed or inactivated vaccines. In pregnant women who are at significant risk of exposure to these infections, these vaccinations are not contraindicated; however, avoidance of first trimester exposure is preferable (ACOG, 1991). Hepatitis A vaccine is available as either a standard immune globulin or an inactivated virus, while hepatitis B is often a recombinant vaccine. Because viral hepatitis can be exacerbated by pregnancy, vaccination for hepatitis A and/or B can be considered for international travelers at risk for acquiring this infection (Rose, 1997).

Malarial Infection

Malarial infection presents a major health concern worldwide. Infection is caused by various species of the parasite plasmodium, and is transmitted through the bite of the female mosquito. Malarial infection is a concern to individuals traveling to tropical areas.

Pregnancy increases susceptibility to malarial infection. Parasitemia is inversely related to parity, with an average 2-fold increase in prevalence in primigravidas compared to multigravidas (Nosten et al., 1991; Mutabingwa, 1994). Clinical manifestations in symptomatic pregnant women can be similar or more severe than in nonpregnant individuals, and include anemia, hypoglycemia, pulmonary edema, fever and headache which may mimic a viral illness. Maternal mortality rates can reach 10% (Weekly Epidemiological Record, 1996).

Placental infection influences perinatal outcome. The average prevalence of placental malaria in primigravidas is 30-40%, while the prevalence in multigravidas is approximately half this rate (Silver, 1997). Overall, obstetrical complications including abortion, stillbirth, and premature deliver are reported to be increased in infected women, with fetal loss rates ranging from 9% to 50% (McGregor, 1984; Sholapurkar et al, 1988). Congenital malaria is relatively rare; however, it can occur even in asymptomatic mothers (Bia, 1992). Prenatal or perinatal transmission to children occurs in up to 7.4% of non-immune mothers (Hulbert, 1992). Congenital malaria is characterized by fever, anemia, splenomegaly in most cases, with jaundice, hepatomegaly and hyperbilirubinemia occurring occasionally.

Anti-malarial Agents

For pregnant women traveling to regions endemic with malaria, chemoprophylaxis with anti-malarial agents is a preventative option. In most regions, plasmodium is sensitive to chloroquine (Aralen), a quinine derivative with anti-malarial properties. Numerous studies suggest that chloroquine is the drug of choice for the prophylaxis and treatment of sensitive malaria species during pregnancy (Rose, 1997). Concern was raised over a case report of a woman who had taken large doses of chloroquine in multiple pregnancies and then had one child with hemihypertrophy and two others with bilateral eye and ear abnormalities (Hart et al., 1964). However, no increase in congenital anomalies was reported in 18 patients taking large doses of chloroquine for treatment of lupus (Parke, 1988; Levy et al., 1991) or in a series of 169 women treated for malaria (Wolfe and Cordero, 1985). The Centers for Disease Control and Prevention does not consider pregnancy a contraindication for prophylactic doses of chloroquine (CDC, 1990).

Mefloquine (Larium) is a quinolone derivative that is considered the prophylaxis of choice for travel to areas with chloroquine-resistant *P. falciparum*. In rats and mice, mefloquine exposure was teratogenic only at maternally toxic doses (Minor et al., 1976). In small numbers of human pregnancies, mefloquine has been administered with no increase in adverse outcomes (Collignon et al., 1989; Karbwang et al., 1990; Nosten et al., 1990; Balacco et al., 1992; Nosten et al., 1994). Studies of 218 and 85 mefloquine-exposed pregnancies respectively did not show an increase in adverse outcomes (Elefant et al., 1991; Harinasuta et al., 1990). There is limited information about the effects of mefloquine use specifically in the first trimester.

Other anti-malarials are composed of pyrimethamine in combination with other agents. Pyrimethamine is a folic acid antagonist, and animal studies have found that it induces multiple malformations (Thiersch, 1954; Sullivan et al., 1971; Schwartsman, 1979; Misawa et al., 1982), including an association between vascular abnormalities and pyrimethamine exposure (Tangapregassom et al., 1985). Based on these animal studies and its action on folic acid, there are theoretical concerns about the use of pyrimethamine during the first trimester of pregnancy. Human studies have not, however, found an increase in abnormalities as a result of prenatal pyrimethamine exposure (Morley et al., 1964;

Bruce-Chwatt, 1983; Main et al., 1983; Heinonen et al., 1977).

Pyrimethamine is combined with sulfadoxine or dapson in the anti-malarials Fansidar and Daraprim, respectively. These anti-malarials are marketed for prophylaxis of chloroquine-resistant strains of malaria. Use of sulfonamides and related drugs during pregnancy has raised theoretical concern because sulfonamides can bind plasma proteins and displace bilirubin. Exposure of a late-term fetus may increase the risk for development of kernicterus as a result of this. Adverse reactions not related to pregnancy have been reported after use of these drugs (MMWR, 1985; Selby et al., 1985; Millar et al., 1986; Millikan et al, 1990). Overall, these drugs are not recommended during pregnancy unless they offer a clear therapeutic benefit over quinine derivatives.

Other anti-malarial agents include chloroguanide (proguanil, Paludrine), halofantrine (Halfan), and primaquine. There is little experience with use of these drugs during human pregnancy; consequently, the risks associated with prenatal exposure to these agents are undetermined.

A traveler can obtain information on the sensitivity of predominant malaria strains in a particular region through the CDC Malaria Hotline at (404) 332-4555.

Protection against insect bites is an important preventative measure, not only against malaria, but other insect-transmitted diseases as well. Diethyltoluamide (DEET) is an insect repellent used in many repellent products. Topical exposure to DEET results in systematic absorption of levels ranging from 6% to 8% of the dose applied (Snodgrass et al, 1982; Selim et al 1995). Animal studies have reported conflicting results regarding its teratogenic potential. There are very limited studies on the human reproductive effects of DEET; consequently, limited use by pregnant women may be advisable. Ways to minimize exposure include using an insecticide with a lower percentage of DEET, and spraying it on clothing rather than directly on skin.

Permethrin is a synthetic pyrethroid insecticide that is often used to treat clothing or netting. Pyrethroids in general do not appear mutagenic (Miyamoto, 1976); however, human reproductive effects have not been studied. In light of these unknown risks, practical considerations for preventing insect bites can also be made. Travelers can place netting around sleeping areas and reduce skin exposure by wearing long-sleeved shirts and pants.

Summary

Overall, travel during pregnancy requires advance preparation and precaution. A patient should have a thorough consultation with her obstetrician before traveling. Airline travel does not present any known risks to pregnancy. Immunization with live viral or bacterial vaccines pose theoretical risks; however, these vaccines are not contraindicated when a woman is at high risk of exposure to the infectious agent. Prevention of malarial infection is an important concern as maternal malaria is associated with poor maternal and perinatal outcome. There are a variety of anti-malarial agents available for chemoprophylaxis, some of which, however, have undetermined risks in human pregnancy. As with any medication, the risks associated with a particular medication should be carefully weighed against its benefits.