THE PREGNANT TRAVELER

Benjamin U. Samuel, MD, and Michele Barry, MD

As women enter full-time careers that require business and professional travel, they may often delay childbearing until those very years when travel becomes imperative during the trimesters of pregnancy. Health practitioners should be able to assess the risks involved in short- and long-term travel, especially when travel is contemplated to remote areas of the world in which no immediate medical facilities are available. The patient's itinerary should be carefully reviewed, and if a particular destination or an activity substantially increases the risk to the mother or the fetus, the pregnant traveler should be fully educated to make the best possible decision whether to undertake the travel. Physicians and other health professionals should be able to offer the following guidelines and precautions that will ensure the safety of the mother and fetus during travel.

PRETRAVEL ASSESSMENT OF PREGNANT TRAVELERS

In advising pregnant travelers, the health practitioners should work closely with obstetricians, especially for assessing the gestational age and the medical, obstetric, social, and demographic risks. Table 1 lists categories that define potential high-risk pregnancies for whom travel should be delayed if possible until after delivery.

Physical examination to assess the gestational age, fetal growth performance, medical and obstetric risks, and identify coexisting medical illness (such as sexually transmitted diseases) should be done and appropriate laboratory investigations performed. Serology for hepatitis B virus infection, cytomegalovirus (CMV), rubella, measles, chickenpox, and toxoplasmosis should be carried out if not already done before conception. Pregnant travelers should carry a copy of their medical records (including blood type and Rh) in case of an
Table 1. HIGH-RISK PREGNANCIES

<table>
<thead>
<tr>
<th>Category</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medical</td>
<td></td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>Pulmonary hypertension</td>
</tr>
<tr>
<td></td>
<td>Valvular lesions with NYHA class III, IV</td>
</tr>
<tr>
<td></td>
<td>Aortic coarctation, cardiomyopathies</td>
</tr>
<tr>
<td>Pulmonary</td>
<td>Chronic lung diseases, severe asthma</td>
</tr>
<tr>
<td></td>
<td>Thromboembolic disease</td>
</tr>
<tr>
<td>Others</td>
<td>Hypertension, diabetes, renal failure</td>
</tr>
<tr>
<td></td>
<td>Hemoglobinopathies, complicated medical diseases requiring monitoring</td>
</tr>
<tr>
<td>Obstetric</td>
<td>High risk of preterm delivery, current fetal growth restrictions</td>
</tr>
<tr>
<td></td>
<td>Pre-eclampsia, antepartum hemorrhage—abruptio placentae, placenta previa, multifetal pregnancy</td>
</tr>
</tbody>
</table>

NYHA = New York Heart Association

emergency. Prenatal vitamins, at times difficult to obtain overseas, should be prescribed in sufficient quantities.

Common sense dictates that travel, in general, should be avoided by pregnant women with complicated medical needs. A traveler with pregnancy-induced hypertension, bleeding, or diabetes may have difficulty being monitored during travel. Although home blood-pressure cuffs, urine dipsticks for protein, and glucometers can be carried, continuity of care in a stable environment is clearly essential for a good health outcome. Many insurance plans do not cover pregnant women overseas and many plans have gestation cutoff dates for travel beyond which they will not cover delivery out of the area.

MODES OF TRAVEL FOR PREGNANT WOMEN

Air Travel and Pregnancy

Domestic airlines stipulate that air travel for pregnant women after 36 weeks' gestation is not allowed and most foreign airlines have a cutoff of 35 weeks. Commercial jetliners cruising at high altitudes are only able to be pressurized to 5000 to 8000 ft above sea level. The Concorde is pressurized 8000 feet above sea level (Chris Patridge, British Airways, personal communication, 1997). In women who do not exercise, arterial $P_O_2$ will drop accordingly with altitude changes such that those with significant anemia or with a compromised oxygen saturation may need supplemental oxygen to prevent symptoms of oxygen desaturation. Sickle cell anemia presents the possibility of crisis during desaturation, and even those with sickle trait may experience hematuria or renal microthrombosis.

The fetal circulation and fetal hemoglobin protects the fetus against desaturation during air flight. In fetal circulation, the fetal venous cord blood (analogous to pulmonary venous blood in the adult, having received its increased oxygen content from the placenta instead of the lungs) is only 32 mm Hg; the $P_O_2$ of arterial cord blood is 10.6 mm Hg. Scholten simulated an environment for the pregnant woman and fetus of 8000 feet by having the mother breathe 15% oxygen and documented only small drops in fetal venous $P_O_2$ despite the
expected maternal arterial \( \text{PO}_2 \) drop from 100 to 55 mm Hg.\(^{137} \) Thus, the fetus is considered safe from desaturation during routine commercial airline flights.

Certain precautions should be taken by pregnant travelers during air flight. As alterations in clotting factors and venous dilation during pregnancy predispose pregnant travelers to superficial and deep thrombophlebitis, walking, stretching and isometric leg exercises should be encouraged, especially on long flights. Because of the extremely low humidity of pressurized flights, significant insensible water loss can be expected.\(^{20} \) Hydration is crucial for placental flow and pregnant travelers should be encouraged to drink nonalcoholic beverages plentifully during long flights. Seat belts should be worn low around the pelvis. As a precaution, seat belts should be worn throughout the flight while seated for the safety of the mother and the fetus in the event of turbulence.

**Other Modes of Travel**

When traveling in automobiles, it is advisable for pregnant women not to sit for prolonged periods because of the risk for venous stasis and possible thromboembolism. The usual recommendation is driving for a maximum of 6 hours per day. Every 2 hours, the automobile should be stopped for at least 10 minutes so that the pregnant woman can walk around and increase venous return from the legs.\(^{23} \) Motor vehicle accidents account for most severe blunt trauma to pregnant women. The American College of Obstetricians and Gynecologists has recommended that pregnant women should wear properly positioned three-point restraints while riding in automobiles.\(^{6} \)\(^{44} \) Travelers should be warned that in many parts of the world, taxicabs and other automobiles do not have safety restraints.

Sea voyages can exacerbate the nausea and vomiting associated with pregnancy. Most cruise liners will carry pregnant women up to the seventh month and have reasonably well equipped medical facilities aboard. Caution must be observed while walking on deck, to avoid potentially severe accidents caused by the motion of the ship and the general imbalance imposed by pregnancy.

**IMMUNIZATION FOR PREGNANT TRAVELERS**

**General Recommendations**

Although the terms vaccination and immunization are used interchangeably, in the strictest sense, vaccination is only the administration of a vaccine, whereas immunization results in the demonstrable presence of protection confirmed usually by serologic testing.\(^{126} \) Passive immunization is the administration of antibodies, usually in the form of antisera of animal origin or immunoglobulins, which results in immediate protection of short duration.\(^{126} \) Active immunization is a process of increasing resistance to infection whereby microorganisms or their products act as antigens to stimulate the individual's immune system. Vaccines (either single component or mixed combined) may contain either living or killed microorganisms, bacterial toxoids, or antigenic material of the microorganisms.

The Food and Drug Administration (FDA) has categorized drugs, vaccines, and toxoids with regard to developmental toxicity and adverse fetal outcome (Table 2). Unfortunately, not all drugs have been assigned to an FDA category,
Table 2. FOOD AND DRUG ADMINISTRATION USE-IN-PREGNANCY RATINGS

<table>
<thead>
<tr>
<th>FDA Category/ Rating</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Category A</td>
<td>Adequate and well-controlled studies in women show no risk to the fetus.</td>
</tr>
<tr>
<td>Category B</td>
<td>No evidence of risk in humans. Either studies in animals show risk, but human findings do not, or, in the absence of human studies, animal findings are negative.</td>
</tr>
<tr>
<td>Category C</td>
<td>Risk cannot be ruled out. No adequate and well-controlled studies in humans, or animal studies are either positive for fetal risk or lacking as well. Drugs should be given only if the potential benefit justifies the potential risk to the fetus.</td>
</tr>
<tr>
<td>Category D</td>
<td>There is positive evidence of human fetal risk. Nevertheless, potential benefits may outweigh the potential risks.</td>
</tr>
<tr>
<td>Category X</td>
<td>Contraindicated in pregnancy. Studies in animals or humans or investigational or postmarketing reports have shown fetal risk that far outweighs any potential benefit to the patient.</td>
</tr>
</tbody>
</table>

and few vaccines have been officially tested in pregnant women. Few drugs fall into category A, a clearly safe category, and few double-blind controlled studies in pregnant women have been carried out so as to categorize the drugs. Most medications in the Physicians’ Desk Reference fall under FDA category C.

