Invited Editorial

Developmental Toxicity of Ribavirin/IFα Combination Therapy: Is the Label More Dangerous than the Drugs?

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Women and their physicians are concerned about the possibility that medications taken during pregnancy may harm the developing embryo or fetus. The most commonly used source of information regarding the potential teratogenicity of prescription drugs in the United States is the official "label," a document that is written by the drug's "sponsor" and approved by the US Food and Drug Administration (FDA). Most physicians have ready access to this information in the Physician's Desk Reference (PDR), a commercial compilation of approved labels that is distributed to physicians annually and without charge.

The Teratology Society and other authorities have criticized the product labels as a source of information on teratogenic risks in human pregnancy because the labels are often incomplete, misleading, and difficult for health care professionals to interpret and use (Brent, 1982; Friedman et al., 1990; Scialli, 1992; Friedman, 1993; Teratology Society Public Affairs Committee, 1994; Alvan et al., 1995; Addis et al., 2000, 2001; Boothby and Doering, 2001; FDA Pregnancy Labeling Taskforce, 2001; Doering et al., 2002; Merlob and Stahl, 2002). Many pregnancy labels are overly simplistic and lack sufficient detail to permit physicians and their patients to make informed decisions about the use of drugs during pregnancy or the management of exposed pregnancies. The article by Bianca and Ettore in this issue of *Birth Defects Research Part A* and other case reports cited by them illustrate how use of the information provided in FDA-approved pregnancy labels can lead to serious harm to pregnant women and their fetuses.

The current format of the pregnancy subsection of prescription drug labels was addressed by the FDA in 1979. The purpose of the section was to provide physicians with information that would enable them to safely prescribe medications to pregnant women. Thus, the label was required to provide information on a drug's potential reproductive and developmental toxicity including its possible effects on the postnatal growth and functional maturation of a prenatally exposed child. The FDA also required that each medication be classified using five-letter (ABCDX) categories. The letters were to be assigned to drugs on the basis of their potential to have adverse reproductive or developmental effects and on whether the potential benefit of maternal treatment outweighed the potential risk to the fetus (FDA Pregnancy Labeling Taskforce, 2001). Drugs are assigned to the various Pregnancy Categories through negotiation with the manufacturer and are usually based entirely on the results of unpublished premarketing studies in animals. Although it was not the intent of the FDA to use the Pregnancy Categories to provide estimates of reproductive or developmental risk (Lo and Friedman, 2002; Uhl et al., 2002), many professionals nevertheless assume that the ABCDX categories represent a gradation of developmental risk that increases from Category A–X (Scialli, 1992; FDA Pregnancy Labeling Taskforce; 2001). In response to criticisms raised about the system, the FDA created a Pregnancy Labeling Taskforce in 1999 to review current regulations on labeling of drugs and biologic products for use in pregnancy and to recommend revisions to the existing regulations (FDA Pregnancy Labeling Taskforce, '01).

Bianca and Ettore (2003) report a normal pregnancy outcome after paternal periconceptional treatment with a combination of two drugs, ribavirin and recombinant interferon alfa-2b (IFα). The case is noteworthy because it was the father, not the mother, who took these medications and because the FDA-approved label for ribavirin/IFα assigns a Pregnancy Category X and includes very strong warnings against pregnancy in the partner of a man who is receiving therapy with this combination of drugs. In their article, Bianca and Ettore cite two other cases in which normal babies were born after paternal exposure to ribavirin/IFα combination therapy around the time of conception (Hegenbarth et al., 2001). In one of these two cases, consultation with the manufacturer led the physicians to recommend elective termination of the pregnancy despite normal fetal ultrasound examination (Hegenbarth et al., 2001). The couple elected to continue the pregnancy after genetic counseling. Presumably, the second couple would have been similarly advised, but the pregnancy was too far advanced for elective termination at the time the couple was seen in clinic.

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That termination of pregnancy was even considered in these cases of paternal treatment illustrates the extreme measures that may be taken when a physician reads a product label that indicates a substantial risk of birth defects related to the treatment that has been prescribed. The ribavirin/IFα combination therapy has been given a Pregnancy Category X, but the pregnancy categories refer to maternal, not paternal, exposures.

TERATOGENIC POTENTIAL OF RIBAVIRIN AND IFα

The developmental toxicity associated with ribavirin/IFα combination therapy has not been studied in either animals or humans. Neither maternal treatment during pregnancy with ribavirin alone nor with IFα alone has been shown to cause birth defects in humans. The preparation that contains these drugs in combination has been assigned Pregnancy Category X because the mode of action and animal teratology studies of ribavirin and IFα suggest a theoretical potential to cause damage to the developing human embryo.

