Objectives

1. Describe the potential concerns of using leprostatic agents (clofazimine and dapsone) during pregnancy or lactation.
2. Discuss the potential concerns of using certain antiviral drugs during pregnancy or lactation.
3. Discuss the potential concerns of using anti-retroviral agents (drugs for treating HIV) during pregnancy or lactation.

Article

Anti-infective Drug Use in Obstetrics – Part IV

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1. Describe the potential concerns of using leprostatic agents (clofazimine and dapsone) during pregnancy or lactation.
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3. Discuss the potential concerns of using anti-retroviral agents (drugs for treating HIV) during pregnancy or lactation.

This article is a continuation of Parts I, II, and III. Again, for each drug that is discussed, the pregnancy risk factor category (as defined by the Food and Drug Administration) is shown in parentheses. To allow for easy reference as these drugs are discussed the categories are as follows:

Category A: Controlled studies in women fail to demonstrate a risk to the fetus and animal studies (if performed) also shows no risk and thus, the possibility of fetal harm appears to be remote.

Category B: Either – No controlled studies in women have been done, but animal studies show no harm OR animal studies suggest a potential for harm, but controlled studies in women do not show harm.

Category C: Either – studies in animals suggest a potential for harm, and controlled studies in women have not been done OR no animal studies or human studies have been done – The potential benefit from use should exceed the potential for risk.

Category D: There is positive evidence that human fetal risk exists; however, the benefits of use may still outweigh the risk (for example, some anti-convulsive drugs).

Category X: There is positive evidence that human fetal risk exists and this risk clearly outweighs any potential benefit from using the drug. Thus the drug is contraindicated.

As stated in Parts I, II, and III, the majority of drugs are classified as category C because of the overall lack of studies in pregnant women.

IX. Leprostatic Drugs

A. Clofazimine (C)
Clofazimine is a bright red dye with antibacterial properties used in the treatment of lepromatous leprosy caused by Mycobacterium leprae. The agent was not teratogenic in mice and rats but did cause fetal toxicity in mice (abortions and stillbirths, retarded fetal skull ossification, and neonatal mortality). It is not known if clofazimine crosses the human placenta, but the molecular weight is low enough that transfer should be expected. A number of reports have described the use of clofazimine during human gestation. No birth defects attributable to the drug have been observed. However, mild to moderate skin pigmentation was observed in one case. Clofazimine is excreted into human breast milk and may result in pigmentation of the skin in the nursing infant. The discoloration is transient but it may take several months to return to a normal color.

B. Dapsone (C)

Dapsone has a wide range of uses, including the treatment of leprosy, dermatitis herpetiformis, Pneumocystis carinii pneumonia, inflammatory bowel disease, rheumatic and connective tissue disorders, and relapsing polyarthritis. It has also been used for prophylaxis against malaria. Reproduction tests have not been conducted in animals, but the drug has caused a slight increase in tumors in pregnant and lactating mice and rats. The low molecular weight suggests that dapsone crosses the human placenta to the fetus. Dapsone has been used in all stages of human pregnancy without demonstrating a relationship to birth defects. However, Heinz-body hemolytic anemia has been reported in a mother and her newborn. Dose-related hemolytic anemia is the most common toxicity reported with dapsone and occurs in patients with or without G6PD deficiency. In addition, newborn hyperbilirubinemia, possibly due to displacement of bilirubin from albumin binding sites, may be a consequence of use near delivery. Dapsone is excreted into human breast milk. The high lipid solubility, weak base properties, and prolonged serum half-life (about 20 hours) of the drug are conducive to ion trapping and accumulation in milk. A case of mild hemolytic anemia in an infant exposed to dapsone in milk has been reported. However, the American Academy of Pediatrics (AAP) classifies the agent as compatible with breast-feeding.