General precautions regarding timing of vaccination also apply when considering immunization of pregnant travelers. Immunization should be postponed in patients suffering from any acute illness, although immunization is not contraindicated in the presence of minor infections without fever or systemic symptoms. Because of theoretical risk to the fetus, live vaccines should not be administered during pregnancy; exceptions are when there is significant risk of exposure to infection to the pregnant woman that justifies the risk of vaccination. It is also best to avoid any form of immunization during the first trimester of pregnancy, if possible. High fevers occurring during the first trimester have been associated with neural tube defects and this may be incurred by vaccination induced febrile response. It is advisable for nonpregnant women receiving any form of live vaccines not to conceive within 3 months of vaccination. Table 3 gives the safety profile of vaccines and other immunobiologics in pregnancy.

Specific Vaccines for Travel

Inactivated vaccines, in general, can be safely administered to pregnant women if their administration is not associated with severe febrile reactions. To maintain adequate immunity against diphtheria and tetanus and to prevent neonatal tetanus, it is necessary to administer booster doses of tetanus-diphtheria vaccine (Td) (for adult use) every 10 years following primary immunization. The Advisory Committee on Immunization Practices (ACIP), AAP, and the American College of Obstetricians and Gynecologists endorse tetanus toxoid administration even during pregnancy. The manufacturers recommend that nonimmunized or incompletely immunized pregnant women and those immunized more than 10 years previously who may deliver a child under unhygienic circumstances or surroundings should receive one or two properly spaced doses of Td (for adult use), preferably during the last 2 trimesters. Those pregnant women traveling to areas endemic for diphtheria need to be vaccinated with Td. Individuals who experience Arthus-type hypersensitivity reactions or fever
higher than 39.4°C should not be given boosters. These reactions are seen in adults who have received frequent (e.g., annual) doses of a tetanus toxoid containing preparation.90

Pertussis-containing preparations, such as DTP, DTaP, or DTP-HbOC, are generally administered to children below the age of 7 and may be associated with high fevers and hence not recommended for pregnant travelers.90 Whooping cough in late pregnancy with transmission of the disease to the infant has been reported even after the patient had completed primary series as a child.99 In fact, there are concerns about the duration of protection offered by pertussis immunization in childhood71,100,101 and pregnant travelers are at risk for acquiring the disease in countries still endemic for pertussis. Until safer pertussis vaccine is made available, no clear recommendations can be made. Erythromycin may be used as treatment and prophylaxis if needed.98 Pertussis immunoglobulin (USP 23, Pertussis Immune Globulin) prepared from immune individuals may be used for passive immunization against pertussis. It has also been used to prevent or modify pertussis in susceptible persons who have been exposed to the infection.98

Bacterial polysaccharide vaccines, meningococcal vaccine, and pneumococcal vaccine are listed as FDA pregnancy category C by the manufacturers because of lack of data. The commonly available meningococcal vaccine in the United States is a tetravalent vaccine from groups A, C, Y, and W135. In a number of other countries only bivalent vaccine from group A and C is commonly used. An A and C bivalent vaccine has been evaluated in pregnant women and infants during an epidemic of meningitis in Brazil and was believed to be safe.96 In general, polysaccharide vaccines have been given to pregnant women without adverse effects.14,53,57,87,140 These vaccines, especially the meningococcal vaccine, should be used when indicated.

The WHO International Health Regulation no longer requires cholera vaccination for international travelers. Cholera continues to be a health risk in parts of Africa, Asia, and Latin America. The currently available injectable, inactivated whole cell cholera vaccine is not efficacious, however. It is best to avoid this vaccine in pregnancy because it can induce a significant febrile response that can be detrimental to the fetus. Newer preparations of killed and live oral cholera vaccine are available outside of the United States and may prove to be efficacious. Of the two killed oral cholera vaccine preparations, the cholera toxin B-subunit–whole-cell cholera vaccine (BS–WC) has been shown to provide in children more than 2 years of age and in women more than 15 years of age, greater than 85% protection against cholera in the first 6 months and 50% cumulative protective efficacy.16,38,40,77 An oral recombinant BS–WC cholera vaccine preparation has been made and has been found to be immunogenic.132,133 Because these vaccines do not contain any live organisms, the theoretical risk to the fetus should be negligible. Until the safety and efficacy of these vaccines in pregnant patients are established, however, no clear recommendations can be made. A live attenuated oral cholera vaccine (CVD 103 HgR strain) is available in Canada and several European countries. Pregnancy information is not available, but because the vaccine contains live organisms, use in pregnancy should be avoided at this time.

There are three vaccines available for the prevention of typhoid. The subcutaneously administered heat/phenol activated typhoid vaccine is no more effective than the live oral typhoid vaccine (enteric-coated, lyophilized, Ty21a strain of *Salmonella typhi*) or the intramuscularly administered Vi capsular polysaccharide typhoid vaccine (ViCPS, Typhim Vi) but can cause substantially more adverse effects than the other vaccines.7,8 Information is not available on the safety of any of the three vaccines during pregnancy. The ViCPS typhoid vaccine
<table>
<thead>
<tr>
<th>Immunobiologic Agent</th>
<th>Type of Vaccine</th>
<th>Comments</th>
<th>Dose Schedule</th>
</tr>
</thead>
<tbody>
<tr>
<td>Measles</td>
<td>Live-attenuated</td>
<td>Contraindicated&lt;br&gt;Pregnancy should be delayed for 3 months after MMR is given</td>
<td>see article</td>
</tr>
<tr>
<td>Mumps</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rubella</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yellow fever</td>
<td>Live-attenuated</td>
<td>Contraindicated except if exposure is unavoidable</td>
<td>Single dose SC</td>
</tr>
<tr>
<td>Poliomyelitis</td>
<td>Trivalent live-attenuated (OPV)</td>
<td>Avoid in previously nonimmune individuals because of the risk for vaccine-associated paralysis&lt;br&gt;ACIP recommends use in outbreak situation</td>
<td>Single dose for immediate protection</td>
</tr>
<tr>
<td>Poliomyelitis</td>
<td>Killed (eIPV)</td>
<td>Preferred over OPV during pregnancy</td>
<td></td>
</tr>
<tr>
<td>Typhoid (Ty21a)</td>
<td>Live-attenuated bacterial, oral</td>
<td>No data in pregnancy&lt;br&gt;Should reflect actual risks of disease&lt;br&gt;Avoid in pregnancy on theoretical grounds</td>
<td>see article</td>
</tr>
<tr>
<td>Typhoid</td>
<td>Vi capsular polysaccharide, parenteral</td>
<td>No data in pregnancy&lt;br&gt;Used only when clearly indicated</td>
<td>Single dose IM</td>
</tr>
<tr>
<td>Typhoid</td>
<td>Heat/Phenol inactivated, parenteral</td>
<td>Avoid in pregnancy because of greater systemic reaction with this vaccine</td>
<td>see article</td>
</tr>
<tr>
<td>Hepatitis A</td>
<td>Formalin inactivated vaccine</td>
<td>Category C drug&lt;br&gt;Use only if clearly indicated</td>
<td>Single adult dose 1 mL IM&lt;br&gt;Booster 6 to 12 months after the primary dose</td>
</tr>
<tr>
<td>Hepatitis B</td>
<td>Recombinant, purified hepatitis B surface antigen</td>
<td>Not contraindicated&lt;br&gt;Preexposure and postexposure prophylaxis indicated in pregnant women at risk for infection</td>
<td>IM-deltoid area 3 doses at 0, 1 and 6 months or 4 doses 0, 1, 2, and 12 months (Engerix vaccine) for rapid immunization</td>
</tr>
<tr>
<td>Disease</td>
<td>Vaccine Type</td>
<td>Uses</td>
<td>Dose Details</td>
</tr>
<tr>
<td>--------------------------</td>
<td>-----------------------</td>
<td>----------------------------------------------------------------------</td>
<td>------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Influenza</td>
<td>Inactivated vaccine</td>
<td>Women in their second or third trimester during influenza season</td>
<td>One dose IM yearly</td>
</tr>
<tr>
<td>Japanese encephalitis</td>
<td>Killed vaccine</td>
<td>Should reflect actual risk of disease and probable benefits of vaccine</td>
<td>Primary immunization 1 mL SC on days 0, 7, and 30</td>
</tr>
<tr>
<td>Rabies</td>
<td>Killed virus</td>
<td>Pregnancy is not a contraindication for postexposure prophylaxis</td>
<td>Only preexposure HDCV may be administered by ID, days 0, 7, and 21 or 28</td>
</tr>
<tr>
<td>Rabies</td>
<td>Human diploid cell rabies vaccine (HDCV) or Rabies vaccine adsorbed (RVA)</td>
<td>Preexposure prophylaxis only when substantial risk for exposure exists</td>
<td>Should not be given with antimalarials</td>
</tr>
<tr>
<td>Meningococcal</td>
<td>Polysaccharide</td>
<td>Use when the risk for infection is high</td>
<td>Single dose SC</td>
</tr>
<tr>
<td>Pneumococcus</td>
<td>Polysaccharide</td>
<td>Vaccine used only for high-risk individuals</td>
<td>Single dose SC or IM</td>
</tr>
<tr>
<td>Hemophilus B conjugate</td>
<td>Polysaccharide</td>
<td>For high-risk persons</td>
<td>see article</td>
</tr>
<tr>
<td>Tetanus-diphtheria</td>
<td>Combined toxoid</td>
<td>Safe in pregnancy</td>
<td>Primary series: IM 2 doses at 1–2 month interval and a third 6–12 months after the second</td>
</tr>
<tr>
<td>Immune globulins (IG), pooled or hyperimmune</td>
<td>Immune globulins, or specific antitoxic serum including antivenin for snake-bite, spider-bite, diphtheria anti-toxin, HBIG, rabies IG, tetanus IG, RHo (D) IG, varicella-zoster IG</td>
<td>Use either for preexposure or postexposure treatment as warranted</td>
<td>Booster: Single dose IM every 10 years</td>
</tr>
</tbody>
</table>

