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Human Immunodeficiency Virus and Pregnancy

Vol 5#3, April 1997

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Human immunodeficiency virus (HIV) is a retrovirus spread by bodily secretions. Sexual intercourse, contaminated needles or blood transfusions, and placental transfer from mother to fetus are the most common modes of transmission. Acquired immune deficiency syndrome (AIDS) is the syndrome of opportunistic infections that occurs as the final stage of the HIV infection. At present, the most rapidly growing rate of HIV infection lies in heterosexual women. This fact, coupled with the gravity of the prognosis for infected women and children, is forcing obstetricians to reconsider their usually conservative attitudes towards the use of drugs and medications in pregnancy. This issue of RISK|| NEWSLETTER will focus on HIV as a cause of birth defects in pregnancy and on the teratogenic potential of the medications used to treat infected persons.

HUMAN IMMUNODEFICIENCY VIRUS

No increase in congenital anomalies was found in 822 children of HIV-positive women in Africa (Embree, 1989; Ryder, 1989; Lepage, 1989), in 96 children in Italy (Semprini, 1990), or in 419 children of infected women in the United States (Alger, 1993; Abrams, 1995). One report delineated a dysmorphic syndrome associated with HIV-infected mothers which included growth retardation, microcephaly, frontal bossing, hypertelorism, flattened nasal bridge, and blue sclerae (Marion, 1986). Two subsequent studies of 30 infants (Qazi, 1988) and 600 newborns (European Collaborative Study, 1991) did not confirm these findings. This phenotype is now thought to be due to the children's ethnic origin, chronic illness, maternal drug abuse during pregnancy, or other factors (Cordero, 1988; European Collaborative Study, 1991).

HIV can be transmitted from an infected woman to her fetus either during pregnancy or at the time of delivery via transplacental or transvaginal exposure to the virus or through breast milk postnatally. The risk of perinatal transmission is approximately 25-30% in untreated pregnancies. Breastfeeding carries an additional 8-20% risk of infection. Perinatal transmission of HIV is multifactorial. Maternal, fetal, viral, immunologic and obstetrical factors all play a role in determining which women are most likely to transmit the virus (Garcia, 1994). Some of the most important determinants of transmission are maternal HIV viral load, a low CD4 count, whether antiviral treatment occurred during pregnancy, the duration of ruptured membranes (greater than 4 hours), use of hard drugs during pregnancy, low birth weight, and vaginal delivery (Landesman et al., 1996; European Collaborative Study, 1994). First-born twins also seem to be at greater risk of infection with HIV than second-born (Kuhn and Stein, 1995). Some studies also suggest that invasive procedures such as amniocentesis and CVS may increase the risk of transmission. Currently, the most important intervention aimed at reducing perinatal transmission is screening reproductive age women and offering antiviral treatment (Garcia, 1994).

CDC/ACOG/AAP all recommend routine voluntary testing of all pregnant women with written informed consent.

AZIDOTHYIMIDINE

Azidothymidine (AZT) is a pyrimidine analog, which appears to work by inhibiting viral reverse transcriptase. AZT has been shown to cross the perfused human placenta and has been detected in fetal liver and muscle but not the central nervous system (Lyman, 1990). In the children of seven HIV-infected mothers, AZT cord blood levels varied but were similar to maternal levels (O'Sullivan, 1993).

The administration of AZT to pregnant women with HIV has been shown to reduce the transmission rate to 8-10% (Garcia, 1994). Maternal HIV RNA levels are highly predictive of perinatal transmission risk and suggest that certain levels of virus late in gestation and/or during labor and delivery are associated with both a high risk and low risk of transmission. AZT exerts a major protective effect by reducing HIV RNA levels prior to delivery (Dickover et al., 1996).

No increase in congenital anomalies was noted among 45 infants whose mothers took AZT during pregnancy. Twelve of these infants were exposed during the first trimester, and no congenital anomalies were found among them. The congenital anomalies reported in three of the infants did not follow any specific pattern (Sperling, 1992). No adverse effects were found among 180 infants who were exposed to AZT in the second or third trimesters (ACTG, 1994). Mild, transient anemia was present in seven of the 45 infants in one study. Three of the seven were born prematurely, however, and it has been postulated that the prematurity might be the cause of their anemia (Sperling, 1992). In another study, two of seven children had mild anemia at birth which later resolved (Ferrazin, 1993). There have also been isolated reports of intrauterine growth retardation and oligohydramnios associated with maternal AZT during pregnancy (Sperling, 1992). As of December 31, 1995, there were 213 total pregnancies reported in the prospective Zivovudine in Pregnancy Registry. Ten pregnancies ended in induced abortions and two ended in spontaneous pregnancy loss. Of the 201 live births, seven were reported as having a birth defect or defects, and 194 did not have any birth defects (Antiretroviral Pregnancy Registry, Bristol-Myers Squibb Co., Glaxo Wellcome, Inc., and Hoffman-LaRoche, Inc.).

