Drug and Environmental Exposure Histories in Selective Patient Populations

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Drug histories and environmental exposures are an important part of all medical histories and are particularly significant in specific at-risk primary care patient populations such as obstetrical patients, primary care genetic referrals, and pediatric patients being evaluated in developmental centers. A review of genetic referrals made by primary care physicians to a satellite genetics clinic over a one-year period showed that 29 percent of all referrals had a significant history of single drug exposure, single environmental exposure, or multiple environmental and drug exposures. Drug and environmental exposures must be an important consideration in all at-risk groups.

There were approximately 1.5 billion prescriptions written in 1981.[1] This estimate does not include the use of over-the-counter medications, cigarette smoking, alcohol, illicit drugs, or home remedies. The number of new products is estimated to increase by over 500 drugs each year.[2] Previous studies of drug use by pregnant women have indicated an approximate average of three to four medications taken per pregnancy.[3-4] A significant number of women reportedly take 10 or more medications during pregnancy.[5-7] There is a great variety of medications administered to the pregnant woman, including iron preparations, topical ointments, antacids, antibiotics, vitamins, diuretics, antiemetics, and cold medications.[8-9]

Evaluation of the impact of prenatal exposure to potentially teratogenic agents may be com-

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Table 1. Categories for Prescription Drugs[13]

Category	Description
A	Controlled studies fail to demonstrate risk to fetus in first trimester; possibility of fetal harm appears to be remote
B	Animal studies indicate no risk to the fetus. There are no controlled human studies or animal studies to show any adverse effect on fetus; controlled studies in pregnant women fail to demonstrate risk to fetus
C	Animal studies have shown drug to have animal teratogenic or embryocidal effects; there are no controlled studies in women, or no studies in either animals or women
D	Positive evidence of human fetal risk; risks may outweigh benefits
X	Studies in animals or humans demonstrate fetal risk based on human experience, or both risks outweigh benefits

pounded by concomitant use of ethanol, illicit "street drugs," and cigarette smoking. The problems of incidental or occupational exposure to chemicals and pesticides and exposure to ionizing radiation are becoming an individual and public concern.[10-11]

In 1973, it was estimated that over 125,000 women were working in jobs that placed them at possible risk for exposure to potentially toxic or teratogenic compounds.[12] Today that number has sharply increased. Growing public awareness of human exposure to environmental hazards, previously regarded as benign, has made pregnant women more aware and concerned about such exposures.[11]

Physicians are taking increasingly more care in selecting medications for women of childbearing age, limiting their use, and reducing the possibility of significant drug interactions. In an effort to assess the benefit-to-risk ratios, the Food and Drug Administration has established five categories to indicate a drug's potential for causing birth defects.[13] The categories incorporate both human and animal data, including information on the level of risk to the fetus (Table 1).

Various adversive effects on the developing human fetus have been implicated in a wide variety of medications; however, only a few drugs have been identified in humans as strongly teratogenic.[4,8,9,14] Fortunately, most frequently prescribed drugs or self-administered drugs have not been clearly or consistently implicated as being teratogenic. Some of the adverse effects of drugs and environmental exposures are summarized in Table 2.

Table 2. Drugs and Environmental Exposure Reported to Have Adverse Effects on the Embryo, Fetus, and Neonate[5,14,15]

Oogenesis	Spermatogenesis	Fertilization-Implantation	Embryo	Fetus	Neonate: Birth	Neonate: Lactation
Hormones	Phenytoin	Hormones	Radiation	Tetracyclines	Vasopressin	Diazepam
X-radiation	Thalidomide	X-radiation	Methylmercury	Quinine	Salicylates	Lithium
	Methadone	Contraceptives (oral)	Diethylstilbestrol	Chloroquine	Vitamin K	Hexachlorobenzene
	Estrogen		Thalidomide	Goitrogens	Naphthalene	Methylmercury
			Phenytoin	Thiouracil	Ganglionic blockers	Sulfonamides
			Trimethadione	Teridax	Reserpine	Atropine
			Alcohol	Salicylates	Narcotics	Anticoagulants
			Warfarin	Heavy metals	Sedatives	Antithyroids
			Aminopterin	Antibiotics	Analgesics	Antimetabolites
			Estrogen	Smoking	Ammonium chloride	Cathartics
			Androgens		Cardiovascular drugs	Dihydrotachysterol
			Progestin			Iodides
			Aminoglutethimide			Narcotics
						Tetracyclines
						Metronidazole