ACIP = Advisory Committee for Immunization Practices; HBG = hepatitis B immunoglobulin; IG = immunoglobulin; IM = intramuscular; eIPV = enhanced potency inactivated poliovirus vaccine; OPV = oral poliovirus vaccine; SC = subcutaneous.

Data from references 25, 48, 90, and 126.
has the advantage of being administered as a single dose. Of the parenteral typhoid vaccines, because ViCPS vaccine is a polysaccharide vaccine, it is less likely to cause a febrile reaction. Because animal reproductive studies have not been conducted, however, this vaccine is classified as FDA pregnancy category C and should be used only when clearly indicated.

Yellow fever vaccine should generally be avoided during pregnancy unless significant exposure will occur. The yellow fever vaccine (17d vaccine) was administered to 101 pregnant women during a 1986 to 1987 yellow fever outbreak in Nigeria without any untoward effects to the fetus or the mother. However, there is a report of evidence of fetal infection caused by yellow fever after immunization in pregnancy. The child was born normally and had only serologic evidence of fetal infection caused by yellow fever. If a pregnant woman is traveling to yellow fever endemic areas, based on the degree of exposure and risk for yellow fever, a waiver may be given if the risks are low and the vaccination is for international requirements only. If travel to high-risk areas is necessary, however, the benefits of the vaccine far outweigh the small theoretical risk to the fetus and mother.

Although poliovirus vaccine live oral (OPV) has been safely administered to pregnant women during a poliomyelitis outbreak in 1985 in Finland and as a part of mass vaccination campaign in Israel, it is best to avoid this live vaccine during pregnancy. For travel to polio endemic areas, enhanced potency inactivated poliovirus vaccine (eIPV) may be administered. Cost is a major limiting factor in the use of eIPV. Much smaller doses have been given by the intradermal route with impressive immune response in previously immune adults and children and as primary immunization in infants. The adequacy of the immune response following intradermal eIPV in pregnant women has not been tested, however.

Japanese encephalitis is an important public health problem in parts of Asia and Oceania. If travel to these areas is considered, then the decision to administer Japanese encephalitis virus vaccine (an inactivated vaccine) to individuals 1 year of age or older should be based on the location and duration of intended stay, housing conditions, the nature of activities, the possibility of unexpected travel to high risk areas, and feasibility of adequate high-level protection against mosquito bites. The vaccine is reactogenic, especially in atopic individuals. The safety of this vaccine in pregnancy has not yet been well established and should be offered to pregnant women after weighing the risks versus benefits.

Measles, mumps, and rubella vaccines either singly or in combination (MMR) are contraindicated in pregnancy. Prevention of hepatitis and the safety of immunoglobulins are discussed below.

HEPATITIS AND PREGNANT TRAVELERS

Prevention of hepatitis in pregnant travelers is important because of the morbidity and mortality associated with hepatitis in pregnancy. Although the highest risk for hepatitis A virus (HAV) occurs with travel to rural areas in the developing world, HAV infection has occurred in travelers on standard tourist itineraries. HAV infection of the mother is not associated with perinatal transmission; however, placental abruption and premature delivery of an infected infant has been reported during acute HAV infection. For pregnant women, the risk for acquiring HAV is no less than for other travelers, and if no prophylaxis is offered, as high as 1 to 10 persons per 1000 travelers per 2- to 3-week visits to the developing world acquire the disease. Passive immunization with human immunoglobulin used to be the main-
stay of prophylaxis for HAV infection until the advent of inactivated hepatitis A vaccine. Passive acquisition of antibodies by way of immune globulin (IG) can successfully prevent symptoms caused by HAV. IG is a human blood product and concern about transmission of other bloodborne pathogens is legitimate. Because of the processing system used in the United States, the commercially available intramuscular products here are virus-free. No fetal risk has been reported with the use of intramuscular or intravenous IG use. Exogenous IG, however, especially 5 mL or more, given in early pregnancy has been associated with fingertip dermatoglyphic changes in the offspring. No other untoward effects have been noted, and the significance of this finding is not known. The main drawback of IG is its relatively short period of efficacy and long-term travelers need additional doses.

Three preparations of formalin inactivated hepatitis A vaccine (HAVRIX, VAQTA, AVAXIM) are available for active immunization. These vaccines have been shown to induce high levels of protective antibodies at 1 month after vaccination in more than 96% of individuals immunized with a single dose. The safety and efficacy of the inactivated hepatitis A vaccine in pregnant women has not yet been established, and the vaccine is classified as FDA pregnancy category C by the manufacturer. Because this is not a live vaccine, the main concern is the possible febrile response associated with vaccination.

For short-term pregnant travelers, IG may be administered intramuscularly just before travel. For long-term travelers, HAV prophylaxis with IG alone may be problematic because of the duration of protection offered and concerns about the second dose of IG being administered away from home under less than optimal conditions; in these cases the inactivated vaccine can be offered. Before offering this vaccine, time permitting, HAV serology should be performed on patients born or who have lived in developing countries. Because prior HAV infection gives life-long protection, those who are positive for HAV antibodies can be reassured that HAV prophylaxis in the form of IG or active vaccine can be avoided altogether.

Hepatitis B virus (HBV) infection is a risk for short-term and long-term travelers exposed to blood or body fluids, especially in countries with high prevalence of HBV, such as the Far East, South East Asia, sub-Saharan Africa, the Amazon basin, and parts of the Middle East. Ideally all pregnant women should be screened for hepatitis B carriage and immunity. The current practice is to screen for hepatitis B surface antigen (HBsAg) only. Infants born to mothers who are carriers of HBsAg should be immediately given hepatitis B immune globulin (HBIG) and vaccinated as well. Hepatitis B vaccine (recombinant) series can be administered to pregnant women (preferably after first trimester for theoretical reasons) who are at high risk and who test negative by serology for past HBV infection. Immunization for HBV will also prevent hepatitis D virus (HDV) infection.

Hepatitis C virus (HCV) is the primary etiologic agent of nonepidemic, parenterally transmitted non-A, non-B hepatitis. The exact worldwide seroprevalence of HCV infection is not known. Travel-associated risk for HCV is clearly related to receipt of blood that has not been screened for HCV. Other risk factors are contaminated needles used for administration of medication, intravenous drug use (IVDU), occupational exposure to blood, hemodialysis, tattooing, and sexual transmission. Prophylaxis with IG in the dose of 0.06 mL/kg IM is usually reserved for postexposure prophylaxis. The exact value of IG for the prophylaxis of HCV or parenterally transmitted non-A, non-B hepatitis, however, has not yet been proven unequivocally. The IG manufactured in the United States does not contain antibody to HCV and is therefore unlikely to prevent HCV infection.
Hepatitis E virus (HEV) infection has a particularly high case-fatality rate (15% to 25%) during pregnancy. HEV or enterically transmitted non-A, non-B hepatitis is a major cause of outbreaks of hepatitis in India, Nepal, Burma, Pakistan, China, the former Soviet Union, and Africa. HEV may be more widespread than initially thought and has been reported also from Mexico, other Central American countries, and from other parts of South East Asia. It is transmitted by fecal-oral route, and most outbreaks are associated with fecal contamination of drinking water. Food-borne transmission has also been identified in some outbreaks, and there also is some evidence for person-to-person transmission. Recurrent HEV epidemics linked to heavy rains, with a periodicity of 5 to 10 years, have been observed in India, China, and the Central Asian Republics of the former Soviet Union. Presently, there is no vaccine against HEV although several recombinant HEV proteins are being evaluated as potential candidates. Passive prophylaxis in the form of either preexposure or postexposure IG administration has been attempted in outbreak situations without any benefit. In travelers to HEV endemic areas, administration of IG made in countries not endemic for HEV (and thus unlikely to contain sufficient levels of protective antibody) has not been effective. Food and water precautions are currently the mainstay of HEV infection prevention in a traveler.

