Drug Therapy in Pregnancy and Lactation

Bruce M. Frey and James O'Donnell

The use of drugs in pregnant and lactating women requires a thorough understanding of the unique interactions between the mother, fetus/infant, and the pharmacologic agents that are used in therapy. Any agent that is consumed by a woman may have adverse effects on the fetus/infant. This article will summarize those factors that should be considered. There exists a paucity of data and information for most drugs relative to pregnancy and lactation. Conclusions that can be drawn remain speculative, and the use of any drug during pregnancy and lactation requires extreme caution. Factors involved in fetal drug exposure include the dynamic changes of maternal physiology related to drug absorption, distribution, metabolism, and excretion. Placental transfer of drug occurs with almost all agents, each to varying degrees. The notion that the placenta provides an impervious barrier must be dismissed. The least understood of factors involving potential fetal harm is teratogenicity. The mechanisms and types of teratogenic agents, poorly understood in humans, is discussed. Most drugs appear in the breast milk and, therefore, carry some degree of potential harm. Minimizing exposure is a goal that can be obtained when taking into account the maternal physiology, basic pharmacokinetic factors, physiochemical interactions between drug and membranes, and the chemical composition of breast milk.

> Even if a woman transgresses some or all of the rules mentioned (re: administration of drugs, sternutatives, pungent substances, and drunkenness, especially during the first trimester) and yet miscarriage of the fetus does not take place, let no one assume that the fetus has not been injured at all. For it has been harmed: it is weakened, becomes retarded in growth, less well nourished and in general, more easily injured and susceptible to harmful agents; it becomes misshapen and of ignoble soul—Soranus, 2nd century.[40]

DRUG EXPOSURE IN PREGNANCY

TWO POPULATIONS OF women exist at risk for drug exposure to their conceptus: those known to be pregnant, and those women who are of reproductive age who become pregnant and are exposed without knowing that pregnancy has initiated. It has been estimated that 15% to 20% of patients were on a drug within the 6 months before the pregnancy and within the first trimester. Some reports describe seven to eight drug exposures in an average pregnancy. Golbus reports that pregnant women take an average of four drugs, excluding vitamins, and 40% of these women take the drugs during the critical period of human development.[1] These exposures include prescription drugs from physicians, over-the-counter (OTC) drugs for self treatment, and recreational drugs including nicotine (tobacco) and alcohol, as well as illegal drugs. All of these substances will enter the maternal circulation, cross the placenta, and with very few exceptions enter the circulation of the developing fetus. Most of the drugs penetrate the placenta poorly and exert minimal effects; however, some agents may produce congenital malformations or other toxic effects on the fetus, even in minute concentration.

Some teratogens cause embryonic or fetal death, ie, abortion. Others, eg, diethylstilbestrol (DES) will not demonstrate their toxicity until seen in progeny (daughters of mothers given DES developing clear cell adenocarcinoma of the cervix).

In order to understand the complexity of maternal drug ingestion, maternal pharmacokinetics, placental transfer, and teratogenicity will be examined.

Maternal Pharmacokinetics

Profound changes occur in maternal physiology during pregnancy, which in turn influence the absorption, distribution, metabolism, and excretion of drugs. These changes are not static, but are dynamic and change constantly during the various stages of pregnancy. Gastrointestinal (GI) effects of nausea and vomiting will affect the ability to ingest and the availability of drugs. Delay in gastric emptying, as well as increased transit time and decreased motility and tone of the gut, may slow absorption and possibly in-

From the Department of Pharmacy, Thomas Jefferson University Hospital, Philadelphia; and the Department of Pharmacy, Rush Presbyterian-St Luke's Medical Center, Chicago, respectively.

Address reprint requests to Bruce M. Frey, PharmD, Department of Pharmacy, Thomas Jefferson University Hospital, Philadelphia, PA 19107.

0897-1900-89/0104-0002$5.00/0

crease the total amount of drug absorbed. Decreased acid secretion during the first two trimesters will alter the absorption of drugs that require an acid milieu, or are absorbed in the small intestine.[2] No significant literature reports any significant effects related to altered GI physiology.

Changes in distribution occur due to an increase in plasma volume (intracellular and intravascular), thus affecting the drug's volume of distribution. This increase in volume of distribution may require an increase in dosage of a particular therapeutic agent. Despite an increase in production of serum albumin, the increased intracellular and intravascular volume allow serum albumin levels to decline[3,4] thus increasing the availability of potentially significant amounts of free unbound drug for those with significant protein binding. Concurrent protein wasting syndromes of malnutrition may further aggravate the situation. Also, the increase of circulating hormones that occur in pregnancy may increase or decrease the hepatic metabolism of a drug by either induction or inhibition of the hepatic microsomes.[4]

Cardiac output increases dramatically to levels 40% larger than normal in pregnancy. This increase results in an equally dramatic rise in renal blood flow of 30% to 35%, which in turn causes a similar increase in the glomerular filtration rate (GFR) and creatinine clearance.[4] Drugs that use this route for elimination (renal) will be more rapidly excreted than in the normal adult, possibly requiring an increased dosage and/or frequency. Few drugs have information available regarding alterations in kinetics secondary to maternal physiological changes. For those agents that are considered medical necessities to continue treatment during pregnancy (ie, anticonvulsants, antibiotics), frequent serum level monitoring becomes even more important. Considering the changes in serum protein, effects on protein binding are accentuated for highly bound agents, and free-drug levels are recommended as being a more accurate indicator of drug levels.

