

WOMEN'S HEALTH II

DRUGS IN PREGNANCY

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Learning Objectives

1. For a new drug, estimate the risk of congenital anomalies to a human embryo using only animal reproduction data.
2. Given a drug known to cause developmental toxicity but required for the treatment of maternal disease, design a treatment plan that represents the lowest risk to the embryo and/or fetus.
3. Evaluate the embryonic and/or fetal risk of birth defects of a particular drug exposure based on the timing of the exposure or on the dose.
4. Develop sufficiently detailed informational material that will enable a pregnant woman to make an informed choice regarding proposed drug therapy.
5. Devise a plan to counsel a pregnant woman who, during the critical period, took a drug that might cause developmental toxicity.

Introduction

Birth defects, together with deformations and chromosomal abnormalities, are a leading cause of neonatal and postneonatal deaths and carry a high social and economic impact. According to the most recent analysis in 1992, the estimated lifetime cost for all infants with one or more of the 18 most clinically significant birth defects in the United States was \$8 billion. The incidence of congenital malformations recognized at birth is between 2% and 4%. In the months and years after birth, the incidence increases to about 5% to 6% as previously hidden defects, especially of the internal organs and the brain, become evident. Although there is a popular misconception that most birth defects are caused by drugs, few result from drug exposure. However, as a group, drug-induced or drug-deficient defects are the only ones that might be preventable (e.g., folic acid 0.4 mg daily to prevent neural tube defects [NTDs] or 4–5 mg daily to prevent anticonvulsant-induced NTDs; insulin supplementation to prevent multiple defects. Moreover, teratogenic drugs do not cause all types of birth defects; rather, the defects typically are a confined group of malformations often referred to as a

syndrome. A second misconception is that drugs cause birth defects only in the first trimester; in fact, they can cause all types of developmental toxicity, including birth defects, throughout gestation. The only prerequisite for a birth defect is for the drug exposure to coincide with a critical developmental event.

Stages of Pregnancy

Pregnancy Dating

Gestational age is usually calculated from the first day of the last menstrual period; this is about 2 weeks before ovulation and fertilization and almost 3 weeks from the time of implantation in the uterus. Pregnancy is also dated by ultrasonography in the second and third trimesters. Ultrasonography is used clinically to correct mistaken dates and discern intrauterine growth restriction (IUGR) and to determine the risk to neonatal viability in threatened preterm birth. Women commonly do not know either the first day of their last menstrual period or the time of conception. In fact, about 50% of all pregnancies are unplanned. Because of this, ultrasound dating is often the most accurate method of measuring gestation. Pregnancy dating is such an important clinical decision that, once a date has been set by the time from last menstrual period or by ultrasonography, it will not be changed unless there is compelling evidence to do so.

The average pregnancy lasts about 280 days (or 40 weeks) from the first day of the last menstrual period. The actual length of gestation is about 264 days or 38 weeks; however, because conception cannot occur until an egg is released from the ovary, by convention, the 2 weeks are included in the dating. The expected date of delivery can be calculated by adding 7 days to the date of the first day of the last menstrual period and then counting back 3 months (Naegele rule). For example, if the first day of the last menstrual period was July 20, then the expected date of delivery would be April 27.

The *embryonic period* is defined as beginning at the fifth week (day 35) after the first day of the last menstrual period and as ending at 10 weeks (day 70) after the first day of the last menstrual period. The end of the embryonic

Abbreviations in This Chapter

ACE	Angiotensin-converting enzyme
FAS	Fetal alcohol syndrome
FDA	U.S. Food and Drug Administration
IUGR	Intrauterine growth restriction
MRHD	Maximum recommended human dose
NOEL	No-observed-effect-level
NTD	Neural tube defect
OTIS	Organization of Teratology Information Specialists
PCA	Patient-controlled analgesia
PPHN	Persistent pulmonary hypertension of the newborn
SSRI	Selective serotonin reuptake inhibitor
TERIS	Teratogen Information System

period coincides with the beginning of the *fetal period*. The embryonic period and the period of organogenesis, when embryologic differentiation occurs, are the same, about 20–55 days after fertilization.

Trimesters

Pregnancy is customarily divided into three equal parts, or trimesters, of about 3 calendar months each. The division is made using 42 weeks, the maximal duration of a normal pregnancy, to assist in distinguishing important milestones such as the chance of spontaneous abortion and the onset of gestational hypertension. This division also distinguishes the first trimester, the period of greatest vulnerability for drug-induced structural anomalies or teratogenicity. However, more precise knowledge of the fetal age is critical for many pregnancy events, including teratogenicity. Therefore, the clinically appropriate unit of measure is weeks and days of gestation completed, such as 31 weeks and 3 days, typically shown as 31³/₇ weeks.