MALARIA AND PREGNANCY

A pregnant traveler visiting a malaria endemic area, either for a short stay or for an extended period, is at significant risk for malaria infection with potential devastating consequences to herself and her infant. In areas of the world with high transmission of Plasmodium falciparum, malaria infection during pregnancy has been identified as a contributor to low birth weight (LBW) and the single greatest risk factor for neonatal and early infant mortality. For a nonimmune pregnant traveler, contracting malaria significantly enhances the chance of losing the fetus. Following malaria infection of the pregnant mother, there can be a high rate of transplacental transmission of malaria, which is directly related to the density and severity of maternal malaria infection. Although congenital malaria is rare, in nonendemic countries it is usually seen in children born to women who have immigrated from malarial areas. The consequences of maternal malaria infection for the infant can be devastating, with the infant at risk for dehydration, thrombocytopenia, splenic rupture, and seizures. Moreover, there is evidence for placental malaria infection to increase the risk for transmission from mother to child of other bloodborne pathogens, especially HIV.

General Guidelines for Malaria Prevention in Pregnant Travelers

In pregnant travelers, malaria prevention requires diligent attempts to reduce transmission by a number of physical means of avoiding mosquito bites. The pregnant traveler should wear protective clothing appropriate for the climate, namely, long-sleeved shirts, trousers, socks, and high-top shoes or boots. The clothing can be treated with permethrin-containing insecticides. House sprays and mosquito coils are useful nontopical repellents. At night mosquito netting is an effective barrier. Insecticide treated bed nets are well tolerated and have been shown to reduce the incidence and severity of malaria transmis-
Pregnant Traveler

sion in highly endemic areas. Permethrin treated bed nets are generally considered to be safe for humans, with no evidence of toxic effects to the mother or the fetus.

Topical insect repellents have largely relied on N, N-diethyl-m-toluamide (DEET) containing preparations. The use of highly concentrated DEET containing insect repellents should be avoided because DEET is absorbed through the skin, and the consequences of DEET toxicity are variable and unpredictable. DEET has been shown to cross the placental barrier in some animal studies and not in others. Because the reproductive effects of DEET in laboratory animals are conflicting and there are no human data available, DEET is currently classified as category B. Toxicity may result from acute exposure to large doses of DEET, however, or from chronic exposure, leading to accumulation of DEET in fatty tissues and the brain. The safety of DEET in pregnancy has not yet been established. Adverse fetal outcome in the form of mental retardation, impaired sensorimotor coordination, and craniofacial dysmorphology in a child whose mother applied DEET daily throughout her whole pregnancy has been reported. DEET has been shown to be weak mosquito repellent useful for 15 to 20 minutes only and is clearly inadequate in malarial settings.

Chemoprophylaxis for Malaria in Pregnant Travelers

The increasing spread of multidrug resistant *P. falciparum* malaria has led to an urgent need for safe strategies for prevention and treatment of malaria in pregnant women.

For travel to areas with chloroquine (CQ)-sensitive *P. falciparum* infection (Table 4), such as endemic areas in the Caribbean, Central America, or the Middle East, CQ remains the drug of choice. It should be given weekly as 300 mg base (equal to 500 mg of CQ phosphate salt), starting 1 week before travel, while traveling in the malarial area and for 4 weeks after leaving the area. CQ readily crosses the placenta but has been found to be safe in pregnancy both in preventive doses and in therapeutic doses for established malaria. When *Plasmodium vivax* or *Plasmodium ovale* coexist with CQ sensitive *P. falciparum,* however, primaquine phosphate, which is used as causal prophylaxis to prevent relapse, should not be given to pregnant travelers. This is because of the rare possibility of a life-threatening hemolytic anemia in the child if the fetus is glucose-6-phosphate dehydrogenase (G6PD) deficient. Alternatively, weekly prophylaxis with CQ can be continued during pregnancy until delivery to forestall a febrile episode caused by symptomatic malaria with its attended fetal wastage. After delivery, primaquine phosphate can be safely given to the mother if she is not G6PD deficient.

If travel to areas with multidrug-resistant *P. falciparum* infection is contemplated, chemoprophylaxis becomes much more complicated (Table 4). Such areas are best avoided during pregnancy if possible. If pregnant women must travel to these areas or if a woman plans to conceive while on an extended stay in these areas, the physician must apprise her of the risks involved, emphasizing preventive measures against mosquito bites while educating her about symptoms of malaria and subsequent need for prompt therapy.

In deciding on an optimal chemoprophylaxis for travel to a chloroquine
Table 4. MALARIA CHEMOPROPHYLAXIS IN PREGNANT TRAVELERS

<table>
<thead>
<tr>
<th>Antimalarials</th>
<th>Dose</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chloroquine (CQ)</td>
<td>300 mg base (equal to 500 mg of phosphate salt per week)</td>
<td>Safe; severe reactions rare</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Antimalarials</th>
<th>Dose</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chloroquine Resistant Areas</td>
<td>(Options for Chemoprophylaxis)</td>
<td></td>
</tr>
<tr>
<td>Mefloquine (MQ)</td>
<td>250 mg weekly</td>
<td>Neuropsychiatric reactions 1:15,000 to 20,000</td>
</tr>
<tr>
<td></td>
<td>Anecdotally safe in pregnancy</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Folate supplements recommended</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Pyrimethamine should be avoided in the first trimester</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Folinic acid supplement needed</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Restricted use only</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Not FDA approved</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Severe cutaneous reactions 1:5000 to 1:10,000</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Generally not recommended (see text)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Seems promising</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Safety of atovaquone in pregnancy not established</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Perhaps more suitable for treatment of established infection</td>
<td></td>
</tr>
</tbody>
</table>

In a double-blind placebo-control trial of MQ antimalarial prophylaxis in the second and third trimester of pregnancy in a highly endemic area along the Thai-Myanmar border, MQ gave more than 86% protection against *P. falciparum* and complete protection against *P. vivax* infections while posing little risk to the fetus. Weekly MQ prophylaxis was well tolerated except for a transient dizziness associated with the initial loading dose (10 mg/kg) used in this study. We do not recommend a loading dose of MQ for pregnant women. MQ was found to be safe in the second half of pregnancy. Indeed, the Centers for
Disease Control and Prevention (CDC) has issued a statement that, if needed, MQ can be used during the second and third trimester of pregnancy for malaria chemoprophylaxis. Nevertheless, although MQ use in pregnancy is being monitored by a registry at the CDC, a disturbing trend has been noted in certain studies. During the first phase of the Thailand study by Nosten et al described previously, there was a significant excess of stillbirths in the MQ group. A second phase of the study, however, which specifically focused on the issue of stillbirth, did not confirm the earlier findings. Although the stillbirth rates in the second phase were similar to the first, the numbers in MQ and placebo groups were equal, and it was concluded that the observation of excess stillbirth rate in MQ recipients in phase I resulted from chance. A recent abstract, describing inadvertent MQ use during pregnancy occurring in the armed forces in Somalia also indicates an increase in spontaneous abortions. A growing number of pregnant women, however, in their first trimester of pregnancy living in highly endemic areas for multidrug resistant \textit{P. falciparum} have received MQ in treatment doses followed by weekly prophylaxis without any significant untoward effects.

In view of its long half-life, it has been recommended that women taking MQ should be warned against becoming pregnant and for 3 months after completing a course. In a limited, retrospective analysis of pregnancy outcome after inadvertent MQ use in early pregnancy, 11 babies already born from 10 deliveries at the time of the study were found to not have any evidence of congenital malformations or perinatal pathology. There is limited data to suggest that late pregnancy is associated with accelerated clearance of MQ when the drug is used prophylactically, necessitating increasing the dose. Optimal treatment schedules have not been developed and further studies are needed to assess the toxicity of prolonged high-dose MQ in late pregnancy. Until such studies are made available, 250 mg of MQ can be given weekly to pregnant women traveling to CQ resistant \textit{P. falciparum} areas with full disclosure of risk described above. Lactation is not an absolute contraindication for MQ use, although low concentrations (3% to 4%) of MQ are excreted in breast milk following a 250-mg dose. Breast milk should not be construed as having enough concentration of MQ to protect a newborn, however.

