Review Article

Drug Therapy

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DRUGS IN PREGNANCY

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BEFORE marketing a new drug, the manufacturer almost never tests the product in pregnant women to determine its effects on the fetus. Consequently, most drugs are not labeled for use during pregnancy. Typically, descriptions of drugs that appear in the *Physicians' Desk Reference* and similar sources contain statements such as, "Use in pregnancy is not recommended unless the potential benefits justify the potential risks to the fetus." Since the risk has been adequately established for only a few drugs, physicians caring for pregnant women have very little information to help them decide whether the potential benefits to the mother outweigh the risks to the fetus. These typical disclaimers, although understandable from the medicolegal standpoint, put large numbers of women and their physicians in difficult situations for several reasons. One is that at least half the pregnancies in North America are unplanned,[1] and every year, hundreds of thousands of women therefore expose their fetuses to drugs before they know they are pregnant. Such women often interpret the statement that use during pregnancy is not recommended as meaning that the drug is not safe during pregnancy. There is evidence that this perception of fetal risk causes many women to consider or even seek termination of otherwise wanted pregnancies.[2,3] Another reason is that with the recent increase in the age at which women have children, conditions that necessitate long-term drug therapy are diagnosed in larger numbers of women before pregnancy. Furthermore, for pregnant women with certain conditions once believed to be incompatible with pregnancy, such as systemic lupus erythematosus and heart diseases, the outcome of pregnancy has improved dramatically in the past few decades.[4]

In this article, we review current knowledge of the fetal and neonatal effects of prescription and over-the-counter drugs given to pregnant women, with an emphasis on the approaches used to determine safety and risk. In addition, we review approaches to communicating such information to pregnant women and their families.

HUMAN TERATOGENESIS

Teratogenesis is defined as the dysgenesis of fetal organs as evidenced either structurally or functionally (e.g., brain functions).[5] The typical manifestations of teratogenesis are restricted growth or death of the fetus, carcinogenesis, and malformations,[6] defined as defects in organ structure or function. These abnormalities vary in severity (e.g., hypospadias that is mild and may be missed, or is severe, necessitating several corrective operations). Major malformations may be life-threatening and require major surgery or may have serious cosmetic or functional effects.

A HISTORICAL PERSPECTIVE

Several milestones highlight the problems of drug therapy facing pregnant women, their families, and health professionals.

Thalidomide

For decades it was believed that the placenta served as a barrier that protected the fetus from the adverse effects of drugs. The thalidomide disaster drastically changed this perception by demonstrating that fetal exposure to the drug during critical periods of development resulted in severe limb defects and other organ dysgenesis (e.g., kidney and heart defects).[6,7] Despite the high rates of malformations (20 to 30 percent) and their characteristic pattern, the teratogenicity of thalidomide was not suspected for years. The suffering it caused has prompted the belief that every drug has the potential to be a new thalidomide.[2,3]

Most known human teratogens are associated with much lower rates of malformations, and the syndromes they cause are not always so pathognomonic, making causation more difficult to confirm. Yet 35 years after the recognition of thalidomide-associated embryopathy, fewer than 30 drugs have been proved to be teratogenic in humans when used

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in clinically effective doses, and even fewer are currently in clinical use (Table 1). Many other commonly used drugs, including salicylates, glucocorticoids, and spermicides, were once thought to be teratogenic but have been shown to be safe in subsequent studies that were larger and better controlled than the initial studies (Table 2).

Bendectin

One example of the gap between the perception of teratogenic risk and evidence-based proof of safety is the case of Bendectin. During the late 1950s and the 1960s, this drug, a combination of an antihistamine (doxylamine) and pyridoxine, was the most widely used medication in the United States for nausea and vomiting associated with pregnancy. During the 1970s, many lawsuits claiming that Bendectin was teratogenic were filed against the manufacturer in American courts. Therefore, the drug was withdrawn from the market by its manufacturer in 1982, which left millions of pregnant women without a drug approved by the Food and Drug Administration (FDA) for the treatment of nausea and vomiting. The rate of hospitalization for severe nausea and vomiting during pregnancy increased by a factor of 2 in both the United States and Canada after Bendectin was withdrawn from the market (Fig. 1).