The second and third trimesters, 15–28 and 29–42 weeks, respectively, are periods of growth and maturation of structures formed during the embryonic period. Although drug-induced birth defects occur much more commonly in the embryonic period, developmental toxicity, including structural anomalies, can be caused by drugs throughout the fetal period.

Reproductive Toxicity

Reproductive toxicity is defined as fertility, lactation, parturition, and developmental toxicity. Only the last two elements are relevant to the discussion of drugs in pregnancy.

Parturition

Parturition occurs at the end of pregnancy with the delivery of the fetus. There are three stages of labor: stage one, from onset of labor to full, 10-cm dilation of the cervix; stage two, from full dilation of the cervix to delivery of the infant; and stage three, from delivery of the infant to delivery

of the placenta. Several drugs are used either immediately before the onset of labor or during labor. Commonly used drugs include anti-infectives for prolonged premature rupture of the membrane, for prevention of neonatal infection in documented or suspected Group B *Streptococcus* colonization of the cervix, and for pyelonephritis and chorioamnionitis; corticosteroids for fetal lung immaturity in preterm labor; anticonvulsants and antihypertensives for toxemia; tocolytics for preterm labor and cervical ripening; agents for labor induction; and analgesics (parenteral, local, regional, and general) for pain control.

All agents used during parturition have the potential to cause toxicity that can adversely affect the fetus and the newborn. For example, anti-infectives can alter the normal maternal vaginal and cervical flora by selecting resistant organisms that can cause sepsis in the newborn and resistant wound infections in the mother. Anti-infectives that should not be used in labor (and their potential neonatal toxicity) include nitrofurantoin (hemolytic anemia), sulfonamides (jaundice and hemolytic anemia), and tetracyclines (teeth staining). Betamethasone and dexamethasone cause maternal hyperglycemia, and thus fetal hyperglycemia; if the mother has diabetes mellitus, they can lead to increased risk of neonatal hypoglycemia. In addition, multiple courses of these corticosteroids are associated with adrenal suppression, lower birth weight, and reduction in head circumference. Three commonly used antihypertensives for gestational hypertension or preeclampsia (methyldopa, labetalol, and hydralazine) can be titrated to safely decrease maternal blood pressure without causing hypotension that would jeopardize placental perfusion and result in fetal hypoxia and bradycardia.

Tocolytic Agents

Tocolytics are drugs used to arrest uterine contractions and are routinely used in attempts to prevent preterm delivery. Magnesium sulfate, the anticonvulsant of choice to prevent seizures in women with preeclampsia, is also used as a tocolytic. When used for either indication, magnesium sulfate can cause hypocalcemia and bone demineralization, particularly with prolonged therapy, and result in rickets in the newborn. Other tocolytics can cause a variety of fetal and neonatal toxicities. For example, terbutaline can cause fetal tachycardia and significant hyperglycemia if the mother has diabetes mellitus. Indomethacin and sulindac, used as tocolytics, can cause severe fetal and neonatal toxicity. Some tocolytic toxicity is duration-dependent; examples include fetal renal toxicity, manifested as oligohydramnios resulting from decreased urine output, and premature closure of the ductus arteriosus. If the ductus closes in utero, persistent pulmonary hypertension of the newborn (PPHN) is a risk. In addition, patent ductus arteriosus in the neonate, which may require surgical closure, has been observed. To prevent these toxicities, treatment courses are limited to no more than 48 hours. Nitroglycerin, when used as an emergency tocolytic, often causes maternal hypotension with resulting decreased placental perfusion and fetal hypoxia that requires rapid delivery of the fetus. Calcium channel blockers (e.g., nifedipine) have a low frequency of toxicity, but hypotension is a potential complication.

Agents for Cervical Ripening and Labor Induction

Cervical softening and effacement must occur before a fetus can be delivered vaginally. These changes occur naturally in most pregnancies, but when they do not, drugs are used to induce cervical ripening. Two prostaglandins, misoprostol and dinoprostone, are routinely used for this purpose. Uterine hyperstimulation that results in fetal distress (i.e., bradycardia) is a complication with either agent and is dose-related. Uterine rupture and placental abruption (in which the placenta tears away from the uterus) are potentially life-threatening complications. Induction of uterine contractions and/or augmentation of labor is routinely accomplished with oxytocin, but this agent can also cause dose-related uterine hypertonicity with fetal bradycardia.