An alternative to MQ in CQ resistant malarial areas is the use of a combination of weekly CQ and the biguanide, proguanil (Paludrine) 200 mg daily. Proguanil seems to be safe in pregnancy. Although anecdotally this combination has been described as safe, there is little published experience with this combination in pregnant women. Moreover, in a number of areas of the world, especially in South East Asia, Thailand, Papua New Guinea, parts of Africa, and South America, \textit{P. falciparum} has become resistant to the biguanides and CQ, thus limiting the use of this combination.

In 1984, the World Health Organization (WHO) recommended the use of pyrimethamine (PYR) with sulfadoxine (SDX) (Fansidar) as a prophylactic or for treatment of malaria at appropriate dosage levels at any stage of pregnancy in areas of the world in which it is needed. The initial concerns about the use of this drug combination in pregnancy were the teratogenic effects of PYR in rats, which is preventable by a folate supplement, and hyperbilirubinemia and kernicterus in the newborn due to use of SDX near term. The fixed drug combination of 25 mg of PYR and 500 mg of SDX (Fansidar) became available in the United States in 1982. In the fall of 1984, the CDC recorded reports of 4 cases of toxic epidermal necrolysis with three fatalities. Subsequent investigation detected a total of 24 cases of severe cutaneous reactions (erythema multiforme,
Stevens-Johnson syndrome, and toxic epidermal necrolysis) among American travelers who had used PYR/SDX once a week for the prevention of malaria, with a fatality rate of 1 in 11,000 to 1 in 25,000 users. The higher than expected incidence of adverse reactions has limited the use of PYR/SDX combination in American travelers. Although the efficacy of antimalarial regimens containing PYR/SDX in preventing peripheral and placental malaria in semi-immune pregnant women has been shown, P. falciparum resistance to this combination is present in South America, Thailand, Myanmar, Cambodia, and in parts of sub-Saharan Africa, limiting its use. The authors do not recommend this as a first-line chemoprophylactic agent.

Pyrimethamine in a fixed dose combination with dapsone is marketed as Maloprim and is used for chemoprophylaxis of malaria caused by CQ resistant P. falciparum. This combination is not without significant side effects (Table 4), however. Maloprim should be avoided in the first trimester of pregnancy because of concerns about teratogenicity caused by pyrimethamine. The dapsone component of Maloprim is of less concern because of dapsone’s established safety in leprosy patients with pregnancy. This combination is not currently included in the labeling approved by the US Food and Drug Administration, however, and should be reserved as a second-line agent for travelers to high risk areas.

Although amodiaquine (related to CQ) is considered safe for chemoprophylaxis in pregnant women, severe fatal agranulocytosis associated with this drug and increasing drug resistance precludes the use of this 4-aminoquinolone for chemosuppression. The cinchona alkaloids quinine and quinidine belong to FDA pregnancy category X (see Table 2). Stillbirths, congenital malformations including auditory nerve hypoplasia, limb anomalies, visceral defects, and visual changes in the fetus have been reported with the use of quinine, especially in large doses, in an attempt to cause abortion by way of its uncommon oxytocic action on the uterus. Neonatal thrombocytopenia and hemolytic anemia in G6PD-deficient newborns have been described with quinine use during pregnancy. The use of quinine or quinidine for chemoprophylaxis for travelers is not recommended, although use as life-saving treatment for severely infected pregnant women with malaria is advocated.

In parts of South East Asia, that is, in the Thai-Cambodia and Thai-Myanmar border areas, a near desperate situation of multidrug-resistance has emerged, necessitating the use of alternative drugs. Halofantrine (Halfan), available outside the United States, has a short half-life and is hence not suitable for chemoprophylaxis. Animal studies have shown that the drug is embryotoxic and is contraindicated in pregnancy. The tetracycline group drug doxycycline has excellent activity against multidrug resistant malaria but the drug is contraindicated in pregnancy because of its adverse effects on the fetus, including discoloration and dysplasia of the teeth and inhibition of bone growth. Doxycycline use in women of child-bearing age on oral contraceptives may slightly increase the risk of pregnancy because of drug interaction. Artemisinin (qinghaosu) and its derivatives belong to the first generation endoperoxide class of antimalarials with a novel mode of action. Because these drugs have short half-lives, they are not suitable for chemoprophylaxis.

The new combination chemoprophylaxis option of proguanil and atovaquone seems to be as effective as MQ and may be of potential use in pregnant travelers, although atovaquone is presently classified as a category C drug. This combination, Malarone, will be marketed as a fixed dose (2.5:1) preparation (Table 4). In preliminary trials in semi-immune individuals residing in highly endemic areas, none of the subjects receiving either 250 mg atova-
quone/100 mg proguanil or 500 mg atovaquone/200 mg proguanil daily developed malaria. The safety and efficacy of this combination in pregnant travelers has not yet been established.

Treatment of Malaria In Pregnant Women

Because no chemoprophylaxis is 100% effective, pregnant women traveling in malaria endemic areas, especially those on an extended visit, should be advised about the symptoms of malaria so that prompt presumptive treatment can be given even on return. Although severe malaria infection in pregnancy is symptomatic, unfortunately most parasitized semi-immune pregnant women living in malaria endemic areas do not uniformly manifest symptoms until the degree of parasitemia reaches dangerously high levels. Fever predicts fewer than 25% of parasitemic semi-immune women, although high fever is a prominent feature in the nonimmune traveler.

Treatment of malaria in returned travelers is addressed in detail in the article by KC Kain and JS Keystone in this issue. Any fever, especially within the first 3 months after return from a malarial region, should prompt quick evaluation of a peripheral blood smear. If travel to CQ sensitive malarial areas has been undertaken, CQ in treatment doses should be used. In severely ill individuals with life-threatening infection, IV quinine or quinidine gluconate is the drug of choice. In areas with PYR/SDX sensitive malaria this combination in treatment doses is an option in pregnant women not allergic to either of the two drugs, but again clinicians do not consider this as first-line. MQ may be given in treatment doses of 750 to 1250 mg as a single dose for those who had traveled to CQ resistant areas.

Patients who develop malaria while on MQ prophylaxis are problematic. Therapy must be individualized, taking into consideration the travel itinerary, drug sensitivity pattern of the malarial parasite in the areas visited by the patient, and balance the adverse effects of several combination antimalarial drugs. The combination of atovaquone (1000 mg) plus proguanil (400 mg) once daily for 3 to 7 days achieves consistently high cure rates (94% to 100%) in adult patients with acute \( P. falciparum \) infection. Although there are no adequate and controlled studies to date using atovaquone in pregnant women, this combination is an option for multidrug-resistant \( P. falciparum \) infection. Artemisinin and its derivatives are the most rapidly acting of all antimalarial drugs investigated thus far. Experience with these drugs in pregnancy is limited. No untoward effects were reported in a small number of pregnant women who were treated with these drugs. The artemisinin compounds have been used successfully in combination with MQ or quinine in the setting of highly drug-resistant \( P. falciparum \) infections and should be used in severely ill patients with suspected drug-resistant malaria from areas with high CQ resistant \( P. falciparum \). Currently, in some parts of South East Asia with highly drug-resistant malaria, artemisinin and its derivatives may be the only reliable treatment option.

Stand-by treatment (SBT) is the use of antimalarial drugs for self-administration when fever or flu-like symptoms occur and prompt medical attention is not available. SBT has been considered for pregnant travelers but is generally not recommended because inappropriate use of SBT can expose the mother and child to significant drug toxicity. Factors determining the choice of a suitable SBT include the level of malaria transmission, the degree and nature of drug resistance, efficacy and toxicity profile of agents used, and the ease of administration. Moreover, the use of SBT for malaria by travelers depends on their knowl-
edge, attitudes and behavior, and is limited by inappropriate behavior and poor malaria awareness.136

DRUGS AND PREGNANT TRAVELERS

It is beyond the scope of this article to comprehensively review drug use in pregnancy and its associated adverse outcome to the mother and infant. So, the authors will address a safety profile of drugs that may be needed by the pregnant traveler. The reader is referred to excellent patient and physician guides, such as The Pregnancy Book for Todays' Women by HI Shapiro and Drugs in Pregnancy and Lactation by GG Briggs, RK Freeman, and SJ Yaffe for a comprehensive listing of drug use in pregnancy and their adverse outcome.28,141

Some of the commonly used drugs that the pregnant traveler may need to use during her travel may be broadly classified under the following traditional categories:

- Antibiotics and other anti-infective agents
- Vaccines
- Analgesics and antipyretics
- Anxiolytics, sedatives, and hypnotics
- Antacids and antidiarrheal agents
- Sunscreen and other topical agents

Of these, antibiotics, analgesics, and antidiarrheal agents may form the bulk of commonly used drugs by the pregnant traveler as well as vaccines administered by health practitioners. Many of these drugs are available over-the-counter with great potential for inappropriate use and adverse interactions.