Placental Transfer

Placental transfer of drugs and other substances occur to varying degrees. The notion that the placenta provides an impervious barrier to these substances must be dismissed. Until the 1940s, it was generally believed that human embryos were protected from environmental agents, such as drugs and viruses, by their fetal membranes and their mothers' abdominal walls and uteri. In 1941 Gregg[5] presented the first well documented evidence that an environmental agent (rubella virus) could produce severe congenital abnormalities if present during the critical stages of human development. However, it was the observations of Lenz and McBride in 1961 that focused attention on the roles of drugs in the etiology of human congenital malformation.[6,7] They described the severe limb and other malformations caused by the use of thalidomide during early pregnancy. As the physiology of the mother changes, so do the degree and nature of placental transfer. The impact of this transfer is

The notion that the placenta provides an impervious barrier to these substances must be dismissed.

poorly understood at this time in relation to not only the short- but also the long-term effects of fetal drug exposure as well.

The mechanism by which most drugs cross the placental membrane is by simple diffusion. Fetal concentrations may reach 50% to 100% of maternal levels for most drugs with some drugs obtaining fetal levels in excess of the maternal levels.[8] The factors affecting the degree of diffusion are molecular weight, ionization, protein binding, lipid solubility, umbilical and uterine blood flow, and the concurrent physiologic status of the mother (Table 1).

Low molecular weight drugs (below 1,000) readily diffuse across the placenta, while large molecular weight drugs do not readily cross. Heparin, a very high molecular weight glucose polymer, does not cross the placenta. For practical purposes, one should expect that any drug given to the mother will cross the placenta and expose the fetus. The lipid solubility of a drug will affect the rate of transfer of a nonionized molecule. Depending on the drug's ionization status in relation to a drug's chemical properties

Table 1. Factors Facilitating Placental Transfer

Low molecular weight <1,000
Nonionized drugs
Degree of protein binding
Lipophilicity
Increased uteroplacental blood flow
Physiologic status of the mother

and the pH of the physiologic solutions, a drug molecule may cross slowly if ionized, but rapidly if nonionized. Placental transfer of drugs that are highly protein bound is decreased due to the small free fraction of drug available, and lack of active mechanisms of the placenta to remove drugs from serum protein. In addition, maternal disease states may affect placental permeability and increase or decrease drug transfer.

A change in umbilical blood flow can have profound effect on the rate of placental transfer of drugs. This blood flow may be altered by maternal BP, maternal disease states, maternal drug therapy, cord compression, and uterine status. Exogenous (such as drugs) or endogenous (such as stress/distress) stimulation of α-adrenergic receptors can reduce blood flow by constriction of uterine blood vessels.

TERATOGENICITY

Teratology is the study of abnormal development of embryos and the causes of congenital malformations. Congenital malformations are anatomical or structural abnormalities that are present at birth, although they may not be diagnosed until later. They may be macroscopic or microscopic, on the surface or within the body. Congenital malformations result from defective embryogenesis (production of embryo).[9] A fundamental concept in teratology is that certain stages of embryonic development are more vulnerable than others.[10] It is now estimated that 7% of human developmental abnormalities result from the actions of drugs, viruses (see Table 2), and other environmental factors.[11] Brent estimates that less than 2% of congenital malformations are caused by drugs and chemicals.[12] Causes of congenital malformations are listed in Table 2 (estimated incidence of causes of major congenital malformations). The teratogenic effects of drugs traditionally have been reported as congenital or anatomic malformation. However, it is now clear that drugs can exert other effects, such as disturbances in growth, intellectual development, and possible long-term risk of carcinogenesis and mutagenesis. The mechanism of teratogenicity is poorly understood. Drugs may directly effect the embryonic or fetal cells or affect the mother, resulting in indirect effects upon the embryo or fetus. Drugs may alter the flow of nutritional substrates with a resultant disturbance of fetal growth.[2] Teratogenic risk is related to the drug, the dosage, duration of therapy, and relation to the stage of fetal development. Fetal risk is greatest during the first three months of gestation, but is possible for drugs to exert their effects on the fetus throughout pregnancy. Most anatomic malformations occur during the embryonic stage (two to eight weeks). During the fetal stage, teratogenic effects will involve minor anatomical defects, but will more likely result in impairment of physical and intellectual growth.[2]

Table 2. Estimated Incidence of Causes of Major Congenital Malformations

Cause	Incidence (%)
Chromosomal aberrations	6
Environmental factors (includes drugs)	7
Monogenic or single gene defects	8
Multifactorial inheritance	25
Unknown etiology	54

