CHAPTER **33**

Drugs In Pregnancy

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It has long been recognized that food, drink, and other compounds ingested during pregnancy affect fetal development. However, it wasn't until the 1960s that the harmful effect of drugs during pregnancy was fully realized. Pregnant women taking the tranquilizer thalidomide produced offspring with severe limb malformations. Yet, multiple studies have demonstrated that nearly all women take either a prescription drug or over the counter medication during their pregnancy. The average woman will take three different medications, and one-fifth will take five or more while pregnant.

Although it is believed that 4-5% of all fetal malformations are caused by drugs, this percentage is relatively low considering the amount of women taking medications during pregnancy. Even the anti-neoplastic agents produce a far lower rate of teratogenic effects than one would anticipate. The term "teratogen" is derived from the Greek *terato* meaning monster. A teratogen is any substance or agent present during embryonic or fetal life, which is capable of inducing abnormal postnatal structure or function.

The chances of developing a teratogenic, mutagenic, carcinogenic, or other adverse reaction to a drug is multifactorial. The effect of medication is related to the type of drug, the dose reaching the fetus, duration of exposure, genotype of mother and fetus, and gestational age. Drugs given during the first three weeks post-conception are likely to be abortifacient. Between weeks 3-10 is the period of organogenesis, when the fetus is most likely to be adversely affected. After week ten, drug effects can still be deleterious as the brain, eyes, ears, liver, and gonads continue to develop. Labor and delivery can also be affected. For all effective purposes, a true placental barrier does not exist, and one must assume that any medication that exerts a systemic effect in the mother will cross the placenta to reach the fetus. To aid physicians in determining the risk factors of various drugs, the FDA in 1979 developed a five category rating system to describe the potential teratogenicity of drugs. This system does not refer to breast-feeding risks.

Category A: Controllable studies in women during the first trimester fail to demonstrate a risk to the fetus. There are only a few category A drugs, including multivitamins or prenatal vitamins.

Category B: i) Animal reproduction studies have not demonstrated fetal risk, and there are no controlled studies in pregnant women, or ii) animal reproduction studies have shown an adverse effect that was not confirmed in controlled studies in women in the first trimester. An example of this category is the penicillins.

Category C: Either studies in animals have revealed adverse effects and there are no controlled studies in women, *or* studies in women and animals are not available.

Category D: There is positive evidence of human fetal risk, but the benefits from use may be acceptable despite the risk. Anticonvulsants are examples of this category.

Category X: Proven fetal risk that clearly outweighs any possible benefit. The drug is contraindicated in pregnant women, or in women intending to become pregnant.

The FDA does not mandate the use of these definitions, therefore most manufactures have not given a letter rating to their drugs. Instead, the manufacturer includes a statement in their product information sheet stating "the safety and effectiveness in pregnant and lactating women have not been established." The risk category found in reports and texts are often assigned by the respective authors, who occasionally disagree with each other. No drug or medication should be taken during pregnancy unless clearly indicated, and the specific indications should be clearly explained to the woman.

COMMON DRUG CATEGORIES

The various categories of drugs utilized by podiatrists will be presented, along with a brief discussion of their safety.

Antibiotics

The penicillins, cephalosporins, and sulfanamides are relatively safe for use during pregnancy. The beta-lactam antimicrobials have a long established record of safety for use during pregnancy. The majority of these drugs are listed in category B. Erythromycin base is safe but the estolate form is hepatotoxic and should not be used. Erythromycin is also in category B and often used with the penicillin-allergic patient.

The aminoglycosides can be utilized when the risks outweigh the harm of non-use. Gentamicin is in category C, while the other aminoglycosides are in category D. Tetracycline, chloramphenicol and ciprofloxacin should not be used in pregnant women. Tetracycline, a category D drug, may cause discoloration of developing fetal deciduous teeth. Exposure close to term may also discolor permanent teeth. In utero exposure to tetracycline has been implicated in impaired growth of the fibula. Ciprofloxacin, with its possible effects on maturing cartilage, and chloramphenicol, with the potential "Gray Baby" syndrome, should be avoided during pregnancy.

Analgesics

Although aspirin is probably the most commonly-utilized analgesic, most authors recommend acetaminophen in its place. Aspirin, while not appearing to be teratogenic, can cause a variety of adverse effects, including some degree of platelet dysfunction and diminished factor XII activity. Aspirin is listed as a category C drug. Its use should be discouraged, especially late in pregnancy. Acetaminophen, on the other hand, is a category B drug. Most nonsteroidal anti-inflammatory drugs (NSAIDs), with the exception of butazoladin, are safe during pregnancy, except during the last trimester. There are no reports of teratogenicity with prostaglandin synthase inhibitors in early pregnancy. NSAIDs are category B drugs. Narcotic analgesics are relatively safe as well. Both meperidine and morphine are category B drugs. Codeine, however, is a category C drug.

Local Anesthetics

The small amount of a local anesthetic used during a podiatric surgery or procedure is relatively safe during pregnancy. Local anesthetics have been shown to have a more rapid onset and an increased sensitivity in isolated nerve studies in pregnant animals. Due to this enhanced potency, dosages should probably be reduced in patients during all stages of pregnancy. Epinephrine, an endogenous hormone, should cause no adverse effects to the fetus.

Antifungal Agents

Topically applied antifungal agents such as clotrimazole, miconazole, and nystatin, are category B drugs, and are safe for use even in early pregnancy. Griseofulvin is listed in category C since there is little experience regarding its use during pregnancy. Recently, a possible association of griseofulvin with conjoined twins has been made.

Antiemetics

Phenothiazines have been used many years in pregnancy without adverse effects. Prochlorperazine, promethazine, and trimethobenzamide are all in category C. Meclizine and cyclizine are in category B.

Social and Illicit Drugs

Because social or recreational drug use is so prevalent in our society, physicians must be aware of their potential adverse effects in pregnant women. Alcohol, in rare to moderate drinkers, produces no more abnormalities in offspring when compared to nondrinkers. Excessive and chronic ingestion, as well as binge drinking, is associated with fetal maldevelopment commonly referred to as fetal alcohol syndrome. Alcohol is now recognized as the leading teratogen in the Western world. It is also the most commonly identifiable cause of mental retardation. Infants of cocaine users have a higher incidence of congenital malformations, still births, and low birth-weight.

CONCLUSION

A physician must be aware of indications, risks, and benefits for medications which might be utilized in the office or prescribed for a pregnant patient. With such a large percentage of pregnant women taking either prescription or over the counter medication, (as high as 90% in some studies), the physician must be aware of potential adverse effects. Drugs in categories A and B are relatively safe to use during pregnancy. It is prudent practice to consult with the patient's obstetrician before prescribing a drug in question.

BIBLIOGRAPHY

Cunningham FG, MacDonald PC, Gant NF: *Williams Obstetrics,* Eighteenth Edition. Norwalk, CT, Appleton and Lange, 1989, pp. 562-569.

Dicke, JM: Teratology: Principles and Practice. *Med Clin North Am,* 73:3, May 1989, pp. 567-582.

Iffy L, Kaminetzky H: *Principles and Practice of Obstetrics and Perinatology* New York, John Wiley and Sons, 1981, p. 724.

Miller, RD (ed): *Anesthesia,* 3rd Ed. New York, Churchill Livingston, 1990, pp. 453-454.