X. Antiviral Drugs

A. Acyclovir (B)

Acyclovir was not found to be teratogenic in pregnant mice, rats, and rabbits at doses resulting in systemic exposures similar to those achieved in humans with therapeutic dosing. Dosing in mid-rat gestation, however, did result in skull, eye, and tail defects. Acyclovir readily crosses the human placenta to the fetus. Numerous reports involving well over a thousand cases (the majority in the manufacturer’s pregnancy registry) have described the use of acyclovir during all stages of gestation. As expected, birth defects have been reported in exposed pregnancies, but none of these have been attributed to acyclovir. The primary uses of acyclovir during pregnancy have been for the treatment of primary infections of genital herpes simplex virus (HSV) type 2 or for life threatening disseminated HSV infections. In both of these infections, the benefits of acyclovir for the mother and fetus far outweigh any known risk. Prophylactic use of acyclovir to prevent recurrent genital HSV infection, however, is controversial because a clear benefit has not been established. Acyclovir is concentrated in human breast milk, reaching levels exceeding those found in maternal serum. No adverse effects from acyclovir in milk have been reported in nursing infants or in neonates given the drug directly. The AAP classifies acyclovir as compatible with breast-feeding.

B. Amantadine (C)

This antiviral drug, used for the treatment and prevention of influenza A and as an anti-Parkinson agent, showed dose-related teratogenicity in rats at doses equivalent to the human dose. No fetal harm, however, was observed in pregnant rabbits. The low molecular weight suggests that amantadine will cross the placenta. Birth defects have been observed in humans but the data are very limited. A case report described a cardiovascular defect (single ventricle with pulmonary atresia) in an infant exposed during the first trimester. The mother had taken the drug for a Parkinson-like movement disorder. In a surveillance study, there were 5 infants with major defects (2 expected) in 51 newborns exposed in the first trimester. One of the defects was a cardiovascular defect (0.5 expected) and one was a limb reduction anomaly (0 expected). Information wasn’t available for the other 3 defects. Because of the small numbers, an assessment of fetal risk cannot be made, but the safest course is to avoid this agent during the first trimester. Small amounts of amantadine are excreted in human breast milk. Although adverse effects in nursing infants have not been reported, the drug should probably not be used during lactation because of the potential for urinary retention, vomiting, and skin rash.

C. Cidofovir (C)

Cidofovir, used for the treatment of cytomegalovirus (CMV) retinitis, is embryo toxic in rats and rabbits at doses much lower than
those used in humans. The drug was also teratogenic (meningocele, short snout, and short maxillary bones) in rabbits. Use of cidofovir in human pregnancy has not been reported. Because of its low molecular weight, however, it should cross the placenta to the embryo and fetus. The lack of human pregnancy experience prevents an assessment of the fetal risk, but the animal toxicity observed in two species suggests that a risk does exist. However, cidofovir is indicated for sight-threatening CMV retinitis so the benefit to the mother may outweigh the unknown fetal risk if this medical problem were to co-exist with pregnancy. In contrast, the use of cidofovir during lactation is contraindicated because of the potential for severe toxicity in a nursing infant.

D. Famciclovir (B)

The pro-drug, famciclovir, is converted in vivo to the active drug penciclovir. It is used for the treatment of herpes simplex virus (HSV) type 1 or 2 or varicella-zoster infections. Famciclovir was carcinogenic (mammary adenocarcinoma) in female rats, but not in male rats or mice. No embryo toxicity or teratogenicity was evident in studies with pregnant rats and rabbits. The placental transfer of famciclovir and its active metabolite, penciclovir, have not been studied, but the low molecular weight is suggestive of such transfer. Only seven cases of human pregnancy exposure, all in the first trimester, have been published. The outcomes of the pregnancies included one ectopic pregnancy, two spontaneous abortions, and four normal infants. The lack of animal teratogenicity decreases (but does not exclude) the possibility of human teratogenicity, but the data are far too limited to make a risk assessment. Famciclovir is concentrated in the milk of lactating rats. No human data are available, but because of the risk of carcinogenicity, famciclovir should probably not be used during breast-feeding.