Ribavirin

Ribavirin is a purine nucleoside that exerts its antiviral effects by inhibiting inosine monophosphate dehydrogenase (Kochhar et al., 1980; Johnson, 1990; Ito et al., 1993). Inhibition of this enzyme blocks the conversion of inosinate to xanthylate and prevents biosynthesis of guanine nucleotides, which are essential components of nucleic acids. Because of its ability to interfere with the biosynthesis of guanine nucleotides, ribavirin treatment during pregnancy may have the potential to disrupt embryonic development.

Treatment of pregnant rats and hamsters with ribavirin in doses within or below the human therapeutic range produced a teratogenic effect that was dependent on both dose and time of exposure (Kilham and Ferm, 1977; Ferm et al., 1978; Hillyard, 1980; Johnson, 1990). The frequency of skeletal malformations was increased significantly among the offspring of pregnant mice treated with ribavirin in doses 1–10 times those used in humans (Kochhar et al., 1980). Increased embryonic and fetal death were observed when pregnant rabbits were treated orally with ribavirin in doses much smaller than those used in humans, but no malformations were seen among surviving offspring (Hillyard, 1980). No teratogenic effect was observed among the fetuses of seven baboons treated during pregnancy with 3–6 times the human oral dose of ribavirin (Hillyard, 1980; Johnson, 1990).

The teratogenic effects observed in rodents after maternal treatment with doses equivalent to those used in humans raise concern that maternal ribavirin treatment may also be teratogenic in humans. No information is available on the outcome of pregnancies in women who were treated with ribavirin during the period of embryogenesis. No adverse effects of ribavirin therapy were noted among the infants of nine women who were treated during the second half of pregnancy (Atmar et al., 1992).

IFα

IFα inhibits both cellular proliferation and protein synthesis. Treatment of pregnant rhesus monkeys with 20 to 500 times the human therapeutic dose of IFα produced a significant increase in the frequency of abortions (USP DI, 2002). No teratogenic effects were observed among the offspring of pregnant rats or rabbits treated parenterally with human IFα at doses 17–170 or 17–200 times, respectively, those used clinically (Matsumoto et al., 1986a,b; Shibutani et al., 1987; Furuhashi et al., 1993). Similarly, no adverse effects were produced consistently in the offspring of pregnant mice treated intramuscularly with IFα in doses 20–200 times those used in humans (Hasegawa et al., 1993).

Information on the effect of IFα treatment in human pregnancy is limited to individual cases described in the medical literature. None of 24 children whose mothers were treated with IFα during the first trimester of pregnancy was found to have congenital anomalies that could be attributed to the treatment (Baer, 1991; Baer et al., 1992; Crump et al., 1992; Delmer et al., 1992; Petit et al., 1992; Reichel et al., 1992; Pardini et al., 1993; Ferrari et al., 1994; Williams et al., 1994; Vianelli et al., 1994; Sakata et al., 1995; Diez-Martin et al., 1996; Lipton et al., 1996; Pulik et al., 1996; Ruggiero et al., 1996; Shpilberg et al., 1996; Mancuso et al., 1998; Cincotta et al., 2000; Trotter and Zygmunt, 2001; Mubarak et al., 2002).

Use of Ribavirin/IFα Combination Therapy in Pregnancy

Because ribavirin has been found to produce teratogenic and embryotoxic effects in animal studies, the manufacturer recommends that ribavirin/IFα combination therapy not be used in pregnant women and that "extreme care must be taken to avoid pregnancy in female patients" (Physicians' Desk Reference, 2002). It is recommended that ribavirin/IFα combination therapy "not be initiated until a report of a negative pregnancy test has been obtained immediately prior to initiation of therapy" and that women of childbearing age use two forms of effective contraception during treatment and during the 6 months after discontinuation of therapy (Physicians' Desk Reference, 2002). This dire warning is similar to that used for thalidomide, one of the most teratogenic treatments known in humans.

EFFECTS OF PATERNAL EXPOSURE TO RIBAVIRIN AND IFα

No adverse effects have been described in the offspring of men who were treated with ribavirin/IFα combination therapy before conception of a pregnancy or while their female partners were pregnant. Concern about male-mediated developmental toxicity associated with ribavirin/IFα combination therapy is based on pharmacokinetic considerations and data from experiments with either ribavirin alone or IFα alone in model systems.