Analgesic Agents

Both intermittent injections and patient-controlled analgesia (PCA) with narcotics are relatively ineffective for labor pain. The use of meperidine has been largely replaced by intravenous fentanyl and morphine because of the tendency for meperidine to cause prolonged neonatal neurobehavioral depression (e.g., lethargy, depressed attention, decreased social responsiveness). When narcotics are used close to delivery, dose-related neonatal respiratory depression is a well-known result. Two agents with narcotic agonist-antagonist properties, butorphanol and nalbuphine, do not provide better analgesia but might cause less respiratory depression in the newborn. Nonsteroidal anti-inflammatory agents are contraindicated for the reasons previously discussed. Regional anesthesia (i.e., epidural, spinal, or combined spinal-epidural with local anesthetics and sometimes combined with morphine or fentanyl) is the preferred method to control labor pain. There is no benefit in waiting for a particular stage of labor to start regional anesthesia, so it should be started on patient demand. Fetal or neonatal toxicity is rare and is primarily a result of maternal hypotension. Transient fetal heart rate decreases have been observed in up to 8% of women receiving epidural or spinal anesthesia. To prevent hypotension, bolus intravenous infusions of 500–1000 mL of nonglucose-containing isotonic crystalloid fluid are given as prehydration. Fetal bradycardia has been associated with paracervical blocks. Drugs used in general anesthesia include nitrous oxide, thiopental sodium, and one of the halogenated hydrocarbons (i.e., desflurane, enflurane, isoflurane, or sevoflurane). All of these agents rapidly cross the placenta and can cause neonatal depression. Keeping the induction-to-delivery time to less than 8 minutes may reduce the incidence of newborn toxicity.

Developmental Toxicity

Developmental toxicity describes exposures or events during pregnancy that cause growth restriction, structural anomalies, functional/neurobehavioral deficits, or embryo/fetal death. Moderate growth restriction, such as that observed with prolonged use of oral corticosteroids (300–400 g), may not be clinically significant. However, severe growth restriction, defined as fetal weight less than the 10th percentile for gestational age and commonly referred

to as IUGR in the fetus or small-for-gestational-age in the newborn, is a serious complication. It involves not only decreased weight, which affects all of the organs, but also a significant decrease in the number of cells in the current and future brain cortex. Several factors, including drugs, can cause IUGR that is associated with an increased risk of neonatal morbidity and mortality, a potentially small and perhaps clinically insignificant decrease in intelligence, and a markedly increased risk of cerebral palsy. Structural anomalies are classified as either major or minor birth defects. Major defects are defined as having cosmetic or functional significance to the child (e.g., a heart defect). Minor defects (e.g., hypoplastic fingernails, micrognathia, strabismus) are defined as defects that occur in less than 4% of the population and have neither cosmetic nor functional significance to the child. Functional/neurobehavioral deficits, such as alcohol-induced mental retardation, may not be recognized for years after birth. For these reasons, the focus of drug-induced toxic effects on the embryo and fetus has shifted from consideration of only structural anomalies to consideration of all four aspects of developmental toxicity.

Causes of Developmental Toxicity

The causes of developmental toxicity can be classified under five general headings: (1) genetic (20%); (2) chromosome abnormalities (3% to 5%); (3) multifactorial inheritance (incidence unknown); (4) environmental, including drugs and environmental chemicals, infections, and maternal metabolic imbalances (10%); and (5) unknown causes (65% to 70%).

Genetic

Genetic causes of structural anomalies may involve a dominant gene from either parent. Typically, there is a family history of the defect, such as achondroplasia (i.e., dwarfism). A spontaneous gene mutation may also occur and cause any type of major birth defect with no family history of the malformation. Finally, both parents may carry a recessive gene that, when passed on in combination to the embryo, can cause a defect. Examples of this type of genetic defect include infantile polycystic kidney disease; and nonketotic hyperglycemia, characterized by lethargy, seizures, hyperglycemia, elevated glycine values, and no recurrent ketoacidosis. None of the defects caused by genetic factors involve drugs.

Chromosome Abnormalities

Chromosome abnormalities may involve an extra chromosome, such as in trisomy 21 (more commonly known as Down syndrome), trisomy 13, and trisomy 18; all of these are related to mental retardation and different malformations. Chromosome abnormalities also may involve an extra X chromosome (i.e., 47,XXX) or a missing X chromosome (i.e., 45,X [Turner syndrome]). None of these abnormalities involve drug exposures.