Methods

The records of referrals to a satellite genetics clinic of a statewide genetics program at a community medical center (June 1, 1981 to June 30, 1982) were reviewed. The referrals were from primary care physicians, most often obstetrician–gynecologists, family physicians, and the city and county public health service. The genetics clinic was located in a 500-bed community medical center with a 34-bassinet nursery and a 15-bed level 2 neonatal unit. The referrals were from a region

extending about 30 miles from the medical center. The referral area had a population of approximately 275,000 with the hospitals in the area delivering approximately 3,700 newborns each year.

In reviewing the records, any significant drug or environmental exposure history was recorded, noting pregnancy status, type of exposure and frequency of exposure. Significant exposure to medications was defined as including prescription categories C, D, and X as outlined in Table 1.

Results

Of the 137 cases referred over a 12-month period, 40 (29 percent) had a significant history for drug or environmental exposure. Furthermore, it was noted that for 15 of these cases, there was no, or minimal, concern regarding drug or environmental exposure at the time the initial history was taken by the referring physician. Exposure in these cases was determined during the course of further evaluation.

Of the 40 cases with drug or environmental exposure, there were 38 maternal exposures. The maternal exposures were for "street drugs," x-ray exposure, over-the-counter and prescription medications, alcohol, cigarette smoking, and chemical exposures. There was one case of a pregnant woman receiving rubella vaccine. The paternal exposures were for agent orange and x-ray exposure. There were multiple drug exposures in over one half of the 40 cases. The data are summarized in Table 3.

The spectrum of medications noted in Table 3 was similar to that reported in other studies.[8-9] Prenatal vitamins and iron supplements were not recorded as "drugs" in reviewing the records. The majority of reported drugs were prescription medications (approximately 40 percent), primarily antibiotics, analgesics, and antianxiety medications. "Street drugs" were the next most common exposure recorded (approximately 13 percent).

Table 3. Drug and Environmental Exposures

Exposure	Female	Male	Total
Prescription drugs	25	—	25
Over-the-counter medications	4	—	4
Street drugs	8	—	8
Cigarette smoking	6	—	6
Alcohol	6	—	6
Chemical	4	3*	7
X-ray	5	1	6
Other	1**	—	1
Total	59	4	63

*Agent orange
**Rubella vaccine

Discussion

Often the potential for teratogenic and toxic effects overshadows other aspects of drug exposure, such as alterations of fetal and neonatal brain function, neonatal withdrawal, and adverse effects on fetal growth. Lithium carbonate, a drug commonly used in treating manic depression, is a case in point.

Lithium carbonate is felt to be a factor in increasing the incidence of congenital heart disease (tricuspid atresia) when taken during early pregnancy.[15] This drug also causes neurologic depression, cyanosis, and cardiac arrythmias when taken prior to delivery.[15]

No medication consumed during pregnancy is completely safe. By the judicious selection of medication, however, drug-associated birth defects or fetal complications may be avoided. Drug use should also be a consideration in the breast-feeding mother. Although reduction or elimination of over-the-counter medications, street drugs, alcohol, cigarette smoking, and x-ray exposure must be considered an individual patient's decision, education of the patient by the medical community is an important part of the decision-making process. In addition, radiation and chemical exposures are areas of increasing public concern where appropriate preventive measures may decrease or eliminate exposure.