Ribavirin

Ribavirin seems to be eliminated slowly from nonplasma compartments. The multiple-dose plasma half-life is reported to be approximately 298 hr (Glue, 1999; Physicians' Desk Reference, 2002), but the half-life in erythrocytes is 40 days (Physicians' Desk Reference, 2002; USP DI, 2002). The extensive accumulation of ribavirin in erythrocytes and other tissue compartments and its slow clearance from the body raise the theoretical possibility that ribavirin may accumulate in sperm in concentrations high enough to

induce a defect; however, there is no evidence that ribavirin treatment actually affects human sperm.

Evidence regarding mutagenic effects of ribavirin treatment is limited and contradictory. Ribavirin has been shown to increase the incidence of mutations and cell transformation in in vitro genotoxicity assays (USP DI, 2002). Mutagenic activity was also observed in the mouse lymphoma assay (USP DI, 2002) and in a mouse bone marrow micronucleus test at ≤1 times the maximum recommended human 24-hour dose of ribavirin (Rao and Rahiman, 1989; USP DI, 2002). Ribavirin did not induce chromosomal aberrations in rat or human leukocytes, however, and had no mutagenic effect in the Ames Test (McEvoy, 1993; Narayana et al., 2002b). In addition, ribavirin was not found mutagenic in a dominant lethal study in rats (Hoffman et al., 1987). Intraperitoneal administration of ≤1 times the maximum recommended human 24-hr dose of ribavirin to male rats altered sperm morphology and decreased sperm production, but it is not clear whether this was a toxic or mutagenic effect (Narayana et al., 2002a,b).

Another mechanism by which paternal ribavirin treatment could theoretically affect embryonic development is transmission through the seminal fluid, systemic absorption by the mother, and subsequent induction of a teratogenic effect (Trasler and Doerksen, 1999). We found no information in the medical literature on semen levels of ribavirin after systemic treatment. Even if high levels of ribavirin were present in human semen, however, it is unlikely that the amount transferred to a pregnant woman during sexual intercourse would be great enough to affect the embryo. For example, the peak plasma level of ribavirin in humans after treatment with 600 mg twice daily is reported to be 3.68 μg/ml (Physicians' Desk Reference, 2002). If one assumes that semen concentrations are similar to peak plasma levels and that the volume of the ejaculate is 6 ml, then an ejaculate would contain approximately 22.1 μg of ribavirin. If 100% of this ribavirin were absorbed by a 55-kg woman after sexual intercourse, she would receive about 0.0004 mg/kg of ribavirin, or approximately 0.003% of a therapeutic dose. Although this estimate is very crude, it seems unlikely that a dose this small, or even a dose 1,000 times greater, would produce a teratogenic effect.

IFα

No studies have been published in which the developmental toxicity of paternal exposure to IFα was investigated in humans or laboratory mammals. IFα has been shown to exhibit genotoxicity in human peripheral blood lymphocyte cultures, although IFα was not found to have mutagenic activity when evaluated in the Ames test or in human lymphocyte cultures in other studies (USP DI, 2002). Indeed, IFα has sometimes been found to suppress the mutagenicity induced by other agents (Suzuki and Suzuki, 1995; Lazutka, 1996; Takahashi et al., 2001).

RIBAVIRIN/IFA COMBINATION THERAPY IN MEN

The FDA-approved product label for the ribavirin/IFα combination gives similar precautions for male and female patients. The label recommends that female partners of male patients treated with this drug combination take extreme care to avoid pregnancy and that treatment not be initiated in male patients whose partners are pregnant (Physicians' Desk Reference, 2002). Male patients are advised to use two forms of effective contraception during treatment and during the 6 months after cessation of treatment.

IS THE LABEL MORE DANGEROUS THAN THE DRUGS?

The combination of ribavirin and IFα has been assigned a Pregnancy Category X and given a chilling warning about male-mediated teratogenic effects because of experimental animal data that raise theoretical concerns about human pregnancy. There is no direct evidence that treatment of pregnant women with therapeutic doses of either drug or both in combination actually does pose a teratogenic risk, and the basis for concern with treatment of the male partner is highly speculative at best. Ribavirin was approved by the FDA in 1985, IFα in 1991, and the combination in 1998. Nevertheless, almost no information is available on the developmental toxicity of either drug alone or both in combination in humans. Unfortunately, a similar lack of information on the teratogenicity of treatment in human pregnancy exists for most prescription drugs, even ones that are used frequently by pregnant women (Lo and Friedman, 2002). When it comes to drug labeling, ignorance is certainly not bliss for pregnant women or their babies.