E. Foscarnet (C)

Foscarnet is used for the treatment of infections caused by CMV, HSV types 1 and 2, Epstein-Barr virus (EBV), varicella-zoster virus, human herpes virus type 6, and human immunodeficiency virus (HIV). The antiviral agent was teratogenic (skeletal malformations or variations) in pregnant rats and rabbits at doses much less than the human exposure based on equivalent comparisons. The low molecular weight of foscarnet suggests that the drug will cross the placenta. Human pregnancy experience is limited to three cases involving exposure in the second and third trimesters. Normal infants were delivered in two cases and no information was available in the third case. Foscarnet has been suggested as a first-line agent for pregnant HIV-positive patients with sight-threatening CMV retinitis. If indicated, the maternal benefits may outweigh the unknown fetal risks. However, the agent causes frequent renal toxicity in adults so, if used in pregnancy, antepartum testing of amniotic fluid volume to monitor for fetal renal impairment is highly recommended. Foscarnet is concentrated in the milk of lactating rats. No reports have described the use of the agent in human lactation. It should be avoided during breast-feeding because of the potential for renal toxicity in the nursing infant.

F. Ganciclovir (C)

Ganciclovir is used in the treatment of CMV retinitis and other viral infections. The agent is embryo toxic in mice and rabbits at doses very close to those used in humans. Congenital malformations observed in mice were hypoplastic testes and seminal vesicles and pathologic changes in the non-glandular region of the stomach. In rabbits, growth retardation and malformations (cleft palate, anophthalmia or microphthalmia – small or absent eyes, aplastic kidneys and pancreas, hydrocephaly, and brachygnathia – small lower jaw) were observed. Ganciclovir crosses the human placenta. Five cases of human pregnancy exposure have been reported, but outcome data are only available in two cases. No fetal or newborn adverse effects were observed in the two cases. The human data are too limited to make an assessment of fetal risk. The use of ganciclovir during human lactation has not been reported. Because of the potential for serious toxicity in a nursing infant, this antiviral agent should probably not be used during breast-feeding.

G. Oseltamivir (C)

There have been no reports describing the use of oseltamivir in human pregnancy. The antiviral agent is used for the treatment of infections caused by influenza viruses, types A and B. Oseltamivir was not embryo toxic in pregnant rats and rabbits, but a dose-related increase in the incidence (within the expected background rates) of skeletal abnormalities and variations was observed in both species. The low molecular weight is suggestive of placental transfer. The lack of human pregnancy experience prevents an assessment of fetal risk. No reports on the use of oseltamivir during human lactation have been published. Excretion into milk should be expected, but the effects of this exposure on a nursing infant are unknown.

H. Ribavirin (X)
Ribavirin is an antiviral agent used for treating respiratory syncytial virus (RSV). The use of this drug during human pregnancy is contraindicated. This antiviral agent was found to be embryo lethal or teratogenic in all animal species tested (hamsters, rats, and rabbits). The malformations observed were defects of the skull, palate, eye, jaw, limbs, skeleton, and gastrointestinal tract. Ribavirin is concentrated in red blood cells and persists for the life of the cell (which is up to 4 weeks). The relatively low molecular weight suggests that ribavirin crosses the human placenta. In one case of human pregnancy exposure, a woman in the third trimester received ribavirin inhalation therapy. No toxicity was observed in the newborn. A 1993 report estimated that the exposure of pregnant health-care personnel to ribavirin-contaminated air was either above or slightly below the permissible exposure limit. Due to the lack of pregnancy experience during the period of organogenesis, the risk of ribavirin for the human fetus cannot be determined. However, health-care personnel who are or who may become pregnant within a month should avoid exposure to aerosolized ribavirin or working in areas where ribavirin treatments are being given. No reports have described the exposure of lactating women to aerosolized ribavirin. Therefore, the risk to a nursing infant from exposure to the drug from breast milk is unknown.

I. Rimantadine (C)

Rimantadine is used in the treatment and prophylaxis of influenza virus A infections. Embryo toxicity was observed in pregnant rats, but the dose given (about 11 times the human dose) was also maternal toxic. Toxicity was not observed in pregnant rabbits. There was, however, an increase in the number of rabbit fetuses with extra ribs. The relatively low molecular weight of rimantadine suggests that the drug will cross the placenta. There are no reports on the use of rimantadine during human pregnancy. The toxicity of this drug in non-pregnant patients is similar to amantadine, a closely related agent. Because of the potential birth defects observed with amantadine (see above), the safest course is to avoid exposure to the drug in the first trimester. Rimantadine is concentrated in the milk of lactating rats. Reports describing the use of this agent during human lactation have not been published. Rimantadine should not be used during lactation due to the potential for serious toxicity in a nursing infant.