Multifactorial Inheritance

Multifactorial inheritance determines the susceptibility of the embryo or fetus to interact with the environment and may result in birth defects. Examples of such defects are cleft lip with or without cleft palate, cleft palate alone, some common cardiac defects, pyloric stenosis, clubfoot,

Hirschsprung anomaly (congenital megacolon), dislocation of the hip, NTDs, and scoliosis. The cause of these defects may be an interaction between one or more genes of the embryo/fetus and environmental factors. Although usually unknown, environmental risk factors have been identified for some defects, including lower socioeconomic class (some NTDs related to diet or other factors), birth order (dislocation of the hip and pyloric stenosis), and drugs. Drugs or chemicals thought to be influential factors in birth defects include thalidomide, phenytoin, hydrocortisone, cigarette smoking, and alcohol. Although the incidence of defects secondary to multifactorial inheritance is unknown, the number appears to be growing. There is, for example, increasing evidence that susceptibility to alcohol resulting in fetal alcohol syndrome (FAS) is genetically determined by the activity of the gene that produces the enzyme alcohol dehydrogenase, which metabolizes ethanol to acetaldehyde. In addition, one of the mechanisms involved in phenytoin-induced defects is thought to be low or absent activity of epoxide hydrolase, the enzyme responsible for metabolizing the intermediate epoxide metabolite of phenytoin. Trimodal distribution of this enzyme is thought to be regulated by a single gene with two allelic forms. Embryos with low enzyme activity (homozygous for the recessive allele) exposed to phenytoin show evidence of fetal hydantoin syndrome, whereas those with intermediate activity (heterozygous) or high activity (homozygous for the dominant allele) are not affected.

Multifactorial inheritance is thought to explain why most pregnant women exposed to known teratogens have normal babies. Even potent teratogens adversely affect only a relatively few embryos or fetuses. For example, the prevalence of birth defects after exposure to thalidomide and phenytoin is less than 20% and less than 10%, respectively. Unfortunately, there is no method, other than family history, to determine susceptibility in the clinical setting.

Environmental Factors

Drugs can cause developmental toxicity, either directly or by interaction with one or more genes in the embryo or fetus. There are about 20 pharmacological classes and more than 90 individual agents of medication and substance abuse known to cause developmental toxicity in humans (Table 1-1). This list continues to expand as researchers design increasingly sophisticated studies with adequate statistical power to detect even small risks of toxicity, such as those observed with corticosteroids, nonsteroidal anti-inflammatory drugs, and selective serotonin reuptake inhibitors (SSRIs). This research includes multicenter case-control studies and prospective cohort studies with detailed examination of infants by a dysmorphologist. One resulting discovery is that clusters of three or more minor malformations are often an indication of a hidden major defect.

Among infectious agents, only some viruses, one protozoan parasite (*Toxoplasma gondii*, the cause of toxoplasmosis), and one bacterium (*Treponema pallidum*, the cause of syphilis) are thought to cause teratogenicity in humans. The viruses include cytomegalovirus, herpes simplex types 1 and 2, parvovirus B-19, rubella, varicella zoster, and the Venezuelan equine encephalitis virus.

Bacteria do not usually cause structural anomalies; they typically cause embryo or fetal death.

The primary maternal metabolic imbalance that causes embryo and fetal toxicity is diabetes mellitus. Poorly controlled diabetes before and during gestation is associated with all four aspects of developmental toxicity, including structural anomalies. The second most common metabolic imbalance is phenylketonuria. If a fetus is homozygous for phenylketonuria, it will have virtually no phenylalanine hydroxylase activity and will be unable to metabolize phenylalanine to tyrosine. Even fetuses that inherit only one autosomal recessive gene, and are considered heterozygous and nonphenylketonuric, will have limited enzyme activity to metabolize phenylalanine. In either case, any phenylalanine that crosses the placenta will increase to toxic concentrations in the fetus and induce mental impairment. This is a functional deficit, the degree of which is dependent on the amount of fetal enzyme activity.

Unknown Factors

At present, the cause of a substantial number of birth defects cannot be determined. However, many defects with no known cause may be the result of multiple genes, spontaneous errors in development, multifactorial interactions, or the synergistic interaction of teratogens.