There was no increase in malformations observed among the offspring of mice, rats and rabbits when they were treated with 1-12.5, 5-25, and 5-21 times the maximum human dose of AZT, respectively (Ayers, 1988; Stahlman, 1989; Siehl, 1992); however, an increased rate of postnatal death was observed among pups born to rats treated with high doses (Stahlman, 1989). Monkeys were given 1.5 mg/kg every four hours throughout pregnancy (equal to the maximum human dose) and no ultrasound differences or behavioral delays were reported in twelve pregnancies (Ha, 1994).

In a study by Connor et al. (1994), pregnant women with mildly symptomatic HIV disease and no prior treatment with antiretroviral drugs during pregnancy were put on a regimen of AZT (given antepartum and intrapartum to the mother and for a period of six weeks to the newborn). The risk of maternal-infant HIV transmission decreased by two-thirds. When AZT was given to 75% of HIV positive women in another study, only 5.7% of the infants were infected as compared to 18.9% of those who did not receive treatment (Fiscus et al., 1996).

In January 1997 the NIH convened an independent panel to review studies which suggested that very high daily doses of AZT may induce tumors in the offspring of pregnant mice given AZT during the last trimester of pregnancy. This panel concluded that the known benefits of AZT far outweighed hypothetical concerns of transplacental carcinogenesis raised in the mouse studies. Little is known regarding the sensitivity, reliability or applicability of these studies to human exposure. Major differences exist between human and mouse AZT distribution, metabolism, and excretion, in duration of gestation and fetal development at birth and many facets of the maternal-fetal relationship. This panel recommended discussion of the theoretical risk of carcinogenesis with the infected woman.

Additionally, careful long-term follow-up of all children exposed in utero to antiretroviral therapy, including those not infected with HIV, is warranted (NIAID, 1997).

The United States Public Health Service Task Force has made recommendations on the use of AZT during pregnancy to reduce perinatal transmission of HIV. These recommendations follow the regimen used in AIDS Clinical Trial Group Protocol 076. HIV-infected women should be orally administered 100 mg of AZT five times daily beginning at 14-34 weeks of gestation and continuing throughout the pregnancy. During labor, these women should receive an intravenous one hour loading dose of 2 mg/kg followed by continuous infusion of 1 mg/kg per hour until delivery. AZT should be administered orally to the newborn at a rate of 2 mg/kg every six hours beginning 8-12 hours after birth and continuing until the sixth week of life. It is recommended that HIV-positive women and/or their children presenting at any time during pregnancy, delivery, or after birth be started on this protocol.

ACYCLOVIR

Acyclovir is a synthetic purine nucleoside analog that is used topically and systemically to treat viral infections. This drug appears to work by inhibiting ribonucleotide production. Acyclovir crosses the placenta at term in humans and can be found in amniotic fluid and cord blood (Frenkel, 1991).

In a study of 49 children of mothers who were exposed to acyclovir during the first trimester of pregnancy, only one congenital anomaly was reported. However, this anomaly was attributed to an inherited familial disease (Andrews, 1988). Fourteen of 466 infants exposed to acyclovir in utero had congenital anomalies (Eldridge, 1993). No specific pattern of defects was identified and this number did not reflect an increase above the 3% background risk of congenital anomalies (Eldridge, 1993). There have been fifty-two case reports brought to the attention of the manufacturer (Burroughs Wellcome Company) in which no congenital anomalies were observed; however, only four of the cases involved first trimester exposure (Andrews, 1992). There were a total of 909 pregnancies reported to the Acyclovir in Pregnancy Registry as of December 31, 1995. Of these, 75 ended in induced abortions and 68 ended in spontaneous loss. Twenty-one of the liveborns had birth defects, and 745 did not (Acyclovir Pregnancy Registry, Glaxo Wellcome, Inc.). This incidence of birth defects did not differ from expected.