J. Valacyclovir (B)

Valacyclovir is converted in vivo to acyclovir. It is not teratogenic in rats and rabbits. Acyclovir readily crosses the human placenta to the fetus. The human pregnancy experience with valacyclovir is less than that with acyclovir, but neither antiviral agent appears to present a risk to the fetus (see acyclovir above). Although the use of valacyclovir has not been reported in human lactation, the active metabolite (acyclovir) is considered compatible with breast-feeding. Therefore, valacyclovir is also probably compatible with breast-feeding.

K. Zanamivir (C)

Zanamivir is used for the treatment of influenza virus A and B. The agent produced no embryo toxicity or teratogenicity in pregnant rats and rabbits. In one rat strain, however, an increase was seen in the incidence of minor skeletal alterations with doses much higher than those used in humans. The drug crosses the placenta in animals and probably crosses the human placenta. No reports describing its use in human pregnancy have been published. The lack of information prevents a full assessment of the human fetal risk. Zanamivir is excreted into the milk of lactating rats, but there is no human data. The risk to a nursing infant from exposure to the agent in breast milk is unknown.

XI. Anti-Retroviral Agents

A. Protease Inhibitors

Amprenavir (C), Indinavir (C), Nelfinavir (B/C), Ritonavir (B/C), and Saquinavir (B/C) are protease inhibitors used for the treatment of HIV infection. No evidence of teratogenicity has been observed in animal reproduction studies involving any protease inhibitor with the possible exception of indinavir. In one rat study, unilateral anophthalmia (absent eye) was observed in some litters exposed to indinavir. Developmental toxicity has occurred with ritonavir (resorption, growth retardation, ossification delay), amprenavir (fetal thymus elongation, growth retardation, and ossification delay), and indinavir (supernumerary and cervical ribs). Amprenavir has also been shown to be embryo lethal in experimental animals. Low amounts of amprenavir and ritonavir have been shown to cross the human placenta, but human data are not available for the other agents. However, the molecular weights of the agents suggest that placental transfer occurs for all protease inhibitors. Moreover, indinavir does cross the placenta of experimental animals.
Most of the published human pregnancy experience comes from the Antiretroviral Pregnancy Registry. Pregnancy experience is limited for all agents in this class. However, no evidence of an increase in the incidence of congenital malformations or a pattern of anomalies has been reported. Although the benefits of maternal therapy probably outweigh the unknown fetal risks, the limited human pregnancy data does not allow an assessment of that risk. Because of a possible relationship between protease inhibitors and diabetes mellitus, pregnant women using a protease inhibitor should be monitored for hyperglycemia.

Data on the use of protease inhibitors during lactation have not been published. Breast-feeding by HIV-positive women is not recommended because of the risk of transmitting the HIV infection from the mother to the nursing infant. Therefore, lactation studies on anti-retroviral agents in HIV positive women will be limited.

B. Nucleotide Analog Reverse Transcriptase Inhibitors

Abacavir (C), Didanosine (C), Lamivudine (C), Stavudine (C), Zalcitabine (C), and Zidovudine (C) are nucleotide analog reverse transcriptase inhibitors (NRTIs) used for the treatment of HIV infection. Didanosine, lamivudine, stavudine, and zidovudine were not teratogenic in experimental animal reproduction studies (rats and rabbits). In addition, didanosine produced no embryo or fetal toxicity in pregnant rats and rabbits given doses 12 to 14 times the human dose. In contrast, abacavir (skeletal defects) and zalcitabine (hydrocephalus at doses much higher than those used in humans) were teratogenic in animals. Abacavir was also embryo toxic (resorption, decreased body weight) and fetal toxic (growth retardation) in rats, but not in rabbits. Lamivudine was embryo lethal in rabbits, but not in rats, at doses similar to human doses. A dose-related increase in early pregnancy loss was also observed with stavudine. Zalcitabine was embryo lethal and fetal toxic (growth retardation, neurotoxicity), but the doses used were more than 1,000 times the recommended human dose based on an equivalent comparison. Zidovudine doses less than 100 times the human dose caused an increase in rat and rabbit abortions. All NRTIs cross the human placenta to the fetus.