Criteria for Establishing Drug-Induced Birth Defects

Criteria have been published for establishing that an agent caused human teratogenicity. Of the eight criteria, four are considered essential, and four are considered helpful but not essential. The four essential criteria are (1) exposure at a critical time; (2) the presence of a specific defect or syndrome; and either (3) consistent findings of two or more epidemiologic studies or (4) a rare exposure associated with a rare defect. The four helpful but nonessential criteria are (1) teratogenicity in animals, (2) biologic plausibility, (3) proof that the agent acts in an unaltered state and not as a metabolite, and (4) secular trends in which the data demonstrate an increase in the prevalence of a specific defect when a drug is available and a decrease when the drug is no longer available. Thalidomide-induced limb reduction defects, phocomelia, and amelia are excellent examples of this last criterion.

Critical Period

The timing of an exposure is critical. If the exposure occurs after a structure is formed, it cannot be implicated as a cause of the defect. Most structures are formed during organogenesis, and this is the period of greatest vulnerability for birth defects. For example, the critical period of fetal exposure for thalidomide is 34–50 days after the first day of the last menstrual period (20 ± 1 days to 36 ± 1 days after conception). Thus, if the thalidomide was taken 52 days after the first day of the last menstrual period, the exposure would not cause limb reduction defects or other malformations associated with this drug. Other examples of time-critical defects include cleft lip (before about 9 weeks of gestation), cleft palate (before 10–11 weeks of gestation),

Table 1-1. Therapeutic and Abuse Drugs Known to Cause or Suspected of Causing Developmental Toxicity^a

Agent	Critical Period	Developmental Toxicity
Abuse drugs		
Cigarette smoking	Throughout	Low risk: defects of heart and great vessels, limbs, skull, genitourinary system, feet, abdominal wall, small bowel, and muscles High risk: abortion, stillbirth, IUGR, placenta abruption, placenta previa, preterm delivery
Cocaine	Throughout	IUGR, vascular disruptive-type defects, cerebrovascular accidents, death
Ethanol (alcohol)	Throughout	Fetal alcohol syndrome defects: craniofacial, central nervous system, heart, renogenital, cutaneous, skeletal, and muscle defects, IUGR, mental retardation Fetal alcohol effects: abortions, mental retardation
ACE inhibitors ^b	2nd–3rd trimesters	Fetal kidney toxicity/anuria, hypotension, oligohydramnios, pulmonary hypoplasia, hypocalvaria, <i>cardiovascular and central nervous system defects</i> , limb contractures, neonatal renal failure, hypotension
Androgens ^b	8 weeks to term	Masculinization of female fetus
Angiotensin II RAs ^b		Same as ACE inhibitors
Anticoagulants		
Warfarin	6th–9th week	Fetal warfarin syndrome defects: nasal hypoplasia, stippled epiphyses, IUGR, hypoplasia of extremities, seizures, developmental delay, scoliosis, hearing loss, heart defects, death
	2nd–3rd trimesters	Hemorrhage-induced brain damage, blindness, optic atrophy, microphthalmia
Anticonvulsants		
Carbamazepine	1st trimester	NTDs, craniofacial defects, nail hypoplasia, developmental delay; folic acid 4–5 mg daily may lower risk of early hemorrhagic disease of the newborn
Paramethadione	1st trimester	Mental retardation, craniofacial and kidney/ureter defects, developmental delay
Trimethadione	1st trimester	Same as paramethadione
Phenobarbital and primidone	1st trimester	Mental retardation; cardiovascular and urinary tract defects; folic acid 4–5 mg daily may lower risk
Phenytoin	3rd trimester	Fetal hydantoin syndrome: facial defects, oral clefts, VSDs, IUGR, mental retardation; folic acid 4–5 mg daily may lower risk
	3rd trimester	Early hemorrhagic disease of the newborn
Valproic acid	1st trimester	NTDs (risk 1% to 2%); facial defects, IUGR, retarded psychomotor development; folic acid might not be protective
<i>Lamotrigine</i>	<i>1st trimester</i>	<i>Cleft lip or palate</i>
Antidepressants		
Lithium	1st trimester	Ebstein's anomaly (low risk)
SSRIs ^b and SNRIs ^b	2nd–3rd trimesters	Seizures, withdrawal, serotonin syndrome, transient neurobehavioral deficits, low birth weights
	<i>After 20 weeks</i>	<i>Persistent pulmonary hypertension of newborn</i>
<i>Paroxetine</i>	<i>1st trimester</i>	<i>Cardiac (mostly ASDs and VSDs but also right ventricular outflow tract obstruction), omphalocele, anencephaly, gastroschisis, abortions (plus above)</i>
Anti-estrogens		
Tamoxifen	8 weeks to term	Ambiguous female genitalia, <i>Goldenhar's syndrome</i>
Anti-infectives		
Fluconazole (high dose)	1st trimester	Craniofacial and skeletal defects, VSDs, pulmonary artery hypoplasia
Tetracyclines ^b	2nd–3rd trimesters	Permanent discoloration of deciduous teeth
Trimethoprim	1st trimester	Cardiovascular defects; folic acid 0.4 mg may lower risk
Quinine (high dose)	1st trimester	Multiple defects after unsuccessful abortion attempt
Antineoplastics		
Busulfan	1st trimester	Cleft palate, pyloric stenosis, eye defects
Chlorambucil	1st trimester	Renal/ureter agenesis, cardiovascular defects