Drugs vary considerably in their teratogenicity. Some cause severe malformations if administered during the organogenetic period (eg, thalidomide); other socially used drugs produce mental and growth retardation if used excessively throughout development (eg, alcohol). In the 20 years since fetal alcohol syndrome was first described, it has been well established that heavy drinking during pregnancy can cause mental retardation, malformations including cardiac defects, joint contractures, and microphthalmia. Nonetheless, over the past decade several studies designed to clarify the impact of alcohol consumption on fetal development have reached differing conclusions about whether light drinking adversely affects birth weight, rates of spontaneous abortion and stillbirth, and neonatal behavior. Whether there's a safe level of drinking for pregnant women is still disputed. One recent attempt to answer this question comes from Sulaiman et al.[13] They describe a survey of over 900 women taken during their first pregnancies. More than 90% of these women said that they

had been drinking before they discovered they were pregnant, and 20% had been consuming ten or more drinks per week. Heavy drinking (>12 drinks per week) during the first 4 months of pregnancy was associated with shorter gestational age and lower five-minute Apgar scores, findings consistent with those from similar studies. However, the authors conclude that "there was no detectable effect on pregnancy of alcohol consumption below 100 g alcohol (ten drinks)/week" and that "social drinking at a low level is very unlikely to have a harmful effect on the fetus" (p 1503). A much larger study, published last year in *Pediatrics,* drew a more conservative conclusion. Mills and Graubard of the National Institutes of Health performed a prospective study of birth defects involving over 32,000 women in their first trimester.[18] The survey found that infants born to women who said they averaged two or fewer drinks per day had roughly the same rate of malformations as those born to women who did not drink at all: 80.3 per 1,000 *v* 78.1 per 1,000, a statistically insignificant difference (although the trend was towards increased malformation with increased consumption). When drinking was related to malformations of individual organ systems, increasing alcohol consumption was significantly associated with malformations of the genitourinary system. Nonetheless, Mills and Graubard[14,15] concluded that "at the levels usually consumed during pregnancy, alcohol is not a significant cause of malformations" (p 314).[14]

Nicotine and caffeine, two other common social drugs, do not produce congenital malformations in human embryos, but the nicotine in cigarettes has an effect on fetal growth.

Nicotine and caffeine, two other common social drugs, do not produce congenital malformations in human embryos, but the nicotine in cigarettes has an effect on fetal growth.[16] Nicotine constricts uterine blood vessels, causing a decrease in uterine blood flow, thereby lowering the supply of oxygen and nutrients in the intervillous space that is available to the embryo. The resulting deficiency in the embryo impairs cell growth and may have an adverse effect on mental development. Caffeine is not known to be a human teratogen, but there is no assurance that excessive maternal consumption of it is safe for the embryo. For this reason, excessive drinking of coffee, tea, and colas that contain caffeine should be avoided.

With the explosion in the consumption of diet soda and other artificially sweetened food products, one must be concerned about possible fetal effects. London[17] reviewed the currently available information on the safety of aspartame and saccharin in pregnancy, and gave recommendations formulated on their use in the periconceptional period and pregnancy. The Council on Scientific Affairs of the American Medical Association reviewed the available data (up to 1985) and concluded, "Because recent epidemiologic studies provide no evidence of increased risk of bladder cancer among users of artificial sweeteners, including saccharin, and because there is no ideal artificial sweetener, saccharin should continue to be available as a food additive." However, based on the limited amount of information available, the report advised "careful consideration of saccharin use by young children and pregnant women."[18] A number of recent reviews on the use of aspartame in pregnancy reported that there were no experimental or epidemiologic data to indicate adverse maternal or fetal effects.[19-21] All the data indicate that this component appears to be safe during pregnancy for normal women as well as for those heterozygous for phenylketonuria (PKU). A pregnant woman homozygous for PKU must consider aspartame an additional source of phenylalanine. While these authors do not disagree with London, a nihilist approach to drug and artificial substance exposure in pregnancy would advise caution to avoid exposure to any substances that are not absolutely necessary. Isolated reports, some with very weak causation, fill books.[22] A mother of a deformed child will attribute a great degree of causation to drug exposure. It is best to avoid those drugs that can be avoided. If women are made aware of the harmful effects of alcohol and certain drugs and viruses, most of them will

not expose their embryos to these agents.[9] These authors believe that most informed women will avoid all unnecessary substances, whether or not there is a hint of causation related to teratogenesis.

Truly a therapeutic dilemma is presented to the physician and the patient. What about the woman with seizure disorder? Assuming that a neurologic consultation has verified the continued need for the anticonvulsant, these drugs are confirmed (phenytoin), and strongly suspected (trimethadione and paramethadione) to be teratogenic.[23,24] The main features of the fetal trimethadione syndrome are developmental delay, V-shaped eyebrows, low-set ears, and cleft lip and/or palate. The fetal hydantoin syndrome consists of the following abnormalities: intrauterine growth retardation, microcephaly, mental retardation, a ridged metopic suture, inner epicanthal folds, eyelid ptosis, a broad depressed nasal bridge, nail and/or distal phalangeal hypoplasia, and hernias.

Isotretinoin and etretinate, two recently introduced synthetic retinoids used to treat dermatologic conditions, are now confirmed teratogens. Some of the described teratogenic effects include meningomyelocoele, meningoencephalocoele, multiple synostoses, facial dysmorphia, syndactylies, absence of terminal phalanges, malformations of hip, ankle, and forearm, low-set ears, high palate, decreased cranial volume, and alterations of the skull and cervical vertebrae on x-ray.[25] Vitamin A has been known to be a teratogen, when given in high dosages to both animals and humans.[26-30]

Not all drugs are teratogenic; in fact, only a handful are known to be teratogenic. Some, as discussed above, have a high index of suspicion. These are listed in Table 3.