Table 5 lists the commonly used antibiotics and anti-infective agents and the FDA pregnancy category (see Table 2) they belong to.

Antiparasitic Agents and Pregnancy

Antiparasitic drugs are of special concern for the physician advising pregnant travelers, especially those visiting countries endemic for these pathogens for an extended period. Antimalarial drugs are discussed in the section “Malaria and Pregnancy.”

Antiparasitic agents, such as quinacrine and emetine/dihydroemetine, are contraindicated in pregnancy. Iodoquinol can pose significant iodine toxicity to the mother and fetus. Paromomycin belongs to the aminoglycoside class of drugs, with potential for ototoxicity and nephrotoxicity. Because little drug is absorbed, however, paromomycin may be used for follow-up therapy after a tissue amebicide in children or pregnant women to eradicate the encysted form of Entamoeba histolytica. Metronidazole, with broad activity against amebiasis, giardiasis, and trichomoniasis, seems to be safe in pregnancy despite initial concerns about the drug.61 Although metronidazole freely passes through the placental barrier, animal studies indicate that it is nonteratogenic.66 A number of recent studies have clearly established the safety of metronidazole in pregnant women and the drug is classified as FDA pregnancy category B.29, 48, 65, 115

The anthelmintic drugs mebendazole, albendazole, and thiabendazole are generally contraindicated in pregnancy because of embryotoxicity and teratoge-
Table 5. SAFETY OF COMMONLY USED ANTIBIOTICS AND ANTI-INFECTIVE AGENTS IN PREGNANCY

<table>
<thead>
<tr>
<th>Agent</th>
<th>Category</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aminoglycosides</td>
<td>D</td>
<td>Use for therapy of severe infections by susceptible organisms and for prophylaxis of appropriate settings except gentamicin, which is C</td>
</tr>
<tr>
<td>Amphotericin B</td>
<td>B</td>
<td>For systemic fungal infections and visceral leishmaniasis Use only if clearly indicated Safety established anecdotally</td>
</tr>
<tr>
<td>Azithromycin</td>
<td>B</td>
<td>Use only when clearly indicated There are no adequate and well-controlled studies in pregnant women</td>
</tr>
<tr>
<td>Carabapenems (e.g., imipenem)</td>
<td>C</td>
<td>Experience is limited</td>
</tr>
<tr>
<td>Cephalosporins and related antibiotics</td>
<td>B (Moxalactam–C)</td>
<td>Considered safe for use</td>
</tr>
<tr>
<td>Chloramphenicol</td>
<td>C</td>
<td>Readily crosses the placental barrier Avoid in pregnancy because of risk for “gray baby” syndrome</td>
</tr>
<tr>
<td>Clarithromycin</td>
<td>C</td>
<td>Has adverse effects on pregnancy outcome in animal studies Avoid in pregnancy</td>
</tr>
<tr>
<td>Clindamycin</td>
<td>B</td>
<td>Crosses the placenta, achieving maximum cord serum levels of nearly 50% of the maternal serum There are no reports of adverse fetal outcome</td>
</tr>
<tr>
<td>Erythromycin</td>
<td>B</td>
<td>Do not use erythromycin estolate; may cause liver failure</td>
</tr>
<tr>
<td>Fluconazole</td>
<td>C</td>
<td>Animal studies show inhibition of estrogen synthesis with resultant fetal abnormalities Use only if the potential benefit justifies the possible risk to the fetus Concurrent use with oral contraceptives (OC) in nonpregnant women may produce drug interactions resulting in either increase or decrease in OC levels in blood</td>
</tr>
<tr>
<td>Itraconazole</td>
<td>C</td>
<td>Teratogenic in animal studies Do not use in pregnancy for the treatment of onychomycosis In women with child-bearing potential, concurrent effective contraceptives should be used throughout itraconazole use and for 2 months after stopping therapy</td>
</tr>
<tr>
<td>Miconazole</td>
<td>C</td>
<td>There is no evidence of embryotoxicity in animal studies Safe use in humans not yet established</td>
</tr>
<tr>
<td>Monobactams (aztreonam)</td>
<td>C</td>
<td>Experience limited Aztreonam crosses the placenta Use during pregnancy only if clearly indicated</td>
</tr>
</tbody>
</table>

Table continued on following page
Table 5. SAFETY OF COMMONLY USED ANTIBIOTICS AND ANTI-INFECTIVE AGENTS IN PREGNANCY (Continued).

<table>
<thead>
<tr>
<th>Agent</th>
<th>Category</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nalidixic acid</td>
<td>B</td>
<td>Safe for use</td>
</tr>
<tr>
<td>Nitrofurantoin</td>
<td>B</td>
<td>Safe but theoretical risk for hemolytic anemia in G6PD deficient infants</td>
</tr>
<tr>
<td>Nystatin</td>
<td>B</td>
<td>Poorly absorbed after oral administration</td>
</tr>
<tr>
<td></td>
<td></td>
<td>No documented adverse effects on the fetus</td>
</tr>
<tr>
<td>Penicillin</td>
<td>B</td>
<td>Safe for use</td>
</tr>
<tr>
<td>Synthetic penicillin and β-lactamase inhibitors</td>
<td>B</td>
<td>Safe for use</td>
</tr>
<tr>
<td>Quinolones</td>
<td>C</td>
<td>Avoid in pregnancy</td>
</tr>
<tr>
<td>Sulfonamides and their combinations</td>
<td>B to C</td>
<td>Sulfonamides alone can be safely used in first 8 months</td>
</tr>
<tr>
<td></td>
<td></td>
<td>May cause jaundice and kernicterus when used near term</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Trimethoprim best avoided in first trimester</td>
</tr>
<tr>
<td></td>
<td></td>
<td>PYR/SDX combinations, see section on malaria</td>
</tr>
<tr>
<td>Tetracycline</td>
<td>D</td>
<td>Should not be used</td>
</tr>
<tr>
<td>Vancomycin</td>
<td>C</td>
<td>Useful especially in penicillin allergic patients</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Use only if clearly indicated</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Experience is limited</td>
</tr>
</tbody>
</table>

Data from references 28, 48, 90, and 126.
countries. If seizures are well controlled on antiepileptics alone, antihelmintic therapy can be withheld until postpartum. For those patients failing anticonvulsant therapy, however, praziquantel should be considered.

Metrifonate, an organophosphorus compound, is freely available in a number of African countries and used for the treatment of infections caused by *Schistosoma haematobium*. Despite lack of evidence of embryotoxicity or teratogenicity, the WHO does not recommend the use of metrifonate in pregnant patients unless immediate intervention is needed. There has been a report of an infant born with meningomyelocele and massive hydrocephalus to a mother who was treated twice in her first trimester of pregnancy with metrifonate.

Pyrantel pamoate (Antiminth, Reese's Pinworm Medicine, Pin-X) is available both in suspension and tablet forms and at times used as self-medication for worm infestation. It has activity against *Enterobius vermicularis*, *Ascaris lumbricoides*, *Ancylostoma duodenale*, *Nectar americanus*, and *Trichosporon orientalis*. There are no adequate and controlled studies to date using pyrantel pamoate in pregnant women. Reproduction studies in animals have not revealed evidence of harm to the fetus. The drug should be used during pregnancy only when clearly indicated, however, and self-medication during pregnancy should not be undertaken.

Drugs that are active against the trypanosomatids (*Trypanosoma* and *Leishmania*) have significant toxicity. However, infections caused by these agents have significant morbidity and mortality. Therapy should be individualized.

**Antiemetics, Analgesics, and Sunscreen Agents**

Drugs for morning sickness have antinauseant and antiemetic features, and most of them are available over-the-counter. Emetriol has been claimed as safe in pregnancy. Table 6 lists the commonly used antiemetics and analgesics in pregnancy.