(Continued on next page.)

Table 1-1. Therapeutic and Abuse Drugs Known to Cause or Suspected of Causing Developmental Toxicity^a (continued)

Agent	Critical Period	Developmental Toxicity
Antineoplastics (continued)		
Cyclophosphamide	1st trimester	Craniofacial, eye, and limb defects; genitourinary tract defects; IUGR; neurobehavioral deficits
Methotrexate	1st trimester	Craniofacial, limb defects, IUGR, neurobehavioral deficits
Antithyroid		
Methimazole	Up to 7 weeks from conception	Aplasia cutis, choanal atresia, esophageal atresia with tracheoesophageal fistula, minor facial defects, hypoplastic or absent nipples, psychomotor delay, goiter
Iodine	2nd–3rd trimesters	Goiter
β-Blockers ^b	2nd–3rd trimesters	Severe IUGR of placenta and fetus (all β-blockers without intrinsic sympathomimetic activity)
Atenolol		Same as β-blockers
Chelator		
Penicillamine	Unknown	Cutis laxa, craniofacial defects
Corticosteroids ^b		
	1st trimester	Cleft lip and/or palate (risk is about 1% or less) with systemic agents; <i>some reports with inhaled corticosteroids</i>
	Throughout	Mild growth restriction (300–400 g)
Dermatologic		
Acitretin	1st trimester	Same as isotretinoin
Etretinate	1st trimester	Same as isotretinoin
Isotretinoin	1st trimester	Microtia, anotia, thymic aplasia, cardiovascular defects
Diagnostics		
Methylene blue (intra-amniotic)	2nd–3rd trimesters	Intestinal atresia and/or occlusion, newborn hemolytic anemia, hyperbilirubinemia, or methemoglobinemia
Diethylstilbestrol	Up to 20 weeks	Multiple defects of the genital tract in female and male; vaginal/cervical clear cell adenocarcinoma in adolescents
Gastrointestinal		
Misoprostol (high doses)	1st trimester	Defects secondary to attempted abortion: vascular disruption, limb defects, Möbius syndrome
Immunomodulators		
Thalidomide	20–36 days after conception (± 1 day)	Limb, skeletal, and craniofacial defects; brain defects; NTDs; respiratory, gastrointestinal, cardiac, and genitourinary defects
NSAIDs		
	1st trimester	Abortion, oral clefts, cardiac defects (ASDs and VSDs), <i>gastroschisis</i>
	After 32 weeks	Premature closure of the ductus arteriosus
Toluene inhalation	Throughout	Similar to ethanol
Vitamins		
Vitamin A (high doses)	1st trimester	Same as isotretinoin

^aDrugs, periods, and toxicities shown in *italics* require confirmation.

^bMultiple agents in class.

ACE = angiotensin-converting enzyme; ASDs = atrial septal defects; IUGR = intrauterine growth restriction; NSAIDs = nonsteroidal anti-inflammatory drugs; NTDs = neural tube defects; RAs = receptor antagonists; SNRIs = serotonin norepinephrine reuptake inhibitors; SSRIs = selective serotonin reuptake inhibitors; VSDs = ventricular septal defects.

and ventricular septal defects (before 8 weeks of gestation). Neural tube defects occur between 17 and 30 days after conception. Although organogenesis is usually the most vulnerable period, the central nervous and urogenital systems are examples of systems that are sensitive to late injury.