Ideally, drug therapy should be avoided, but various maternal disease states will require therapy that may potentially affect the fetus. In these situations, the benefit to the mother must clearly outweigh the risk to the fetus. However, a healthy mother is needed to foster growth and development of the fetus, and, therefore, sometimes administration of drugs that may harm the fetus is necessary for the immediate benefit to the mother and eventual benefit to the fetus.

The Food and Drug Administration (FDA) has classified risk associated with drug use during pregnancy and has assigned required labelling risk categories to drugs released after 1980 (see Table 4). These categories provide only a framework by which to evaluate a drug during pregnancy. Drugs categorized as minimal risk may cause harm if improperly used. Many clinicians consider these classifications of little help in solving the dilemma of prescribing drugs in pregnancy. Few studies exist; there is a paucity of information, and a great fear of adverse effects.

LATE PREGNANCY AND LABOR

Late pregnancy effects, before the time of labor and delivery, are potentially dangerous to the fetus. Reports of deafness (aminoglycosides), hemorrhage (warfarin, salicylates), preventing parturition (NSAIDS), and thyroid toxicity (antithyroid agents and iodine) are not uncommon.

Drugs administered during labor and delivery are known to cause harmful effects on the fetus, directly and indirectly. Local anesthetics may cause cardiotoxicity in the fetus, leading to decreased fetal cardiac output and subsequent fetal oxygen deprivation. Postpartum local anesthetic excess fetal levels may cause CNS and cardiac effects in the newborn (ie, seizures, respiratory depression, bradycardia). Several mechanisms exist by which the fetus may receive a higher concentration of drug than the mother. The largest amounts of data available have been generated from the effects of local anesthetics.[31] First and foremost, direct injection of a drug into the baby will create extremely high concentrations locally. Direct injections of local anesthetics into the fetal head or the intrauterine area while attempting local nerve blocks in the maternal pelvis can cause profound seizure activity and bradycardia from the high concentration of these drugs in the CNS.[32,33]

More subtle is the phenomenon of local blood flow producing relatively high fetal concentrations of local anesthetics. Injections into the maternal pelvis may cause locally high concentrations of the drug in the placenta and infant as well as high incidence of fetal bradycardia.[34,35] Since protein binding may be decreased in the newborn, seemingly lower concentrations of local anesthetics, as compared to concentrations in the mother, may actually represent higher free concentrations of these drugs. Lidocaine is a weak

Table 3. Teratogens Known to Cause Human Malformations

Teratogens	Congenital Malformations
Androgenic Agents	
Ethisterone	Varying degrees of masculinization of female fetuses: ambiguous external genitalia caused by labial fusion and clitoral hypertrophy.
Norethisterone	
Testosterone	
Estrogens	
Oral contraceptives	Vacteral (vertebral, anal, cardiac, tracheo-esophageal, and limb malformations).
Diethylstilbesterol (DES)	Adenocarcinoma of cervix in female offspring of pregnant women administered DES.
Drugs and Chemicals	
Alcohol	*Fetal alcohol syndrome:* intrauterine growth retardation (IUGR); mental retardation; microcephaly; ocular anomalies; joint abnormalities; short palpebral fissures.
Aminopterin	Wide range of skeletal defects; IUGR; malformations of the central nervous system, notably meroanencephaly (a large part of the brain is absent).
Busulfan	Stunted growth; skeletal abnormalities; corneal opacities; cleft palate; hypoplasia of various organs.
Phenytoin (Dilantin)	*Fetal hydantoin syndrome:* IUGR; microcephaly; mental retardation; ridged metopic suture; inner epicanthal folds; eyelid ptosis; broad depressed nasal bridge; phalangeal hypoplasia.
Lithium carbonate	Various malformations, usually involving the heart and great vessels.
Methotrexate	Multiple malformations, especially skeletal, involving the face, skull, limbs, and vertebral column.
Large doses of retinoic acid (vitamin A).	Facial abnormalities; neural tube defects, such as spina bifida cystica
Isotretinoin	Meningomyelocoele, meningoencephalocoele, multiple synostoses, facial dysmorphia, syndactylies, absence of terminal phalanges, malformations of hip, ankle, and forearm, low-set ears, high palate, decreased cranial volume, and alterations of the skull and cervical vertebrae on x-ray.
Etretinate	
Tetracycline	Stained teeth; hypoplasia of enamel; long bone development
Trimethadione	Developmental delay; V-shaped eyebrows; low-set ears; cleft lip and/or palate.
Infectious Agents	
Cytomegalovirus	Microcephaly; hydrocephaly; microphthalmia; microgyria; mental retardation; cerebral calcifications.
Herpes simplex virus	Microcephaly; microphthalmia; retinal dysplasia.
Rubella virus	Cataracts; glaucoma; chorioretinitis; deafness; microphthalmia; congenital heart defects.
Varicella	Skin scarring; muscle atrophy; mental retardation.
Venezuelan equine encephalitis	Cataracts; brain destruction.
Toxoplasma gondii	Microcephaly; mental retardation microphthalmia; hydrocephaly; chorioretinitis; cerebral calcifications.
Treponema pallidum	Hydrocephalus; congenital deafness; mental retardation; abnormal teeth and bones.
High levels of ionizing radiation	Microcephaly; mental retardation; skeletal malformations.

Adapted and reprinted with permission.[9]

base with a pH slightly above that of the physiologic. A weak base will tend to be trapped in a compartment that is relatively more acidic (ie, ion trapping). By having an acidotic asphyxiated fetus, lidocaine may be trapped in the fetal compartment.