The absence of scientific data permits wide latitude in what can be considered appropriate for the product label. Unfortunately, the product labeling for ribavirin/IFα provides no information about the likelihood of a poor pregnancy outcome if a woman becomes pregnant while taking the medication, or if she and her partner conceive while he is being treated. No mention is made about the importance of dose, stage of pregnancy, or route of exposure as critical factors in any teratogenic risk that may exist.

One-half of all pregnancies in the United States are unplanned (Westoff, 1988; Forrest, 1994). The label does not address what should be done about an inadvertent pregnancy. A physician or pregnant woman could conclude easily that abortion is indicated strongly if pregnancy occurs in a woman who is taking ribavirin/IFα or whose partner is being treated with these drugs. The label does not suggest counseling regarding the actual risks or available options.

A number of drugs that have been assigned a Pregnancy Category of X based on theoretical concerns or animal studies do not seem to be highly teratogenic in humans when taken in usual therapeutic doses. For example, lovastatin, a drug that inhibits cholesterol biosynthesis and is used to treat hyperlipidemia, has been classified as Pregnancy Category X because of theoretical concern that maternal treatment could interfere with essential cholesterol biosynthesis in the developing embryo. Normal infants, however, have been born to 39 of 44 women who took lovastatin during part or all of the first trimester in published cases and clinical series (Manson et al., 1996). Among the five infants reported with congenital anomalies, no recurrent pattern of malformations was evident (Ghidini et al., 1992; Rosa, 1994; Hayes et al., 1995; Manson et al., 1996).

Finasteride is another example of a drug that has been given a Pregnancy Category X because of its theoretical potential for teratogenicity. Finasteride, which inhibits conversion of testosterone to dihydrotestosterone, is given

orally to treat male pattern baldness. Finasteride also is used in larger doses to treat benign prostatic hypertrophy. Theoretical concern that administration of finasteride to a pregnant woman who is carrying a male fetus may interfere with development of the external genitalia and the lack of approved indications for treatment in women are the basis for the Category X classification of this drug (Uhl et al., 2002). Hypospadias and other anomalies of the external genitalia of male offspring have been observed after maternal treatment with finasteride in animal studies, but only at doses much higher than those used to treat baldness (Anderson and Clark, 1990; Clark et al., 1990; 1993; Imperato-McGinley et al., 1992; Hib and Ponzio, 1995; Prahalada et al., 1997). No nongenital congenital anomalies in either male or female offspring have been described in any of the animal studies.

The package labeling advises pregnant women or women wishing to become pregnant to avoid even touching crushed finasteride tablets. No published information is available regarding systemic absorption after the handling of crushed tablets, so it is not clear why pregnant women are given this precaution. Nevertheless, this warning implies that the drug is so toxic that mere skin contact and absorption of an infinitesimal dose will cause adverse effects to the embryo. No such precaution is given to pregnant women who might handle crushed tablets containing thalidomide or isotretinoin, drugs that are well known to be teratogenic in humans.

The philosophical basis for including a strong warning about developmental hazards in the label of a drug that has been found to have teratogenic potential in preclinical studies is that if treatment of pregnant women is avoided, the teratogenic potential will also be avoided. This can be seen as "erring on the side of caution." But whom does this label really protect? The embryo or the manufacturer? One can only wonder how many normal pregnancies are terminated unnecessarily because of these drastic and frightening warnings when inadvertent exposures occur. The cases reported by Bianca and Ettore (2003) and Hegenbarth et al. (2001) illustrate how significant an impact the developmental toxicity labeling can have on the management of exposed pregnancies. In many pregnancies, like the ones reported by these authors, the conditions of exposure are such that a teratogenic effect would be highly unlikely, even if the drug were known to be strongly teratogenic in human pregnancy.

The solution to this problem is not only better labeling, but also finding out what the actual teratogenic risk associated with human treatment with these drugs is. There are several well-validated scientific methods that can be used to study the outcomes of such pregnancies to establish the risks or safety of drug treatments (Edmonds, 1997; Erickson, 1997; Honein et al., 1999; National Research Council, 2000; Chambers et al., 2001; Kimmel, 2001). Women should not have to terminate wanted pregnancies because data on the teratogenic risks of approved prescription drugs have not been collected and analyzed systematically. Prescription drug labels should contain scientifically accurate, up-to-date, and balanced information regarding developmental toxicity. Women who are concerned about developmental risks associated with drug treatment should be directed to providers who can interpret this information in the context of an exposure that has occurred in a particular pregnancy.

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