Dose Relationship

There always is a dose relationship between drug exposure and developmental toxicity. The threshold dose, below which there is no toxic effect, varies from drug to drug. As the dose increases above the threshold, so does the severity and frequency of developmental toxicity until, eventually,

the lethal dose is reached. The no-observed-effect-level (NOEL) in animal reproduction tests is commonly used for drug product inserts. Although this is an important value, particularly in the evaluation of animal reproduction data, the human NOEL for therapeutic drugs is rarely known with certainty because studies to determine this value would obviously be highly unethical. Observational studies have identified the NOEL for drugs such as thalidomide and possibly for cardioselective β -blockers (e.g., atenolol dosage less than 50 mg/day) and paroxetine (e.g., dosage less than 25 mg/day). However, even in these cases, the dosages are an estimate because pregnancy drug exposure is rarely quantified in terms of milligram per kilogram, milligram per square meter, or exposure. Because human height and weight is highly diverse, as is systemic exposure to drugs, this critical element for determining developmental toxicity cannot be assessed.

Drugs Known to Cause Developmental Toxicity

Drugs known to cause developmental toxicity are shown in Table 1-1. The critical period is usually during organogenesis, but several agents can cause toxicity later in pregnancy. Angiotensin-converting enzyme (ACE) inhibitors, angiotensin II receptor antagonists, atenolol and other β -blockers without intrinsic sympathomimetic activity, corticosteroids, tetracycline, nonsteroidal anti-inflammatory agents, ethanol, cigarette smoking, cocaine, and toluene inhalation can all produce various types of developmental toxicity after the first trimester.

Estimating Embryo and Fetal Risk

Human embryo and fetal risk can be estimated by answering the four questions below. Assistance is also available from the Organization of Teratology Information Specialists (OTIS) Web site, www.otispregnancy.org.

Are There Human Pregnancy Data for the Drug?

Pregnant women are exposed to drugs in three ways: (1) they become pregnant while taking a drug for a current condition; (2) they take a drug during an undiagnosed pregnancy; or (3) they take a drug when the pregnancy is known. The first two reasons are common because about 50% of pregnancies are unplanned. Regardless of the reason for drug exposure, the most important data for estimating embryo and fetal risk are published human pregnancy experiences. Unfortunately, these data are almost always absent for new drugs because pregnancy is an exclusion in premarketing clinical trials. When a woman enrolled in a clinical trial becomes pregnant, she usually is removed from the trial, and there is little if any follow-up of her pregnancy outcome. Even for drugs that have been on the market for 20 years, more than 90% have inadequate data to determine the risk of teratogenicity or other forms of developmental toxicity. An example could be a woman who takes a drug

not currently known to cause defects. Subsequent research determines that the drug is a teratogen with a birth defect prevalence of 6%. The overall rate is now about 9% (i.e., 6% plus 3% background risk). If there were published information on 50 women who took a critical dose at a critical time (which in itself is unlikely), the background rate, on average, would predict that about one or two infants would have major birth defects. However, in this theoretical case, there would instead be, on average, four or five infants with defects. Unless there were a cluster of similar defects, it would be difficult to determine that this small increase was drug-related and not a normal variation. Thus, although human data are essential, adequate data are usually unavailable.

Do Other Drugs in the Same Pharmacological Class or with the Same Mechanism of Action Cause Developmental Toxicity?

Drugs in the same pharmacological class or with similar mechanisms of action will usually produce similar effects, or a similar lack of effect, in the embryo and fetus. This class effect is common. For example, all drugs in the following classes can produce similar toxic effects in the embryo or fetus: tetracyclines, nonsteroidal anti-inflammatory drugs, ACE inhibitors, androgens, and corticosteroids. Drugs with similar mechanisms may also cause the same defects, such as ACE inhibitors and angiotensin II receptor antagonists, and SSRIs and serotonin norepinephrine reuptake inhibitors. However, if the pharmacological classes are too broad, comparisons can lead to erroneous conclusions. For example, the antidiabetic class is too broad because it combines agents with markedly different mechanisms. This is also true for the broad classes of antidepressants, antihypertensives, antibiotics or anti-infectives, and antineoplastics. Many new drugs also belong to new pharmacological classes, such as monoclonal antibodies used in cancer and other diseases. Thus, estimating risk by this method may not always be possible.

Does the Drug Reach the Embryo or Fetus?

Drugs can produce both direct and indirect toxic effects on the embryo and fetus. For example, a drug might cause maternal hypotension, thereby causing anemia or decreased placental perfusion resulting in growth restriction; or, in an extreme example, the drug might cause maternal death resulting in fetal death. For a drug to cause direct toxicity, sufficient amounts must reach the maternal circulation, cross the placenta, and surpass the threshold concentration for harm. In addition, the transfer rate must be high enough to exceed the unknown fetal clearance rate. However, clinically, there are no direct methods to quantify drug concentration in the embryo or fetus. The best that can be done is to make a qualitative estimate of the amount of drug reaching the fetal compartment.