A third potential source of drug toxicity where drug concentrations in the fetus would exceed the concentration in the mother is related to transplacental drug transfer. Drugs are normally transported across the placenta in a relatively lipid soluble form. Lipid solubility is the ability of something to traverse fat containing membranes. When compounds are transported to the fetus they may then be metabolized by the fetal liver. The result of that metabolic process may be a more water soluble (ionized) and less lipid soluble compound. Since water soluble com-

Table 4. Classification of Safety of Drug Use in Pregnancy

Category A	Controlled studies in women fail to demonstrate a risk to the fetus in the first trimester (and there is no evidence of a risk in later trimesters), and the possibility of fetal harm appears remote.
Category B	Either animal-reproduction studies have not demonstrated a fetal risk but there are no controlled studies in pregnant women or animal-reproduction studies have shown an adverse effect (other than a decrease in fertility) that was not confirmed in controlled studies in women in the first trimester (and there is no evidence of a risk in later trimesters).
Category C	Either studies in animals have revealed adverse effects on the fetus (teratogenic or embryocidal or other) and there are no controlled studies in woman or studies in women and animals are not available. Drugs should be given only if the potential benefit justifies the potential risk to the fetus.
Category D	There is positive evidence of human fetal risk, but the benefits from use in pregnant women may be acceptable despite the risk (eg, if the drug is needed in a life-threatening situation or for a serious disease for which safer drugs cannot be used or are ineffective).
Category X	Studies in animals or human beings have demonstrated fetal abnormalities or there is evidence of fetal risk based on human experience or both, and the risk of the use of the drug in pregnant women clearly outweighs any possible benefit. The drug is contraindicated in women who are or may become pregnant.

pounds are not readily transported out of the fetus, they may accumulate to higher concentrations than would normally be predicted based on the amount of drug transported into the fetus.

Aside from their actions as parturition inhibitors, indomethacin, as a representative of the NSAID class, is a good example of a tocolytic drug in which a very unusual adverse response was observed in the newborn. Indomethacin is a prostaglandin synthetase inhibitor. It is found to be extremely effective at stopping premature labor. On the basis of clinical and animal trials, however, it appears that this drug is capable of closing the ductus arteriosus in the fetus.[36] Since blood does not need to pass through the lungs in utero, this vessel allows oxygenated blood from the placenta to reach the fetal circulation. At birth, this structure closes and eventually disappears. By causing closure of the ductus arteriosus in utero, indomethacin causes the development of pulmonary hypertension and a high degree of fetal morbidity.

Oxytocics, by increasing the strength of contraction of the uterus, can decrease uteroplacental blood flow, causing fetal oxygen deprivation and manifesting as fetal distress. This should be obvious for drugs known to be oxytocics. Oxytocics can cause excessive mechanical contractions that can impel the head of the fetus through an occluded birth canal (cephalopelvic disproportion), and are known to cause severe brain damage to the infant.

Drugs that cause changes in BP in the mother may compromise the fetal oxygen supply, resulting in fetal injury. Drugs used for narcotic anal-

Oxytocics can cause excessive mechanical contractions that can impel the head of the fetus through an occluded birth canal (cephalopelvic disproportion), and are known to cause severe brain damage to the infant.

gesia of the mother and the treatment of maternal hypertension may be associated with a variety of side effects in the fetus. Certain well recognized side effects of narcotic analgesics are important to consider. The major cause of concern for the fetus relating to narcotic effects is postpartum respiratory depression. Since no respiratory effort is needed until immediately postdelivery, a relatively long-term exposure in utero to narcotic agents is not necessarily a hazardous event until the first breath is desired. It does appear that the infant is more sensitive to the respiratory depressant effects of the narcotics, in particular, morphine. From a therapeutic standpoint, narcotic induced respiratory depression can be reversed by a narcotic antagonist such as naloxone, but not until the airway is preserved

and artificially supported if necesssary. Narcotic analgesics given in labor will affect the physiology of the mother, affect the strength of contractions, slow labor, and if given within one hour of birth, be retained in potentially dangerous levels in the newborn, leading to respiratory insult and decreased thermoregulation.

DRUG THERAPY IN THE LACTATING WOMAN

Breast milk is the only food that an infant needs for the first 4 to 6 months of life.[37] At the present time, approximately 50% of babies discharged from hospitals at least are started on breast feeding.[38] The benefits of breast feeding are: (1) it is the best nutritional source for an infant; (2) it provides immunological benefits; (3) it enhances bonding between mother and child; and (4) it is less costly than commercial formula. However, with this increased use of breast milk comes the increased concern by health professionals and parents about the safety and potential toxicity of drugs that may be excreted in the breast milk. The appearance of drug in breast milk is determined by the very same factors that determine the concentration of drug elsewhere in the mother. These factors consist of the maternal pharmacology, breast characteristics, milk composition, infant behavior, and the chemical properties of the drug. An understanding of these factors may lead to a more educated decision when recommending a medicated woman to breast feed.