The drug was withdrawn despite a substantial body of evidence that the rate of major malformations among the children of women who had received Bendectin during pregnancy did not differ from the rate in the general population.[24,25] Withdrawal of the drug from the American market did not decrease the rate of any specific category of malformation, as would be expected for a truly teratogenic drug estimated to have been used by up to 40 percent of pregnant women at one time.[26,27]

In Canada, the drug continues to be marketed under the trade name Diclectin. A review committee has advised the Canadian Minister of Health that the drug is safe.[27] A recent study revealed that severe nausea and vomiting of pregnancy often lead women to terminate or consider the termination of otherwise wanted pregnancies.[28] Other formulations of dox-

TABLE 1. DRUGS WITH PROVEN TERATOGENIC EFFECTS IN HUMANS.*

DRUG	TERATOGENIC EFFECT
Aminopterin†, methotrexate	CNS and limb malformations
Angiotensin-converting–enzyme inhibitors	Prolonged renal failure in neonates, decreased skull ossification, renal tubular dysgenesis
Anticholinergic drugs	Neonatal meconium ileus
Antithyroid drugs (propylthiouracil and methimazole)	Fetal and neonatal goiter and hypothyroidism, aplasia cutis (with methimazole)
Carbamazepine	Neural-tube defects
Cyclophosphamide	CNS malformations, secondary cancer
Danazol and other androgenic drugs	Masculinization of female fetuses
Diethylstilbestrol†	Vaginal carcinoma and other genitourinary defects in female and male offspring
Hypoglycemic drugs	Neonatal hypoglycemia
Lithium	Ebstein's anomaly
Misoprostol	Moebius sequence
Nonsteroidal antiinflammatory drugs	Constriction of the ductus arteriosus‡, necrotizing enterocolitis
Paramethadione†	Facial and CNS defects
Phenytoin	Growth retardation, CNS deficits
Psychoactive drugs (e.g., barbiturates, opioids, and benzodiazepines)	Neonatal withdrawal syndrome when drug is taken in late pregnancy
Systemic retinoids (isotretinoin and etretinate)	CNS, craniofacial, cardiovascular, and other defects
Tetracycline	Anomalies of teeth and bone
Thalidomide	Limb-shortening defects, internal-organ defects
Trimethadione†	Facial and CNS defects
Valproic acid	Neural-tube defects
Warfarin	Skeletal and CNS defects, Dandy–Walker syndrome

*Only drugs that are teratogenic when used at clinically recommended doses are listed. The list includes all drugs proved to affect neonatal morphology or brain development and some of the toxic manifestations predicted on the basis of the pharmacologic actions of the drugs. Data are from Briggs et al.[8] CNS denotes central nervous system.

†The drug is not currently in clinical use.

‡Sulindac probably does not have this effect.

Table 2. Common Drugs Initially Thought to Be Teratogenic but Subsequently Proved Safe.

Drug	Initial Evidence of Risk	Subsequent Evidence of Safety
Diazepam*	Oral clefts[9]	No increase in risk in large cohort and case–control studies[10-12]
Oral contraceptives	Birth defects involving the vertebrae, anus, heart, trachea, esophagus, kidney, and limbs[13]; masculinizing effects on female fetuses resulting in pseudohermaphroditism[14]	No association between first-trimester exposure to oral contraceptives and malformations in general or external genital malformations in two meta-analyses[15,16]
Spermicides	Limb defects, tumors, Down's syndrome, and hypospadias[17]	No increase in risk in a meta-analysis[18]
Salicylates	Cleft palate[19] and congenital heart disease	No increase in risk in large cohort studies[20,21]
Bendectin (doxylamine plus pyridoxine)	Cardiac and limb defects[22,23]	No increase in risk in two meta-analyses[24,25]

*Diazepam taken near term may cause the neonatal withdrawal syndrome or cardiorespiratory instability.

ylamine in combination with pyridoxine are available in other countries (e.g., South Africa, Spain, and Thailand).