Vitamin B₆ (pyridoxine) is useful in pregnancy-induced nausea and vomiting, but the benefit may decline over time. The safety of promethazine is well established and should be the preferred first-line drug for intractable nausea and vomiting in pregnancy. Travel, especially in the first trimester, may be complicated by motion sickness. If travel cannot be postponed, meclizine and dimenhydrinate used for pregnancy-induced nausea and vomiting are useful for treating motion sickness. Other approaches that have been found to be useful anecdotally include seasickness bands and ginger tablets.

Aspirin is an ingredient in a great number of over-the-counter analgesic medications and should be avoided in pregnancy. The potential adverse effects of aspirin when used in pregnancy have been reviewed. In high risk mothers receiving aspirin, the risk of abruptio placenta and prenatal death is increased. Moreover, aspirin use near term may increase the risk of intracranial hemorrhage and other adverse hematologic effects, such as subconjunctival hemorrhage, hematuria, and purpura, in the newborn. Acetaminophen, a category B drug (Tylenol, Datril, Phenaphen) is safe but like all drug use in pregnancy should be taken in moderation.

Sunscreen agents are of two types, chemical agents that because of their chromophore groups absorb a particular range of wavelengths of the ultraviolet light spectrum, and physical agents such as titanium dioxide and zinc oxide. Many of the available products combine sunscreen agents from different groups to widen the protection afforded. Information on cutaneous absorption, tissue
Table 6. COMMONLY USED ANTIEMETICS AND ANALGESICS AND PREGNANCY FDA RATINGS

<table>
<thead>
<tr>
<th>Drug</th>
<th>FDA Category</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vitamin B&lt;sub&gt;6&lt;/sub&gt;, pyridoxine</td>
<td>B</td>
<td>Preferred</td>
</tr>
<tr>
<td>Doxylamine and vitamin B&lt;sub&gt;6&lt;/sub&gt;</td>
<td>B</td>
<td>May be available as over-the-counter medication</td>
</tr>
<tr>
<td>Dimenhydrinate (Dramamine)</td>
<td>B</td>
<td></td>
</tr>
<tr>
<td>Promethazine (Phenergan)</td>
<td>B</td>
<td>Preferred drug</td>
</tr>
<tr>
<td>Meclizine, cyclizine</td>
<td>B</td>
<td>Although classified as B, not a first-line drug</td>
</tr>
<tr>
<td>Diphenhydramine (Benadryl)</td>
<td>B</td>
<td></td>
</tr>
<tr>
<td>Metoclopramide (Reglan)</td>
<td>B</td>
<td>Potent antiemetic and lactation stimulant</td>
</tr>
<tr>
<td>Acetaminophen (Tylenol, Datril, Phenaphen)</td>
<td>B</td>
<td>Should be taken in moderation</td>
</tr>
<tr>
<td>Aspirin and other salicylates</td>
<td>C to D</td>
<td>Should be avoided, especially late in pregnancy</td>
</tr>
</tbody>
</table>

Data from references 28, 48, 90, and 126.

distribution, and elimination of these topical agents is limited. In addition, little information is available regarding safety of chronic sunscreen usage.

TRAVEL RELATED DIARRHEAL ILLNESS AND PREGNANT WOMEN

Between 20% to 70% of visitors to developing countries experience traveler’s diarrhea, and the pregnant traveler is no exception to this. In fact, pregnant women may be at greater risk because of decreased gastric acidity and increased transit time of food through the intestine. The consequences of diarrheal illness in pregnant mothers may be devastating with premature labor and shock. Hence, any fluid loss should be promptly replenished. Oral rehydration therapy started early at the onset of symptoms forms the basis of treatment of acute diarrhea in nonpregnant individuals and pregnant mothers. It is prudent for pregnant travelers to rural areas to carry with them oral rehydration salt (ORS) packets. The ORS most preferable is the WHO formula containing sodium chloride 3.5 g/L, potassium chloride 1.5 g/L, trisodium citrate 2.9 g/L, and glucose 20.0 g/L. This standard ORS has 90 mmol of sodium and 111 mmol of glucose per liter with a total osmolarity of 311 mmol/L. This is well suited for rehydration in developing countries in which diarrhea is predominantly bacterial in origin. Once initial rehydration is achieved, the ORS solution may be sufficiently diluted to give 60 mmol of sodium per liter and used as maintenance therapy. In developed countries, in which viral diarrhea that is associated with less electrolyte loss is more common, commercially available ORS may provide only 35 to 60 mmol of sodium and 90 to 200 mmol of glucose per liter and may not be suitable for traveler’s diarrhea dominated by bacterial etiologies. Of the im-
proved ORS formulations, rice-based ORS seems to be superior to the WHO glucose based ORS for patients with cholera.\textsuperscript{19}

Chemoprophylaxis for traveler’s diarrhea in any form is not suitable for the pregnant traveler. For self-administration, to control the frequency of bowel movements, loperamide or diphenoxylate are the two antimotility drugs (category B drug) preferred but generally not recommended unless antibiotics are also administered.\textsuperscript{28} Zaldaride maleate, a potent intestinal calmodulin inhibitor, has recently been shown to decrease the severity and duration of traveler’s diarrhea.\textsuperscript{50} The safety and efficacy of this drug for symptom control in pregnant patients with traveler’s diarrhea have not yet been established and availability of this drug is limited. Bismuth subsalicylate (Pepto-Bismol) is an FDA pregnancy risk category C drug. In contrast to bismuth, salicylate is well absorbed with potential adverse effects on the fetus. It is best to avoid bismuth subsalicylate in pregnant travelers.

Antibiotics such as tetracyclines and quinolones (ciprofloxacin) are contraindicated in pregnancy (see section on “Drugs and Pregnant Travelers”). Trimethoprim, a component in cotrimoxazole (Bactrim, Septra) crosses the placenta well. Published case reports and placebo-controlled trials have failed to demonstrate an increase in fetal abnormalities have suggested a link between this drug and congenital defects.\textsuperscript{28} Sulfamethoxazole use in late pregnancy can cause kernicterus in the newborn (see Table 5). Both drugs are classified as category C. A possible alternative choice of antibiotics for travelers’ diarrhea in pregnant women who are not penicillin allergic is ampicillin/amoxicillin. Many common enteric pathogens are resistant to these drugs, however.\textsuperscript{102} Erythromycin is active against Campylobacter-induced traveler’s diarrhea and is safe to take during pregnancy.\textsuperscript{28} Quinolone resistant campylobacter is now most often treated with azithromycin. Insufficient data on azithromycin is available to recommend its routine use in pregnancy. Second- or third-generation cephalosporins have been suggested as alternatives.\textsuperscript{83} Oral aztreonam, a poorly absorbed monobactam with activity against a broad range of gram-negative bacteria, including major enteric pathogens implicated in travel-associated diarrhea, seems to be promising but is expensive and not easily available.\textsuperscript{49}

Partial, short-term protection against traveler’s diarrhea caused by entero-toxigenic \textit{E. coli} has been achieved by active immunization with B-subunit-whole-cell cholera vaccine (BS-WC). The BS-WC, a killed vaccine, was shown to give short-term protection without any adverse effects (protective efficacy = 86\%) against diarrhea caused by entero-toxigenic \textit{E. coli} when given to women and 2- to 15-year-old-children in large field trials in Bangladesh.\textsuperscript{39, 40} The efficacy of this vaccine in nonpregnant, adult travelers to Morocco was recently evaluated.\textsuperscript{112} The BS-WC induced a 52\% protection against enterotoxigenic \textit{E. coli} and 65\% protection against mixed infections.\textsuperscript{112} These results need to be confirmed, especially for travel to other areas of the world, and the safety in pregnant travelers must be established before any recommendations can be made for the routine use of BS-WC.