Maternal Pharmacology

Drug dosage, frequency, and route will affect the amount of drug available during the formation of breast milk and will therefore affect the amount of drug to which the infant will be exposed. Of all the factors considered, route of administration is the simplest to analyze. If a drug is not absorbed, there is no risk. By increasing the dosage or frequency, there will be a greater potential of the drug appearing in the breast milk. Alterations seen in maternal physiology that occur postpartum as well as that of a lactating woman may effect serum drug levels and therefore the amount of drug in breast milk. If a drug exhibits a high degree of protein binding, decreased levels of serum albumin will cause an increase in the levels of free drug.[39] Increased total body water in the postpartum woman will affect the volume of distribution of certain drugs. The rate at which a lactating mother can metabolize drugs will determine the drug's concentration available to enter breast milk and ultimately the infant. The elevated levels of hormones seen in the postpartum and lactating woman may inhibit or enhance the metabolism of drugs by affecting the hepatic microsomal enzyme systems. Maternal disease states may also affect metabolic rates, as may concurrent drug therapy. Drug clearance in the immediate postpartum period may be increased, thus necessitating increased dosages of kidney excreted drugs. Any renal compromise in the postpartum mother will increase circulating levels of renal excreted drugs, and potentially present more drug to the breast for excretion.

Breast factors. Blood flow to the breast is an important but often overlooked contributor to the amount of drug in breast milk. If blood flow to the breast is minimal, then the amount of drug that is available to be incorporated into the milk is decreased. Stress, cold, and α-adrenergic agonist drugs may decrease blood flow. Breast engorgement and binding both serve as feedback mechanisms for the body. They relay messages that inhibit the formation of more milk. If drug concentration is high in plasma and the breast is empty, then more drug may be transported into milk during its manufacture in the breast.

The paucity of transport mechanisms across breast cell membranes makes passive diffusion and ionization important factors to be considered. There is little evidence to support breast cell drug metabolism.[37] The concentration of most lactating women's drug metabolites themselves are poorly studied. Reabsorption of a drug from the breast cell can occur. Given an adequate period of time, a drug may be reabsorbed to the extent that minimal concentrations of drug appear in the breast milk.

Milk factors. The chemical composition of breast milk and colostrum will significantly affect the concentration of drug that will be reached in this body fluid. Little known is the fact that the fluid that is excreted from the breast changes from the immediate postpartum period and will reach a stable product at 3 months. The initial fluid to be excreted is colostrum. This substance is mainly composed of protein, water, and minimal amounts of both fat and carbohy-

drate. Mature breast milk is composed of protein, fats, and carbohydrates in contrast to colostrum. Because of the difference in composition, the pH of each of these fluids differs, which will ultimately have an impact on the ionization state of substances contained in them. Weakly basic drugs such as isoniazid are less concentrated in colostrum than in mature milk.[37] This fact combined with other chemical properties of the drug may have effects on the concentration of drug that a nursing infant receives.

Since the protein composition of colostrum differs from that of mature milk, the amount of drug-protein binding may be different; however, this area of information is poorly studied. The effect of fat concentration is better understood. This concentration difference combined with a drug's lipid solubility will alter the appearance of drug in the fluid that is to be excreted by the breast. Compounding this interaction of drug and fat is the fact that the fat content of mature milk varies with the time of day and the length of each feeding. The content of milk fat is highest early in the morning and at the end of each feeding.[37]

Infant factors. Infant suckling behavior can dramatically alter the concentration of drug in breast milk. If the infant empties only one breast during a feeding, it is possible that one breast will have a different concentration of drug than the other. If the breasts remain engorged during the period of time that serum levels are the highest, then the likelihood of the drug appearing in breast milk is minimal. The amount of milk consumed during each feeding and the size of the infant will determine the concentration of drug achieved. This, however, may not offer a greater prediction into the adverse effects that an infant may suffer. A small quantity of drug may pass into the breast milk and be absorbed by the infant. The ability of the infant to metabolize and/or excrete the drug will determine its pharmacologic activity. However, there are certain diseases that may enhance the toxicity of even small amounts of drug. Along with the amount of breast milk consumed during each feeding, the amount of feeding each day will also affect the total amount of drug that the suckling infant will ingest. Every-two-hour feeding schedules may expose the infant to more drug than every-four-hour feedings. Another confounding influence is the relationship between the maternal drug ingestion and its time relation to feeding. A drug that will have a peak serum level at the same time that the breast is manufacturing milk will potentially result in a much higher drug level in the milk than a drug that peaks after milk formation occurs.

Drug factors. When making decisions about drug use and breast feeding, one must consider the physico-chemical properties of the individual drugs. These factors include the pKa, solubility, protein binding, and molecular weight.[37] One must always keep in mind that even small amounts of drug, may exert an adverse effect in the nursing infant. Drugs of low molecular weight (300 or less) may diffuse through the water-filled pores in the basement membrane. Large molecular weight drugs are more dependent on other factors for penetrations into breast cells. This ability to diffuse or pass through the water-filled pores also allows the drugs to back-diffuse into the serum. Drugs that are highly protein bound appear in small amounts in the breast milk due to the amounts of free drug

Table 5. Drugs That Are Contraindicated During Breast-Feeding

Drug	Reported Sign or Symptom in Infant or Effect on Lactation
Amethopterin*	Possible immune suppression; unknown effect on growth or association with carcinogenesis
Bromocriptine	Suppresses lactation
Cimetidine†	May suppress gastric acidity in infant, inhibit drug metabolism, and cause CNS stimulation
Clemastine	Drowsiness, irritability, refusal to feed, high-pitched cry, neck stiffness
Cyclophosphamide*	Possible immune suppression; unknown effect on growth or association with carcinogenesis
Ergotamine	Vomiting, diarrhea, convulsions (doses used in migraine medications)
Gold salts	Rash, inflammation of kidney and liver
Methimazole	Potential for interfering with thyroid function
Phenindione	Hemorrhage
Thiouracil	Decreased thyroid function; does not apply to propylthiouracil

*Data not available for other cytotoxic agents.

