Drugs during Pregnancy: Do They Affect the Unborn Child?

Birth defects occur with disturbing frequency; 2 percent of live-born infants suffer from major defects and at least 20 percent of all pregnancies terminate in spontaneous abortions, usually the result of gross fetal abnormalities. Although some of these defects have a genetic origin, the causes of many are still unknown. The thalidomide tragedy of the early 1960's stimulated the awareness of clinicians and researchers to the possibility that drugs—everything from heroin to aspirin—taken by the pregnant woman could contribute to the birth defect problem. This possibility was the topic of a recent symposium sponsored by the National Foundation-March of Dimes.*

The symposium participants agreed that in view of the inadequacy of our current knowledge of the effects of drugs on the fetus, a woman would be wise to avoid all drugs—both prescribed and self-administered—unless she were certain she was not pregnant. They stressed, however, that some diseases, such as heart disease, epilepsy, and bacterial infections, often require drug therapy for the protection of both the mother and her unborn child. The ratio of benefit to risk is the critical factor that determines whether medication should be used; the difficulty lies in assessing this ratio for the dynamic, complex living system called the maternal-fetal-placental unit.

Despite the uncertainty about the effects of most drugs on fetal development, they are extensively used by pregnant women. John O. Forfar of the University of Edinburgh, Scotland, surveyed drug use during pregnancy. He found that 82 percent of the women in the study received prescribed medication and that 65 percent took self-medicated drugs. The major drug categories included iron, analgesics, vitamins, barbiturates, diuretics, antiemetics, antibiotics, sulfonamides, cough medicines, antihistamines, hormones, tranquilizers, bronchodilators, hypnotics, and appetite suppressants (listed in decreasing order of usage). Forfar also found that 57 percent of the women smoked and over 85 percent used alcohol during pregnancy. Similar results have been reported in the United States.

Drugs administered to the mother will not directly affect the fetus unless they are capable of crossing the placenta. There is no direct connection between the maternal and fetal circulatory systems but they are closely juxtaposed within the placenta to allow transfer of materials between the two systems. Bernard L. Mirkin of the University of Minnesota, Minneapolis, reviewed the factors thought to influence placental transport of drugs. Although there are exceptions, compounds pass through the placenta more readily if they are highly lipid-soluble, are not ionized, and are of low molecular weight. Drug transfer increases with increased rate of both fetal and maternal blood flow through the placenta, and with placental age. Mirkin has shown that diphenylhydantoin, an anticonvulsant drug, can cross the placenta of mice, rats, and humans; and that digoxin, a drug used to treat heart disease, can do so in rats and ewes.

The capacity of the placenta to metabolize and detoxify drugs will also affect the dose received by the fetus. Mont R. Juchau and his colleagues at the University of Washington School of Medicine, Seattle, are investigating human placental enzyme systems that could catalyze drug detoxification reactions. They have found that the placenta does have a limited capacity to perform some of the reactions by which drugs are normally metabolized.

Drug Detoxification

Drug detoxification usually requires two steps: oxidation, frequently resulting in the addition of a hydroxyl group; followed by combination of the oxidized product with glucuronic acid to form glucuronide derivatives. The glucuronides may then be excreted in the urine. The liver is a rich source of the enzymes, which are located in the membranes of the endoplasmic reticulum (ER). The human fetus, unlike those of many other species, does have some of the enzymes required for drug metabolism. Sten Orrenius, Anders Rane, and their colleagues at the Karolinska Institutet, Stockholm, found that microsomes (the fraction of homogenized cells that contains the membranes of the ER) prepared from human fetal liver catalyzed the oxidation of both drugs and naturally occurring substrates. They did not, however, catalyze the formation of glucuronides.

The possibility exists that the products of drug metabolism will actually be more toxic than the original compounds. For example, James R. Gillette of the National Heart and Lung Institute, Bethesda, Maryland, reported that when the analgesic acetaminophen is oxidized, the resultant compound binds to liver cells; if the dose of acetaminophen is extremely high, liver damage occurs as a result of such binding. Phenobarbital, a commonly used sedative, enhances the damage.

Drugs and environmental contaminants can influence the metabolism of such normal body constituents as steroid hormones, fatty acids, and thyroxine—all of which play important roles in development and maturation. Allan H. Conney of Hoffmann-LaRoche, Inc., Nutley, New Jersey, has found that some chemicals, including phenobarbital, diphenylhydantoin, and DDT, induce the oxidative enzymes in the ER of liver and consequently stimulate oxidation of steroid hormones. These chemicals thus diminish the activity of estrogens, androgens, progestational steroids, and glucocorticoids. Phenobarbital, for example, decreases the promotion of uterine growth by estrogens in rats. Other chemicals, including carbon tetrachloride, chlorthion, and carbon monoxide, inhibit the activity of the microsomal enzymes and potentiate steroid action.

Thus, there is an increasing body of evidence about the fate of these drugs and about their interaction with the drug-metabolizing enzymes and with each other; nevertheless there is still little information about their teratogenicity or their toxicity to the fetus. Few drugs have been linked to specific birth defects with any degree of certainty.

Effective prediction of the teratogenic effects of a drug, especially in humans, is another problem. Daniel W. Nebert of the National Institute of Child Health and Human Development (NICHD), Bethesda, Maryland, has been investigating the use of cultured cells to predict drug toxicity. Nebert's method is based on the observation that there are genetic differences in the inducibility of the microsomal enzyme aryl hydrocarbon hydroxylase (AHH) in certain strains of mice. The chemical inducer of AHH is more toxic to mice that produce much enzyme than it is to animals that produce little or no enzyme in response to the chemical. The products of AHH activity are apparently more toxic than the original chemical. The responses of cultured fetal cells paralleled those of the parent

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strains in vivo. Nebert concluded that such cultured cells could be used to predict the toxicity of chemicals in the intact animal. He postulated that a similar method could be used to predict teratogenicity. There is, however, a wide gap between the observation of an effect on an enzyme system in vitro and the correlation of that observation with a birth defect.

