TABLE 67–1 Pregnancy: Physiologic and Pharmacokinetic Changes

Physiologic Change	Pharmacokinetic Change
Increased plasma volume and body water, approximately 50% in a normal pregnancy	Once absorbed into the bloodstream, a drug (especially if water soluble) is distributed and "diluted" more than in the nonpregnant state. Drug dosage requirements may increase. However, this effect may be offset by other pharmacokinetic changes of pregnancy.
Increased weight (average 25 lb) and body fat	Drugs (especially fat-soluble ones) are distributed more widely. Drugs that are distributed to fatty tissues tend to linger in the body because they are slowly released from storage sites into the bloodstream.
Decreased serum albumin. The rate of albumin production is increased. However, serum levels fall because of plasma volume expansion. Also, many plasma protein-binding sites are occupied by hormones and other endogenous substances that increase during pregnancy.	The decreased capacity for drug binding leaves more free or unbound drug available for therapeutic or adverse effects on the mother and for placental transfer to the fetus. Thus, a given dose of a drug is likely to produce greater effects than it would in the nonpregnant state. Some commonly used drugs with higher unbound amounts during pregnancy include dexamethasone (Decadron), diazepam (Valium), lidocaine (Xylocaine), meperidine (Demerol), phenobarbital, phenytoin (Dilantin), propranolol (Inderal), and sulfisoxazole (Gantrisin).
Increased renal blood flow and glomerular filtration rate secondary to increased cardiac output	Increased excretion of drugs by the kidneys, especially those excreted primarily unchanged in the urine. These include penicillins, digoxin (Lanoxin), and lithium.
	In late pregnancy, the increased size and weight of the uterus may decrease renal blood flow when the woman assumes a supine position. This may result in decreased excretion and prolonged effects of renally excreted drugs.

pregnancy and lactation. Other drugs are used mainly to influence some aspect of pregnancy. These drugs are discussed in greater detail and include those used to induce abortion (abortifacients), drugs used to stop preterm labor (tocolytics), and drugs used during labor and delivery.

MATERNAL–PLACENTAL–FETAL CIRCULATION

Drugs ingested by the pregnant woman reach the fetus through the maternal–placental–fetal circulation, which is completed about the third week after conception. On the maternal side, arterial blood pressure carries blood and drugs to the placenta. In the placenta, maternal and fetal blood are separated by a few thin layers of tissue over a large surface area. Drugs readily cross the placenta, mainly by passive diffusion. Placental transfer begins approximately the fifth week after conception. When drugs are given on a regular schedule, serum levels reach equilibrium, with fetal blood usually containing 50% to 100% of the amount in maternal blood.

After drugs enter the fetal circulation, relatively large amounts are pharmacologically active because the fetus has low levels of serum albumin and thus low levels of drug binding. Drug molecules are distributed in two ways. Most are transported to the liver, where they are metabolized. Metabolism occurs slowly because the fetal liver is immature in quantity and quality of drug-metabolizing enzymes. Drugs metabolized by the fetal liver are excreted by fetal kidneys into amniotic fluid. Excretion also is slow and inefficient owing to immature development of fetal kidneys. In addition, the fetus swallows some amniotic fluid, and some drug molecules are recirculated.

Other drug molecules are transported directly to the heart, which then distributes them to the brain and coronary arteries. Drugs enter the brain easily because the blood–brain barrier is poorly developed in the fetus. Approximately half of the drug-containing blood is then transported through the umbilical arteries to the placenta, where it reenters the maternal circulation. Thus, the mother can metabolize and excrete some drug molecules for the fetus.

DRUG EFFECTS ON THE FETUS

The fetus, which is exposed to any drugs circulating in maternal blood, is very sensitive to drug effects because it is small, has few plasma proteins that can bind drug molecules, and has a weak capacity for metabolizing and excreting drugs. Once drug molecules reach the fetus, they may cause teratogenicity (anatomic malformations) or other adverse effects. The teratogenicity of many drugs is unknown. However, since 1984, the Food and Drug Administration (FDA) has required that new drugs be assigned a risk category (Box 67–1).

Drug teratogenicity is most likely to occur when drugs are taken during the first trimester of pregnancy, when fetal organs are formed (Fig. 67–1). For drugs taken during the second and third trimesters, adverse effects are usually manifested in the neonate (birth to 1 month) or infant (1 month to 1 year) as growth retardation, respiratory problems, infection, or bleeding. Overall, effects are determined mainly by the type and amount of drugs, the duration of exposure, and the level of fetal growth and development when exposed to the drugs. Both therapeutic and nontherapeutic drugs may affect the fetus.

Fetal effects of commonly used *therapeutic* drugs are listed in Box 67-2. Effects of *nontherapeutic* drugs are described in the following paragraphs.

Alcohol is contraindicated during pregnancy; no amount is considered safe. Heavy intake may cause fetal alcohol