Pregnant travelers with persistent diarrhea following return require careful evaluation to determine the etiologic agent and specific therapy instituted. Empirical therapy, which is usually given to returned travelers with persistent diarrhea, is not suitable for pregnant patients unless they are severely ill.\textsuperscript{51}

The authors recommend stringent hygienic measures to prevent traveler’s diarrhea in pregnant travelers. Immediate adequate rehydration is key to maintaining placental blood flow. Second-line measures could include loperamide, diphenoxylate, or antibiotics described previously but would be used only in severe cases of traveler’s diarrhea.
EXERCISE DURING TRAVEL AND PREGNANCY

It is beyond the scope of this article to review the merits and potential risks of exercise and sports during pregnancy; this was reviewed by Artal in 1996.12 The pregnant traveler vacationing in ski resorts should be aware that however much an expert skier she may be, many accidents can happen during skiing. Additionally, changes in the body's center of gravity as pregnancy advances and increased joint laxity in pregnancy may add to these risks. This can have devastating consequences on the outcome of pregnancy. It is probably best not to ski or trek at high altitudes, especially in remote sites because treatment for potential accidents is often difficult to obtain expeditiously. Low oxygen tension and pressure changes can cause intrauterine growth retardation and premature labor in women spending most of the pregnancy above 8000 ft. There is no contraindication, however, to moderate exercise for a limited period of time at altitudes between 8000 and 11,000 ft.86 It is not advisable for pregnant women to water ski or indulge in other sports that might force water and air into the vagina or traumatize the uterus.88 Scuba diving during any stage of pregnancy is not considered safe; the fetus is placed at risk for possible decompression sickness or congenital abnormalities.20, 31, 55

Vigorous exercise, especially in a hot and humid climate, should be avoided because this can substantially increase maternal body temperature and also the fetus's temperature. Excessive exposure to heat, either from hot tubs and saunas or by heavy exertion in a hot climate, can cause maternal hyperthermia, which can result in neural tube defects.96 The safe limits of exposure to heat during pregnancy have not been established. The exact risk for fetal malformation caused by warm tub baths and saunas in early pregnancy is uncertain, and hot tubs and saunas in "moderation" for healthy women with uncomplicated pregnancy may be well tolerated.74, 153 Any exercising pregnant woman, but especially those in hot climates, should pay extra attention to hydration.

GENERAL ADVICE FOR PREGNANT TRAVELERS

It is prudent for pregnant travelers to adhere strictly to food and water hygiene. The pregnant traveler should drink either boiled water or water that has been filtered and disinfected. Because chlorination may not eliminate all microorganisms, there is an increasing shift to the use of iodine for purifying water. There are a number of portable antimicrobial water purifiers in the market. Most of them use a combination of microfilters to remove suspended particles and cysts and resin-bound iodine to eliminate bacteria and viruses. The main concern for pregnant travelers is the amount of residual iodine in the filtered water, which varies with different filters. Most people are unaffected by excess iodine intake, and the daily consumption of iodine by most individuals in the United States far exceeds the Recommended Dietary Allowance (RDA) of 150 μg/day. Iodine intake up to 1000 μg/day is probably safe for most of the population.113 Excessive iodine intake in pregnancy (RDA in pregnancy = 175 μg/day), however, should be avoided because of the danger of inducing goitrous hypothyroidism in the fetus, for the fetal thyroid is extremely sensitive to the blocking effect (Wolff-Chaikoff effect) of iodide.103, 156 Purification devices with exchange resin microfilters and carbon filtration reduces residual iodine levels to acceptable limits for pregnant patients.20 Nevertheless, the authors recommend that pregnant travelers use boiled water and depend less on other methods for obtaining potable water.
Airport security machines are magnetometers and are not harmful for the fetus. Prenatal exposure to radiation can have devastating effects that may be seen either at birth or much later in life. Potential sources of such exposure, namely, fallout from nuclear weapons tests or nuclear reactor accident sites, such as Chernobyl and Three Mile Island, should be identified and the pregnant traveler advised to avoid such areas and take precautions with food sources from these areas. Radiation is greater at higher altitudes. In-flight radiation may not be of great concern for the occasional traveler, but airline crewmembers and business "frequent flyers" may receive significant exposure, especially during a solar charged particle (proton) event. These events are associated with solar flares, and they occur without warning. Even without solar flares, a flight from New York to Tokyo or London to Tokyo can expose the pregnant woman to the equivalent of one chest radiograph. Travelers in the Concorde and those in polar flights may be exposed to greater amounts of radiation because the former attains very high altitudes (59,000 ft), well above most jet aircrafts (caused by loss of the attenuating effects of earth's atmosphere) and the latter because of decrease in geomagnetic shielding over the polar regions. Radiation levels over the polar regions at typical subsonic cruising altitudes of 39,000 feet are about twice those over the equator at the same altitudes.

Exposure to ultraviolet light can intensify the mask of pregnancy. Most topical sunscreens are poorly absorbed through the skin and are probably safe in pregnancy. The safety of these agents, however, over long-term use in pregnant women is not known.

Table 7 lists some agencies that offer medical assistance for travelers. None of them currently offers complete, comprehensive assistance, and many do not cover pregnant patients late in pregnancy. Pregnant travelers are advised to inquire with these agencies well ahead of anticipated departure date, and especially ask about out-of-country delivery coverage. Pregnant women should be educated about signs and symptoms of serious, pregnancy-related illness for which immediate medical help should be sought. These include, but are not limited to, bleeding, severe abdominal pain, uterine contractions, premature rupture of membranes, hypertension, proteinuria, hematuria, headache, visual disturbances, severe edema, accelerated weight gain, and jaundice.

CONCLUSION

In modern society, pregnant women tend to travel either for business or recreation, and thus, often present to the traveler's health clinic for advice. In general, such travel by healthy pregnant women has no harmful effect on the pregnancy. By following guidelines addressed throughout the article, health professionals should be able to assess the risks of travel, and enable the mother and her new travel companion, the developing fetus, to travel safely.

ACKNOWLEDGMENTS

The authors appreciate the critical review by Joshua Copel, MD, Professor of Obstetrics and Gynecology at Yale University and the expert secretarial assistance of Josephine Onofrio and Carolyn Karbowski.
<table>
<thead>
<tr>
<th>Agency</th>
<th>Address</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Access America</td>
<td>600 Third Avenue, Box 807 New York, NY 10163 Tel: 800 851-2800</td>
<td>Medical insurance subsidiary of Blue Cross/Blue Shield Offer coverage for travel in North America and for limited period overseas</td>
</tr>
<tr>
<td>AEA International</td>
<td>4050 Columbia Seafirst Ctr 701 5th Ave Seattle, WA 98104–7016 Tel: 800 468-5232 206 340-6000 FAX: 206 340-6006</td>
<td>Medical evacuation, repatriation, medical referral, 24-hour telephone medical service Alarm centers located around the Pacific rim Subscribers have access to services worldwide Global coverage but focus is in the Pacific rim</td>
</tr>
<tr>
<td>Credit card and insurance companies, banks</td>
<td>USA: 417 Center Street, Lewiston, NY 14092 Tel: 716 754-4883 Canada: 40 Regal Road Guelph, Ontario, N1K 1B5 1287 St. Clair Avenue West Toronto, Ontario M6E 1B8</td>
<td>Directory listing of IAMAT centers throughout the world, and furnishes the names of physicians</td>
</tr>
<tr>
<td>International Association for Medical Assistance to Travellers (IAMAT)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>International SOS Assistance</td>
<td>8 Neshaminy Interplex Suite 207 Trevose, PA 19053-6956 Tel: 800 523-6586 215 245-4707</td>
<td>Assistance in finding English-speaking physicians 24-Hour worldwide medical information and assistance Medical monitoring, dispatch a doctor, evacuation, repatriation and many others</td>
</tr>
<tr>
<td>Internet/WWW OBGYN.net</td>
<td><a href="http://www.obgyn.net/country">www.obgyn.net/country</a></td>
<td>Country-specific information on associations, hospitals, research, medical schools, culture, and much more Made possible through the efforts of OBGYN.net international representatives</td>
</tr>
<tr>
<td>Local US or British embassy or consulate</td>
<td>Respective countries</td>
<td>Provide names of physicians in the area For English-speaking physicians</td>
</tr>
<tr>
<td>Local medical school or university</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Medical Alert Foundation</td>
<td>P.O. Box 381009 Turlock, CA 95380 Tel: 209 668-3333 800 IDALERT</td>
<td>Worldwide organization Members receive a bracelet or necklace bearing a red Medical Alert emblem with a brief description of the wearer’s medical problem and a 24-hour “hotline” number Accepts collect calls from physicians or public health officials from all over the world</td>
</tr>
<tr>
<td>SAFETrip</td>
<td>P.O. Box 5375 Timonium, MD 21093 Tel: 800 537-2029 410 453-6300 Fax: 410 453-6301 E-Mail: <a href="mailto:medexasst@aol.com">medexasst@aol.com</a></td>
<td>Offered by MEDEX Assistance Corporation Provides emergency assistance, close monitoring of treatment, evacuation, and others</td>
</tr>
</tbody>
</table>
References


Address reprint requests to
Michele Barry, MD
Tropical Medicine and International Travelers Clinic
Yale University School of Medicine
20 York Street
New Haven, CT 06504