†Drug is concentrated in breast milk.

Reproduced by permission of *Pediatrics,* Vol 72, p 375, copyright 1983.[41]

Table 6. Drugs That Require Temporary Cessation of Breast-Feeding

Drug	Recommended Alteration in Breast-Feeding Pattern
Metronidazole	Discontinue breast-feeding 12-24 h to allow excretion of dose
Radiopharmaceuticals	Radioactivity present in milk, consult nuclear medicine physician before performing diagnostic study so that radionuclide which has shortest excretion time in breast milk can be used; prior to study the mother should pump her breast and store enough milk in freezer for feeding the infant; after study the mother should pump her breast to maintain milk production but discard all milk pumped for the required time that radioactivity is present in milk
Gallium-69 (^{69}Ga)	Radioactivity in milk present for 2 wk
Iodine-125 (^{125}I)	Risk of thyroid cancer; radioactivity in milk present for 12 d
Iodine-131 (^{131}I)	Radioactivity in milk present 2-14 d depending on study.
Radioactive sodium Technetium-99m (^{99m}Tc), ^{99m}Tc macroaggregates, ^{99m}Tc O_4	Radioactivity in milk present 96 h Radioactivity in milk present 15 h to 3 d

Reproduced by permission of *Pediatrics*, Vol 72, p 375, copyright 1983.[41]

available to penetrate the cell membrane. If the drug readily binds to milk protein, the drug may be concentrated in the cell and potentially expose the infant to the effects of the drug.

The lipid solubility of a drug will determine the degree to which it penetrates the acinir cells. Drugs that are highly lipid soluble diffuse across membranes easier than those of low lipid solubility.[37] This may allow more drug to be present in the cell but may also allow greater ease in back diffusion from the cell to the plasma.

The pKa of the drug and pH of the fluid will determine the degree of drug ionization that occurs. Ionized molecules have a more difficult time transferring across the cellular membranes. Upon inspection it would appear to confer a safety factor on ionized drugs, but one must consider this fact with the other factors of molecular size, solubility, and protein binding. To complicate matters further, the pH of colostrum and breast milk vary because of composition. Breast milk is relatively acidic and colostrum basis compared to plasma pH. Further pH variations can occur between mothers, as well as pH variations in the same mother.[37] Under these conditions, it can be stated that weakly basic drugs are concentrated in breast milk and, conversely, weakly acidic drugs are more concentrated in plasma. If the pH gradient of plasma to breast milk changes, then the degree of drug ionization changes. Weakly basic drugs are less concentrated in colostrum than in mature milk. This is the result of the relative alkalinity of colostrum in relation to plasma. If a drug is nonionized in the plasma but when exposed to the environment of the acinir cell the pH is such that it becomes ionized, then the breast cell acts like an ion trap, concentrating the drug and increasing the risk to the infant. If it remains nonionized, then the molecule will pass from the cell to the plasma.

MINIMIZING RISK

For most drugs, the true significance of the factors relating to drug therapy and lactation is not known. Few comprehensive studies have been performed, and few of these involve humans. A majority of the literature is based on the observation that an amount of drug was detectable in the breast milk, but little consideration was given to all the factors that can affect drug concentration in a body fluid. The complexity, not to mention the legal and ethical issue in studying drug therapy in the lactating woman is great, but a need to perform these studies continues.

In order to minimize the exposure of a fetus/child to drugs, the simple solution would be to avoid drug exposure altogether. This is not always possible, due to maternal disease states that require drug therapy. Some agents by their very nature should be avoided, but others do require a careful review before use. The categories of drugs that generate the most frequently asked questions and needless disruption of breastfeeding are antibiotics, sedatives, and analgesics. Almost without exception, these drugs can be given safely to breastfeeding women and are not easily absorbed by infants' gastrointestinal tracts.[40] Tables 5 and 6 are reproduced and reader is referred to the original reference for more comprehensive literature sources.[41]