No increase in congenital anomalies were reported in the offspring of nineteen marmosets receiving 1-3 times the maximum human dose (Stahlman, 1992), in the offspring of mice given 1-6 times the maximum human dose (Moore, 1983), or, in the offspring of rats or rabbits given 1-1.6 times the maximum human dose (Moore, 1983). Conversely, an increased rate of fetal death, growth retardation and malformations (of which craniofacial and skeletal were the most common) was reported in offspring of rats given 5-10 times the human dose (Chahoud, 1988). Rats given 2 times the human dose parentally produced an increased number of offspring with growth retardation or fetal demise (Mamede, 1995). Thymic hypoplasia and immunological dysfunction were reported in rats exposed to 3-10 times the human dose in utero (Stahlmann, 1995). The relevance of these animal studies to humans is unknown, however.

ZALCITABINE

Zalcitabine, or ddC, acts as a chain terminator of viral-induced DNA synthesis. It inhibits viral replication by binding to reverse transcriptase. The major side effect of ddC use in humans is peripheral neuropathy associated with axonal degeneration.

There have been no reports or epidemiological studies on the effect of ddC on human pregnancies. The prospective Zalcitabine in Pregnancy Registry included five cases as of December 31, 1995. One pregnancy was pending delivery. The remaining cases involved first trimester exposure and there were two infants born without birth defects and two induced abortions (Antiretroviral Pregnancy Registry,

Bristol-Myers Squibb Co., Glaxo Wellcome, Inc., Hoffman-LaRoche, Inc.).

In monkeys, it has been determined that total ddC exposure of the fetus is approximately half that of the mother (Slikker, 1992). ddC is concentrated in the fetal kidney and is present in the brain at approximately 20% of fetal blood concentrations (Sandberg, 1995). Teratology studies have been performed in mice exposed to up to 2000 mg/kg/day (the maximum human dose is 10 mg/kg/day). Starting at 1000 mg/kg/day of ddC, an increased frequency of growth retardation, micrognathia and bent long bones was present. Doses of 400 mg/kg/day resulted in mild developmental toxicity, manifested as open eyelids and cleft palate (Lindstrom, 1990). An increased frequency of hydrocephalus was observed in the offspring of rats given 220 times the maximum human dose of ddC late in pregnancy (Hall, 1994). The rodent central nervous system development resembles that of the human third trimester fetus at this time. The relevance of animal studies to human teratogenicity of ddC is unknown.

DIDANOSINE

Didanosine, or ddI, is a dideoxynucleoside in which modification of the molecule prevents phosphodiester linkages necessary for nucleic acid replication. ddI appears to work by binding to reverse transcriptase. The major side effect of ddI in human usage is peripheral neuropathy. ddI has been shown to cross the placenta in humans (Pons, 1991).

No epidemiological studies on the teratogenicity of ddI in human pregnancies have been reported. Cultured human trophoblasts exposed to high concentrations of ddI for relatively long periods of time did not show evidence of toxic effects, which may indicate a lack of adverse effects on the human placenta (Esterman, 1995). There have been three reports of pancreatitis and hyperglycemia in patients taking ddI, one of whom was pregnant (Bouvet, 1990; Seidlin, 1992; Munshi, 1994).

ddI exposure in mice at 2-60 times the human dose was not teratogenic and did not produce fetal toxicity (Sieh, 1992). Rats and rabbits exposed to 12-14 times the human dose did not experience any adverse fertility or fetal effects (Bristol Laboratories, Evansville, IN). It is unknown whether these animal studies are applicable to human pregnancies.

STAVUDINE

Stavudine, or D4T, is a nucleoside analog, which can produce peripheral neuropathy as a major side effect. No human studies have been reported on the teratogenicity of D4T.

Early mouse embryos exposed to 10uM of D4T (the maximum human dose) failed to progress to the blastocyst stage (Toltzis, 1994). The Manufacturer (Bristol-Myers Squibb, Princeton, NJ) reports no increase in birth defects in rats and rabbits exposed to 400 and 183 times the maximum human doses, respectively. However, at high doses in rats, a small increase in neonatal mortality and a minor delay in skeletal ossification were identified. The relevance of these studies to human pregnancy is unknown.

OTHER MEDICATIONS USED IN HIV TREATMENT

No information on the teratogenicity of lamivudine (3TC), nevirapine, or any of the protease inhibitors in either animals or humans is currently available.

CONCLUSION

Health care professionals must be aware of the potential impact of HIV infection and medications on pregnancy. Unfortunately, since many of these drugs have been recently developed, there is a lack of information regarding their teratogenic potential. Additional studies are required in order to determine the safety of the drugs used for treatment of HIV during pregnancy. A careful risk-benefit analysis must be formulated by health care professionals when deciding if and when to prescribe these medications in

pregnancy. The reduction of transmission of HIV to the offspring does appear to be significant when these medications are applied during pregnancy.

QUESTIONS?

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