Of the NRTIs, only two studies, one involving lamivudine (10 subjects) and the other zidovudine (6 subjects), have described the detection of the drug in breast milk. Breast-feeding was not allowed in either study. In both investigations, lamivudine and zidovudine milk concentrations exceeded those in the maternal serum. Current recommendations advise against breast-feeding by HIV-positive women because of the risk for infection in the nursing infant. However, in a 1999 double-blind placebo-controlled study, HIV-positive women received an oral zidovudine regimen of 300 mg twice daily until labor, 600 mg at the beginning of labor, then 300mg twice daily for 7 days postpartum. At 6 months of age, their nursing infants had a 38% reduction in the vertical transmission of HIV-1 (p = 0.027). No increase in adverse effects was observed in the groups of infants exposed to zidovudine compared to controls.

C. Non-Nucleoside Reverse Transcriptase Inhibitors

Delavirdine (C), Efavirenz (C), and Nevirapine (C) are non-nucleoside reverse transcriptase inhibitors (nnRTI) used for the treatment of HIV. Delavirdine was teratogenic (ventricular septal defects) and fetal toxic (reduced pup survival) in pregnant rats at doses nearly equivalent to those used in humans. No malformations were observed in pregnant rabbits, but maternal toxicity, embryo toxicity, and abortions were observed at doses only 6 times the human dose. When efavirenz was given to pregnant monkeys at doses producing serum concentrations similar to those achieved in humans, an increased incidence of birth defects (anencephaly, unilateral anophthalmia, microphthalmia, and cleft palate) was observed. The agent was embryo toxic (resorption) in pregnant rats, but no teratogenic or toxicity was observed in pregnant rabbits. In contrast, systemic exposures of nevirapine similar to those seen in humans produced no teratogenicity or embryo toxicity in pregnant rats and rabbits, but did impair female rat fertility and caused growth retardation in rat fetuses. Only the human placental transfer of nevirapine has been studied, but the low molecular weights of the other two agents suggest that they also will cross the placenta. Efavirenz has been shown to cross the placenta in experimental animals.

Most of the published human pregnancy experience with nnRTIs comes from the Antiretroviral Pregnancy Registry. The data for
the three agents is too limited to allow a prediction of fetal risk, but the animal data, especially for delavirdine and efavirenz, suggests that a potential risk does exist. However, even if there is a fetal risk, the maternal benefit of treating an HIV infection with any nRTI may outweigh that risk. Of the three agents, though, nevirapine appears to be the least toxic based on animal reproduction testing.

Nevirapine is excreted into human breast milk, but no data are available for the other two agents. Nevirapine was measured in milk following a single oral dose (100 or 200 mg) given to 10 women about 6 hours before delivery. The drug was still present in milk (mean concentration of 103 ng/ml) 7 days after delivery. Breast-feeding by HIV-positive women is not recommended because of the risk of transmitting the HIV infection to the nursing infant.

References or Suggested Reading:

10. The Antiretroviral Pregnancy Registry for abacavir (Ziagen), amprnavir (Agenerase, APV), delavirdine mesylate (Rescriptor), didanosine (Videx, ddl), efavirenz (Sustiva, Stocrin), indinavir (Crixivan, IDV), lamivudine (Epivir, 3TC), lamivudine/zidovudine (Combivir), nelfinavir (Viracept), nevirapine (Viramune), ritonavir (Norvir), saquinavir (Fortovase, SQV-SGC), saquinavir mesylate (Invirase, SQV-HGC), stavudine (Zerit, d4T), zalcitabine (Hivid, ddC), zidovudine (Retrovir, ZDV). Interim Report. 1 January 1989 through 31 July 2000. 2000(December); 11 (No.2):1-55.

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He is the primary author of the textbook entitled Drugs in Pregnancy and Lactation, currently in its 6th Edition, copyright 2001, Lippincott, Williams, and Wilkins, Philadelphia, Pennsylvania. He also has several publications in peer-review medical journals and has lectured at many institutions across the United States and Canada regarding the use of drugs in pregnancy and lactation.