REFERENCES

1. Golbus MS: Teratology for the obstetrician: Current status. Obstet Gynecol 55:269, 1980
2. Rayburn WF, Zuspan FP (eds): Drug Therapy in Obstetrics and Gynecology. Norwalk, CT, Appleton-Century-Crofts, 1982, Chapter 1, p 3
3. Stern L: Drug Use in Pregnancy. Australia, ADIS Health Science Press, 1984, Chapter 4, p 47
4. Chow A, Jewwesson P: Pharmacokinetics and safety of antimicrobial agents during pregnancy. Rev Infect Dis 7:287-313, 1985
5. Gregg NM: Congenital cataract following German measles in the mother. Trans Ophthalmol Soc Aust 3:35, 1941
6. Lenz W: Kindliche Missbildungen nach Medikament wahrend der Graviditat? Ditsch Med Wochenshr 86:25-55, 1961
7. McBride WG: Thalidomide and congenital abnormalities. Lancet 2:1358, 1961
8. Mirkin B: Perinatal Pharmacology, Placental Transfer, Fetal Localization and Neonatal Distribution of Drugs. Anaesthesiology 43:156-170, 1975
9. Moore KL: Causes of human congenital malformations, in The Developing Human, Clinically Oriented Embryology (ed 4). Philadelphia, Saunders, 1988, p 131
10. Persaud TVN, Chudley AE, Skalko RG: Basic Concepts in Teratology. New York, Liss, 1985
11. Thompson MW: Genetics in Medicine (ed 4). Philadelphia, Saunders, 1986
12. Brent RL: Radiation teratogenesis, in Sever JL, Brent RL (eds): Teratogen Update: Environmentally Induced Birth Defect Risks. New York, Liss, 1986
13. Sulaiman ND, Florey CduV, Taylor DJ, et al: Alcohol consumption in Dundee primagravidas and its effects on the outcome of pregnancy. Br Med J 296:1500-1503, 1988
14. Mills JL, Graubard BI: Is moderate drinking during pregnancy associated with an increased risk of malformations? Pediatrics 80:309-314, 1987
15. Morse, G: Drinking during pregnancy: A safe level? J Watch 2:47-48, 1988
16. Werler MM, Pober BR, Holmes LB: Smoking and Pregnancy, in Sever JL, Brent RL (eds): Teratogen Update: Environmentally Induced Birth Defect Risks. New York, Liss, 1986
17. London RSL Saccharin and aspartame: Are they safe to use during pregnancy? J Reproductive Med 33:17-21, 1988
18. American Medical Association, Council on Scientific Affairs: Saccharin: Review of safety issues. JAMA 254:2622, 1985
19. Sturtevant FM: Use of aspartame in pregnancy. Int J Fertil 30:85, 1985
20. Franz M: Is it safe to consume aspartame during pregnancy? A review. Diabetes Educator 12:145, 1986
21. Bikel H, Trefz FK: Aspartame: In substoff mit bohem Phenyulalaningehalt. Monatsschr Kinderheilkd 134:478, 1986
22. Shepard T: Catalog of Teratogenic Agents (ed 2). Baltimore, Johns Hopkins University Press, 1976
23. Goldman AS, Zachai EH, Yaffe SJ: Fetal trimethadione syndrome, in Sever JL, Brent RL (eds): Teratogen Update: Environmentally Induced Birth Defect Risks. New York, Liss, 1986
24. Hanson JW: Fetal hydantoin effects, in Sever JL, Brent RL (eds): Teratogen Update: Environmentally Induced Birth Defect Risks. New York, Liss, 1986
25. Moore KL: Causes of human congenital malformations, in The Developing Human, Clinically Oriented Embryology (ed 4). Philadelphia, Saunders, 1988, p 149
26. Rosa FW, Wilk Al, Kelsey FO: Vitamin A cogeners, in Sever JL, Brent RL (eds): Teratogen Update: Environmentally Induced Birth Defect Risks. New York, Liss, 1986
27. Shenefelt RE: Morphogenesis of malformations in hamsters caused by retinoic acid: Relation to dose and stage at treatment. Teratology 5:103-118, 1972
28. Lorente CA, Miller SA: The effect of hypervitaminosis A on rat palatal development. Teratology 18:277-284, 1978
29. Geelen JAG: Hypervitaminosis A induced teratogenesis. CRC Crit Rev Toxicol 351-374, 1979
30. Fantel AG, Shepard TH, Newell-Morris LL, et al: Teratogenic effects of retinoic acid in pigtail monkeys (Macaca nemestrina 1. General features. Teratology 15:65-71, 1977
31. Nau H: Clinical pharmacokinetics in pregnancy and perinatology. Dev Pharmacol Ther 8:140-181, 1985
32. Amato M, Carasso A, Ruckstuhl C: Neonatal mepivicaine poisoning following episiotomy. Z Geburtshilfe Perinatol 187:191-193, 1983
33. Van Dorsten JP, Miller FL: Fetal heart rate changes after accidental intrauterine lidocaine. Obstet Gynecol 57:257-260, 1981
34. Ralston DH, Shnider SM: The fetal and neonatal effects of regional anesthesia in obstetrics. Anesthesiology 48:34-64, 1978
35. Liston WA, Adjepon-Yamoah KK, Scott DR: Foetal and maternal lignocaine levels after paracervical block. Br J Anaesth 45:750-754, 1973
36. Csaba, Sulyok, Ertl: Relationship of maternal treatment with indomethacin to persistence of fetal circulation syndrome. J Pediatrics 92:484, 1978
37. Wilson J, Brown R, Chered D, et al: Drug exception in human breast milk. Clin Pharmacokinetics 5:1-66, 1980
38. Briggs G, Bodendorfer T, Freeman R, et al: Drugs in Pregnancy and Lactation. Baltimore, Williams & Wilkins, 1983, p xii
39. Mendenhall N: Serum protein concentrations in pregnancy. Concentrations in maternal serum. Am J Obstet Gynecol 106:388-399, 1970
40. Jacobi AM, Caporelli V: Drugs and breastfeeding: It's almost always okay to breastfeed. But do you know why? RN-RX News, Vol 1, No 2. Chicago, Rush-Presbyterian St Luke's Medical Center, 1988
41. Anon Committee on Drugs: The transfer of drugs and other chemicals into human breast milk. Pediatrics 72:375-383, 1983