Isotretinoin

The experience with thalidomide led drug regulators, drug manufacturers, and the medical community to believe that appropriate labeling of teratogenic drugs, with warnings not to take them around the time of conception, would be effective in preventing fetal exposure to the drugs. The naiveté of this belief became evident after isotretinoin was introduced in North America in the early 1980s for the treatment of acne. For years before its clinical introduction, this drug had been known to cause malformations in animals.[29] Despite explicit warning labels, scores of children with retinoid embryopathy were born in the years after the drug was introduced.[30] Such warnings are not sufficient, because women taking isotretinoin may not plan their pregnancies, or their birth-control methods may fail. In addition, some women and men are functionally illiterate, and they may not read or understand the content of a drug label.[31]

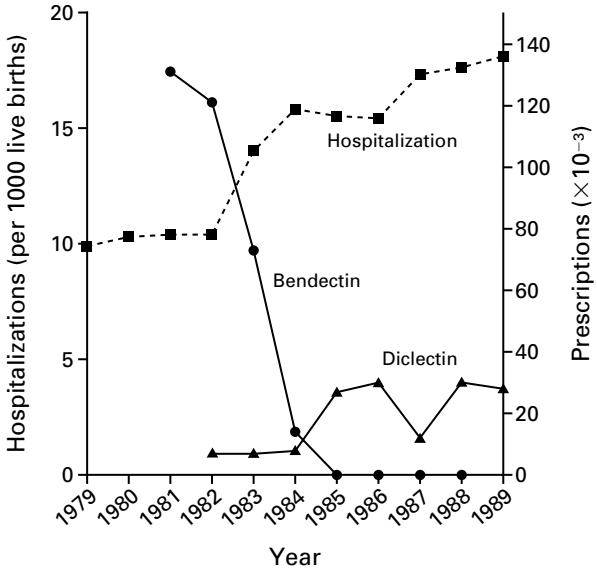

Figure 1. Rates of Hospitalization among Pregnant Women with Severe Nausea and Vomiting and Numbers of Prescriptions for Bendectin and Diclectin in North America, 1979 through 1989.

Bendectin was withdrawn from the U.S. market in 1982, whereas Diclectin, the same drug, remained on the market in Canada. Adapted from Neutel and Johansen with the permission of the publisher.[26]

The initial experience with isotretinoin led to the development of a more comprehensive program to prevent teratogenesis. The Retinoid Pregnancy Prevention Program includes explicit and detailed printed warnings as well as a line drawing of a malformed child,[32] and as part of the program, women are asked to sign a consent form indicating that they agree to use two effective methods of contraception before therapy is started. Since the program was implemented in 1989, a substantial number of fetuses have been exposed to the drug. As many as 30 percent of the women with exposed fetuses did not use any mode of contraception, even though they were cognizant of the high fetal risk.[32] Many of these women explained that they did not believe they were fertile, since they had not conceived during periods of months or years when they had not used contraceptive methods.[33]

CURRENT TRENDS IN PREVENTING FETAL EXPOSURE TO TERATOGENS

The advent of effective injectable hormonal contraceptives has made it possible to minimize the risk of an unplanned pregnancy during therapy with a known teratogen. This approach was first implemented in South America, where sexually active women with cutaneous leprosy were injected with medroxy-

progesterone before receiving a prescription for thalidomide.[34] Yet numerous new cases of thalidomide-associated embryopathy have been reported in the children of women who continued to take the drug after the period of contraceptive efficacy (three months) or who received the drug from their male partners.[34]

Because any new drug may be teratogenic, it is important to develop more effective methods to prevent fetal exposure. One such method may be the use of implantable hormonal compounds (e.g., levonorgestrel implants), which can provide long-term, reversible contraception for up to five years. Levonorgestrel implants have documented efficacy in young women in whom oral methods of contraception are likely to fail.[35] Implants should be considered by sexually active women who are taking a teratogen medicinally (e.g., phenytoin or warfarin) or as part of a pattern of substance abuse (e.g., alcohol or cocaine). Furthermore, women taking teratogenic drugs who are not sexually active should be informed of the availability of effective postcoital contraceptives.[35,36]

THE PROCESS OF ESTABLISHING RISK OR SAFETY OF DRUGS IN PREGNANCY

Every year, many new drugs are approved and marketed. By this stage, several thousand people have usually participated in studies of the drugs, but the majority have been men. Since there are scarcely any data on fetal effects at the time of marketing, data from studies in animals provide the initial guidelines.