Prediction of teratogenicity may have a firmer foundation when the mechanisms that regulate the orderly course of human fetal development have been identified. At present, these mechanisms, as well as the actual sequence of biochemical and physiological events of development, are largely unknown, It is known that a complex interplay of hormones—maternal, placental, and fetal—is necessary.

Dorothy B. Villee of Harvard Medical School, Boston, Massachusetts, reviewed some aspects of steroid metabolism by the human fetus. According to Villee, the fetal adrenal contains a unique zone that differs from the adult adrenal cortex in its synthetic capabilities. One major difference is that the fetal adrenal zone does not synthesize progesterone because it lacks an essential enzyme, 3β-hydroxysteroid dehydrogenase; it can convert progesterone from other sources (the placenta or the maternal ovaries) to steroids typical of the adrenal cortex. The fetal testes can synthesize progesterone and convert it to testosterone. Human chorionic gonadotropin, a placental hormone, appears to regulate both of these fetal glands.

Proper function of the fetal testis is essential for normal sexual development of the male. According to Alfred Jost of the University of Paris, the human fetus will develop as a female unless a testis actively secreting male hormones imposes the male developmental pattern. Therefore, an excess of androgens can masculinize both the genital organs and, later, the behavior of the female. Such masculinization can occur naturally as a result of certain tumors of the adrenal cortex. Moreover, Jost pointed out that synthetic progestational compounds, including some used in oral contraceptives, may actually be derivatives of male hormones and may thus cause masculinization of females. Such steroids can cross the placenta.

Feminization of males is also possible. Another progestational compound, cyproterone acetate, apparently blocks the normal masculinizing action of testosterone in the male fetus. Natural progesterone, which is secreted in large quantities during pregnancy and is necessary to maintain the pregnancy in its early stages, does not harm the fetus and may be beneficial to it.

Role of Fetal Hormones

Hormones also influence the biochemical differentiation of the fetus—the expression of fetal enzymes. Olga Greengard of Harvard Medical School found a developmental pattern for the synthesis of different groups of enzymes in fetal rat liver and thinks that fetal hormones serve as the natural stimuli for the expression of some of these enzymes. Thyroxine, glucorticoids, and glucagon are hormones that may be involved in the initiation of enzyme synthesis. For example, the pancreatic hormone glucagon plays an important role in the adaptation of the newborn rat to life outside the uterus because it both activates and induces the synthesis of enzymes needed for glucose synthesis. Glucagon is normally secreted after birth in response to low concentrations of blood glucose, but administration of the hormone a day or two before birth evokes the same enzymes changes before their scheduled time. Thus the fetus has the capacity to respond prematurely to normal stimuli. Greengard points out that a drug given toward the end of gestation should not produce morphological defects (organ formation is already complete) but could produce biochemical defects by interfering with the orderly development of enzyme patterns.

Just as it is difficult to establish the teratogenicity of a drug in the human, it is equally difficult to determine whether maternal exposure to a drug has produced fetal damage. Kurt Hirschhorn of the Mount Sinai School of Medicine, New York, concluded that in our present state of knowledge it is virtually impossible to detect many types of fetal damage. Amniocentesis —the withdrawal of amniotic fluid with a needle inserted through the abdominal wall into the uterus—followed by the culture of amniotic cells and their subsequent examination is useful for the diagnosis of some conditions, particularly those caused by chromosomal abnormalities. However, the chromosome composition of amniotic cells does not always accurately represent that in the fetal cells. Other mutations may not be detectable at all. According to Hirschhorn, current indirect methods of visualizing the fetus and examining it for morphological abnormalities can either detect only the most severe deformities or may themselves harm the fetus. Direct visualization of the fetus is still in a very early state of development.

Although most participants at the symposium considered the possibility that drugs administered to the mother could be harmful to the fetus, there is another side to the coin—namely, that medication could be given to the mother to prevent or ameliorate a condition or disease dangerous to the fetus or the newborn infant. Ronald A. Chez of the Pregnancy Research Branch, NICHD, reviewed some recent examples of such fetal therapeutics. Hyperbilirubinemia and respiratory distress syndrome are two common diseases of the newborn. Hyperbilirubinemia is characterized by abnormally high blood concentrations of bilirubin, a product of hemoglobin breakdown; it may result in poor motor and mental function in the child.

Phenobarbital, given to women before they deliver, decreases the bilirubin concentration in the blood of their babies, apparently by increasing the activity of an enzyme needed for bilirubin metabolism and excretion. However, this effect of phenobarbital is not specific; Conney and others have described effects of barbiturates on microsomal enzymes involved in the metabolism of natural steroid hormones and drugs. These effects must be evaluated in the fetus before phenobarbital is used routinely to prevent hyperbilirubinemia.

Respiratory distress syndrome, which is prevalent in premature infants, has been associated with a deficiency of one of the fatty materials coating the inner lung surface. This deficiency prevents normal respiratory function. There is evidence that administration of glucocorticoids to the pregnant woman before delivery can correct the defect. Again, further studies on the fetal effects of the hormones are required.

The symposium highlighted the paucity of our current knowledge of human developmental and fetal pharmacology. Because of the widespread use of drugs by pregnant women, clinicians and researchers are concerned about their possible effects in the fetus—especially about subtle effects, including behavioral changes, that might not be immediately aparent. In addition to discouraging the unnecessary use of drugs, these investigators would like to design safer drugs to prescribe when needed.—JEAN L. MARX