Women's Health: Pregnancy and Childbirth

The Use of Drugs During Pregnancy and Lactation

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Synopsis

It is a regulatory fact that only 14 drugs are approved for use during pregnancy; none of them is specifically approved for use in nursing mothers. With the current emphasis on breast feeding, more data describing levels of drugs in fetal blood and drug levels in breast milk are necessary. Some of the pharmacologic properties useful in predicting drug transmission during lactation include lipid solubility, ionization constant, and molecular size (which predisposes a drug to crossing membrane barriers to the fetus and the milk).

BEFORE DISCUSSING THE CURRENT state of knowledge of drugs in pregnancy and breast milk, a few facts should be mentioned. First, most of our data about drugs in humans, at least in this country, are from studies done on young adult, healthy males. Very few studies have been carried out on females and certainly not many studies on women categorized by different phsyiologic states such as menstruation, preganancy, lactation, and one of particular interest and concern to me, the postpartum state.

There is reason to believe that these altered physiological states will indeed change drug absorption, distribution, kinetics, metabolism, and excretion. There is some concern that they also may change the mode of drug action. Also, we need to be aware that there are very few drugs (in fact, probably fewer than 12) which are specifically approved for use during pregnancy. I am unaware of any drug that is specifically approved for use during lactation, and with the current legal climate, it is probably unlikely that those numbers for both pregnancy and lactation will change.

It is indeed understandable that young parents today wish to have a baby who is as perfect as possible. When things go wrong, as they will in the United States in about 1 birth out of 40, it is easy to look for and to blame something. Because we have witnessed an increase in the per capita use of medications of all kinds during pregnancy, that is one area that immediately receives scrutiny.

Although nearly all drugs cross the placenta, certainly those with a molecular weight of approximately 300 or less and with a reasonable amount of lipid solubility, those drugs without question known to cause structural damage to the fetus (teratogens), are very few: anticancer drugs, thalidomide, and three seizure medications (phenytoin, trimethadione, and valproic acid). The latter drugs represent a special challenge to the obstetrician and physician who care for these women in trying to minimize the occurrence of a seizure and the risk to the infant. The list also includes the anticoagulant warfarin; a relatively new vitamin A derivative used to treat acne, isotretinoin; and one of the antibiotics, tetracycline. The risk or the incidence of damage when one of these drugs is ingested varies widely from nearly 100 percent with thalidomide to about 6 percent with phenytoin.

There is increasing concern about possible delayed effects, such as the increased incidence of clear-cell carcinoma of the vagina in adolescents and young adults exposed to diethylstilbestrol (DES) *in utero*. We also now know that male offspring are not free from problems related to this compound; adult males whose mothers were exposed to DES may have abnormalities in the structure of the genitourinary system and in the spermatozoa.

Maternal ingestion of alcohol and the use of cigarettes are known hazards to the fetus. The precise amount that is dangerous is keenly debated; is there any amount of alcohol or cigarette smoke active or passive that is safe? Almost everyone would agree that the best amount is zero.

Alcohol is a very small, lipid-soluble, unionized compound. It crosses instantaneously from the mother to the fetus and into milk in the lactating woman. Cigarette smoke contains hundreds of compounds, but three of them, nicotine, cyanide, and

carbon monoxide, singly or alone, can cause interference with umbilical artery diameter and hence decrease the blood supply to the fetus.

A large number of drugs are given to the mother during the intrapartum period for sedation or analgesia, or both that will transiently affect physiological processes in the infant. These include all anesthetic agents: narcotics, sedatives, tranquilizers, muscle relaxants, magnesium sulfate, hypoglycemic agents, propanolol, terbutaline, and ritodrine. The magnitude of this effect depends on the timing and the dose of administration in relation to the time of delivery. Gestational age is very important and so is the state of nutrition.

These effects, although they may be prompt and profound, are usually transient. Of great importance is the possible interference of initial bonding between the mother and a physiologically altered, sick infant.

Concern also exists as to whether the exposure of the mother to these compounds and the ingestion during pregnancy of psychoactive agents, either prescribed or illicit, will cause subtle but real deficits in intellectual and behavioral functioning, a condition called behavioral teratology.

The problem with this issue is that we may never be able to measure it adequately. If a child has a learning disability in eighth grade, is it because his or her mother had marijuana during pregnancy, or is it because he or she falls in the lower end of the bell-shape distribution of learning ability?

In the area of drugs and lactation, we have a bit more knowledge. We have been placing great emphasis on breast feeding in this country, particularly among pediatricians and also among lay organizations, and in 1987 at least 1.8 million newly born infants will be placed at breast. They will be breastfed from 2 to 12 months of life or longer. Obviously, the drug exposure during that period of time could be considerable.

We have better data on lactation than we do on pregnancy, primarily because we can measure the amount of drug in the mother, using either her saliva or her serum, and we can also measure it in the milk. Furthermore, we can measure blood levels in the infant, and if one wishes to do noninvasive procedures, one can get an indirect estimation by testing the urine of the infant.

Fortunately, for nearly all therapeutic agents, drug exposure of the nursing infant is very small, and perhaps undetectable. Lithium and major tranquilizers should not be used; if they are, the infant should not breast feed. For most of the new cardiac and antiarrhythmic drugs, as well as the psychoactive drugs, insufficient data are available to determine risk.

It is important, during lactation as well as pregnancy, to maintain maternal health and minimize risk to infants. For example, a nursing mother who has early mastitis or frank breast abscess can be safely treated with a large number of antibiotics with minimal or no risk to the infant because exposure of the infant is very small.

A large area of unknown problems concerns the exposure of the nursing mother to environmental agents, particularly to those agents which are very soluble in body fat (for example, the active ingredients in marijuana, pesticides, organic solvents, and tobacco smoke).

The experience in Norway can be cited to illustrate one problem. That country banned the use of DDT in 1970. None was available, nor was it used. In 1977, 7 years after its total ban, lactating women were excreting detectable amounts of DDT in their milk, which means that they harbored that material for 7 years, presumably becoming exposed as young children, and through adolescence and into the childbearing years.

We need many more studies on this type of problem to determine whether there is a long-term risk so that we can avoid panic situations and maximize the health of the nursing infant.

In conclusion, no one would argue that no drug exposure is best. We need to do what we can to preserve maternal health during pregnancy and lactation, and we need to collect data on the amount of drug that might be excreted into milk, incidence statistics concerning the epidemiology of some of these problems that might be connected with exposure to certain drugs during pregnancy.

These systematic national studies are very expensive, very time consuming, and involve something which is very difficult to find, particularly in universities, and that is a long-term commitment by a stable group of compulsive researchers who are willing to follow pregnant women not only through pregnancy and lactation but their children for many years beyond. That is one of the wonderful things about the National Institutes of Health (NIH) Collaborative Study, which is still giving us information after 25 years.

We also like to think that these kinds of problems can be overcome with successful cooperation between university health centers, the Food and Drug Administration, the NIH, and many of the lay organizations that have been very helpful to us so far.