The Value of Studies in Animals

Typically, studies of reproductive toxicology in animals compare the outcome of pregnancy in groups of animals receiving a range of doses of the drug in question during the period of organogenesis with the outcome in untreated (control) animals. The occurrence of thalidomide-associated embryopathy led to the erroneous belief that human teratogenicity could not be predicted on the basis of studies in animals. However, every drug that has since been found to be teratogenic in humans has caused similar teratogenic effects in animals (Table 3), except misoprostol, which causes a morphologic pattern known as the Moebius sequence in humans. In at least one case, that of isotretinoin, the studies in animals probably prevented a disaster similar to that of thalidomide.[29]

However, there are drugs that have teratogenic effects in animals when administered in high doses that are not teratogenic in humans given clinically relevant doses. For example, high doses of glucocorticoids[19,70-75] or benzodiazepines[76,77] can cause oral clefts in animals, but clinically relevant doses in humans have no such effects.[10-12,75] Similarly, salicylates[78-80] cause cardiac malformations in animals but not in humans.[20,21] Such discrepancies have led to unwarranted anxiety on the part of women, their families, and physicians and may have contributed to unnecessary terminations of pregnancies.[3] Although studies in animals may identify teratogenic effects, it can be difficult to extrapolate these effects to humans.

Epidemiologic Studies

In addition to studies in animals, a variety of other approaches are used to identify possible drug teratogenicity and to assess the relation between drug exposure and fetal outcome. The first accounts of adverse fetal outcomes after exposure to a marketed drug are usually published in the form of case reports. These reports can be either very useful or useless in establishing teratogenic risk on the basis of relatively simple statistical considerations. If the drug in question is taken by relatively small numbers of women (e.g., isotretinoin[30]) or causes a rare malformation (e.g., ear agenesis[81]), then a small number of cases can establish a strong association. Warfarin,[9] diethylstilbestrol,[82] and isotretinoin[83] were originally identified as human teratogens on the basis of case reports. If, on the other hand, the drug is taken by many pregnant women (e.g., Bendectin), a small number of case reports of abnormalities may simply reflect the spontaneous occurrence of malformations in the general population, which ranges from 1 to 5 percent, unless there is a characteristic pattern of malformations (as, for example, with alcohol or thalidomide). To date, prenatal exposure to many of the known human teratogens has been associated with characteristic patterns of malformations, and this has become an important tenet in establishing teratogenicity.

Epidemiologic studies are typically designed to determine whether mothers who took a specific drug during pregnancy have a larger number of malformed children than mothers who did not (cohort studies) or whether mothers of children with a specific malformation took the drug more often than mothers of children without the malformation (case–control studies).

With the international development of teratology-information services,[84] a new source of data for prospective observational research has emerged. Pregnant women taking prescription or over-the-counter drugs voluntarily call these centers for risk-assessment counseling, usually during the first trimester. Since the exposure data are recorded prospectively, the probability of recall bias is reduced, and follow-up of exposed pregnancies can extend well beyond parturition. Collaboration among these services can yield the large samples needed to study rare events more effectively.[53,61,85]

Drug manufacturers may perform postmarketing cohort studies of prospectively reported exposures.