Although drug history and chemical or occupational exposures are a consideration in the history of all patients, they are especially important as an

Table 4. Information Centers in the United States

California Teratology Registry
Department of Pediatrics
T0083
University of California School of Medicine
La Jolla, CA 92093
(619) 294-3584

Environmental Mutagen, Carcinogen and Teratogen Information Department
Oak Ridge National Laboratory
PO Box Y
Oak Ridge, TN 37830
(615) 574-0603

Environmental Teratology Information Center
PO Box 12233
National Institute of Environmental Health Sciences (NIEHS)
Maildrop 18-01
Research Triangle Park, NC 27709
(919) 541-3418

Teratology Service Program
Department of Pediatrics
Division of Medical Genetics
UMDNJ-Rutgers Medical School
CN-19
Academic Health Science Center
New Brunswick, NJ 08903
(201) 937-7889

Pregnancy Hotline
Pennsylvania Hospital
8th and Spruce Street
Philadelphia, PA 19107
(215) 829-Kids

integral part of the histories of all at-risk populations. Most at risk are obstetrical patients, pediatric patients being evaluated in developmental centers, and those referred for genetic counseling and evaluation. Consulting and informational services on environmental and occupational exposures, toxicology, and teratology should be available on a statewide basis or regional basis to genetic, obstetrical, and occupational medicine services as well as to pediatric centers and primary care physicians. There are at present few such informational services (Table 4).

While the amount of information on specific drugs and environmental agents continues to expand, there is little information on multiple-agent exposures. In this study, multiple-agent exposures were seen in over one half of the cases. Collaborative data bases will be needed to provide such information. There is increasing individual and public awareness of the hazards of certain environmental agents and of the use of certain drugs in pregnancy. Medico-legal concerns, teratology research, and collaborative clinical studies will accelerate this process.

References

1. Prescription data reported. American Medical News, January 1983, p 18
2. Fact Book. Washington, DC, Pharmaceutical Manufacturers Association, 1973
3. Nora JJ, Nora AH, Somerville RJ, et al: Maternal exposure to potential teratogens. JAMA 1967; 202(12): 1065-1069
4. Goldman AS: Drugs and pregnancy. In Yaffe SJ (ed): Pediatric Pharmacology. New York, Grune & Stratton, 1980, pp 101-118
5. Bleyer WA, An WY, Lange WA, Raisz LG: Studies on the detection of adverse drug reactions in the newborn. I. Fetal exposure to maternal medication. JAMA 1970; 213: 2046-2048
6. Hill RM: Drugs ingested by the pregnant woman. Clin Pharmacol Ther 1973; 14:654-659
7. Peckham CH, King RW: A study of intercurrent conditions observed in pregnancy. Am J Obstet Gynecol 1963; 87:609-624
8. Schardein JL: Drugs as Teratogens. Boca Raton, Fl, CRC Press, 1976
9. Redmond GP: Fetal Drug Effects. In Yaffe SJ (ed): A Physiological Perspective in Pediatric Pharmacology. New York, Grune & Stratton, 1980, pp 119-135
10. Chemical and Radiation Hazards to Children. 84th Ross Conference on Pediatric Research, November, 1982. Columbus, Ohio, Ross Laboratories, 1982
11. Finding teratogens, assessing risk is no insurmountable task. Pediatr News 1982; 16(10):38
12. Yager JW: Congenital malformations and environmental influence: The occupation environment of laboratory workers. J Occup Med 1973; 15:724-728
13. Pregnancy categories for prescription drugs. FDA Drug Bull 1982; 112(3):24-25
14. Goldman AS: Critical periods of prenatal toxicity. Symposium on fetal disease. Clin Perinatol 1979; 6(2): 203-218
15. Kalter H, Warkany J: Congenital malformation—Etiologic factors and their role in prevention, part I. New Engl J Med 1983; 308:424-431
16. Arnon RG, Marin-Garcia J, Peeden JN: Tricuspid valve regurgitation and lithium carbonate toxicity in a newborn infant. Am J Dis Child 1981; 135:941-943