Table 3. Teratogenic Effects of Drugs in Animals and Humans.*

Drug	Effects in Animals	Effects in Humans
Angiotensin-converting–enzyme inhibitors	Stillbirths and increased fetal loss in sheep and rabbits[37]	Prolonged renal failure and hypotension in the newborn, decreased skull ossification, hypocalvaria, and renal tubular dysgenesis[38]
Carbamazepine	Cleft palate, dilated cerebral ventricles, and growth retardation in mice[39]	Neural-tube defects[40]
Cocaine	Dose-dependent decrease in uterine blood flow, fetal hypoxemia, hypertension, and tachycardia in sheep[41]; reduced fetal weight, fetal edema, and increased resorption in rats and mice[42]	Growth retardation involving weight, length, and head circumference[43]; placental abruption[44,45] and uterine rupture
Ethanol	Microcephaly, growth deficiency, and limb anomalies in dogs, chickens, and mice[46-48]	Fetal alcohol syndrome: prenatal and postnatal growth deficiency, CNS anomalies (microcephaly, behavioral abnormalities, and mental retardation), characteristic pattern of facial features (short palpebral fissures, hypoplastic philtrum, and flattened maxilla), and major organ-system malformations[49]; with age, facial features may become less distinctive, but short stature, microcephaly, and behavioral abnormalities persist[50]
Isotretinoin	CNS, head, limb, and cardiovascular defects in rats and rabbits[29]	Retinoid embryopathy resulting in some or all of the following abnormalities[30]: CNS defects (hydrocephalus, optic-nerve blindness, retinal defects, microphthalmia, posterior fossa defects, and cortical and cerebellar defects); craniofacial defects (microtia or anotia, low-set ears, hypertelorism, depressed nasal bridge, microcephaly, micrognathia, and agenesis or stenosis of external ear canals); cardiovascular defects (transposition of great vessels, tetralogy of Fallot, and ventricular or atrial septal defects); thymic defects (ectopia and hypoplasia or aplasia); and miscellaneous defects (limb reduction, decreased muscle tone, spontaneous abortion, and behavioral abnormalities)
Lithium	Heart defects in rats[51]	Ebstein's anomaly and other heart defects[52,53]
Methyl mercury	CNS abnormalities in rats[54]; growth retardation, motor disturbances, microencephaly, and brain lesions in rhesus monkeys[55]	Fetal Minamata disease: diffuse neuronal disintegration with gliosis, cerebral palsy, microcephaly, strabismus, blindness, speech disorders, motor impairment, abnormal reflexes, and mental retardation[56]
Phenytoin	Cleft palate, micromelia, renal defects, and hydrocephalus in rabbits, mice, and rats[57-59]	Fetal hydantoin syndrome[60]: prenatal and postnatal growth deficiency, motor or mental deficiency, short nose with broad nasal bridge, microcephaly, hypertelorism, strabismus, epicanthus, wide fontanelles, low-set or abnormally formed ears, positional deformities of limbs, hypoplasia of nails and distal phalanges, hypospadias, hernia, webbed neck, low hairline, impaired neurodevelopment and low performance scores on tests of intelligence[61]
Thalidomide†	Limb-shortening defects in rabbits (most sensitive species)[62]	Limb-shortening defects,[63] loss of hearing, abducens paralysis, facial paralysis, anotia, microtia, renal malformations, congenital heart disease
Valproic acid	Exencephaly in hamsters and mice[64,65]	Neural-tube defects[66,67]
Warfarin†	Maxillonasal hypoplasia and skeletal anomalies in rats[68]	Fetal warfarin syndrome: skeletal defects (nasal hypoplasia and stippled epiphyses), limb hypoplasia (particularly in distal digits), low birth weight (<10th percentile), hearing loss, and ophthalmic anomalies[69]; CNS defects with exposure after first trimester; dorsal midline dysplasia (agenesis of corpus callosum and Dandy–Walker malformations) or ventral midline dysplasia (optic atrophy)[6]

*CNS denotes central nervous system.

†Initial studies in animals failed to show teratogenicity; hence, documentation in humans preceded that in animals.

Such studies were useful in establishing the safety and risk of Bendectin, isotretinoin, fluoxetine, and acyclovir.[30,86]

Because most studies of teratogenic risk are limited in size, meta-analyses of studies of similar design are becoming more frequent. A detailed, stepwise methodologic approach to meta-analysis of teratologic studies has been described.[24] The appropriate use of this approach depends to a large extent on establishing sound a priori criteria for methodologic quality and ensuring the inclusion of data from all available studies, in order to obviate any publication bias against negative results.

Long-term studies are increasingly important, because it is becoming clear that the long-term effects of teratogenic drugs on neurobehavioral development can have a more devastating effect on children and their families than structural anomalies. To date, several drugs have been shown to affect brain development, including carbamazepine, isotretinoin, phenytoin, valproic acid, and warfarin (Table 1). Carbamazepine and valproic acid may cause cognitive brain dysfunction as part of the neural-tube defects they induce. Originally, isotretinoin was found to cause structural abnormalities that affected brain development, but recent studies have suggested that even phenotypically normal children may have abnormal neurodevelopment.[87] Warfarin was initially associated with chondrodysplasia punctata and mental retardation and has subsequently been found to cause the Dandy–Walker brain malformation in an estimated 1 to 2 percent of exposed fetuses.[6,69]

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