Several chemical and other factors determine whether an active drug crosses the placenta. These factors include maternal blood concentration, plasma elimination half-life, molecular weight, lipid solubility, pK_a (the pH at which equal concentrations of the acid or conjugate base forms of a substance are present), plasma protein binding, and placental metabolizing enzymes. Not surprisingly, maternal blood concentration is the most important factor. If the drug

is not in systemic circulation, there will be no drug to cross the placenta, irrespective of the other factors. For example, the systemic bioavailability of inhaled corticosteroids is low; therefore, these agents present minimal risk of direct embryonic or fetal harm. Most drugs have molecular weights of less than 600 dalton; these agents should easily cross the placenta. Another critical factor is the plasma elimination half-life. If the half-life is long, the opportunity for drug transfer will also be long. Lipid solubility, ionization, and the degree of plasma protein binding also can be used to make general estimates of drug transfer. Although ionization at physiologic pH and high plasma protein binding will inhibit transfer across any biologic membrane, both are in equilibrium with their un-ionized and unbound forms. If the elimination half-life is long, the un-ionized and unbound fractions will have time to cross the placenta. For example, warfarin is about 99% protein bound, but it has a mean plasma elimination half-life of about 40 hours and is a human teratogen. A second example is neostigmine, a quaternary ammonium compound that is ionized at physiologic pH, yet crosses the placenta. The placenta is a rich source of metabolizing enzymes and can deactivate some drugs. For example, betamethasone and dexamethasone are partially metabolized (47% and 54%, respectively) to inactive 11-ketosteroid derivatives.

Does the Drug Cause Developmental Toxicity in Animals?

Before drugs are labeled for use by the U.S. Food and Drug Administration (FDA), they must be tested in pregnant animals. Exceptions to this rule include agents that produce effects only in humans, such as abciximab. Excluding these, drugs must be tested on at least one rodent, usually a rat or a mouse, and one nonrodent, usually a rabbit. Animal exposures are designed to include organogenesis, as well as other stages of pregnancy. At least three doses are chosen for testing. In general, the highest dose tested is the one that produces slight maternal toxicity, such as weight loss, and the lowest dose corresponds to the approximate human dose. The middle dose is chosen to fit in between these doses. The doses are usually reported in milligrams per kilogram per day, or other appropriate units, and are compared with the human dose based on body surface area or exposure. For example, the product information might state “the lowest dose causing congenital malformations in pregnant rats during organogenesis was 10 mg/kg/day or 4 times the maximum recommended human dose (MRHD) based on milligrams per square meter.” Depending on the toxic potency of the drug, all three doses may be a fraction of the MRHD. For exposure during organogenesis, the end points include the potential for growth restriction with reduced fetal body weights, structural defects, death (e.g., pre- and postimplantation losses, decreased live births), and developmental delay (e.g., delayed skeletal ossification). Prenatal and postnatal studies extending through weaning are also conducted to determine the potential for functional deficits.

Although there are no definite methods for interpretation of animal studies, almost all drugs known to cause human developmental toxicity also cause developmental toxicity in at least one experimental animal species. In some instances, only one of several species is adversely affected. With this

understanding, a panel convened by the FDA and other groups concluded that if a drug, tested at dosages that did not cause maternal toxicity, did not cause developmental toxicity at doses of 10 times or less the human dose based on body surface area or area under the curve, then the drug could be considered to have low risk of human embryonic and fetal toxicity. Conversely, if a drug did cause toxicity at doses less than or equal to 10 times the human dose, then it would be classified as having risk, but the risk magnitude would be unknown. This conclusion is similar to guidelines released by the U.S. Environmental Protection Agency in 1991. However, if the dose causing developmental toxicity also causes maternal toxicity (e.g., weight reduction, poor appetite), the embryonic and fetal results cannot be interpreted. One source has quantified the risk of developmental toxicity, based on the number of experimental animal species that had such toxicity, as moderate risk (one species), risk (two species), or high risk (three or more species). These assessments were based on the animal data for all drugs known to cause human developmental toxicity.

Role of the Pharmacist

Most birth defects are not caused by drugs and are not preventable, but some are; therefore, pharmacists providing services to women of reproductive age can make a difference. Preventing just one drug-induced birth defect or other type of developmental toxicity can result in a significant decrease in emotional suffering and in the huge economic costs associated with these outcomes. Screening the therapy of women of reproductive age for drugs known to cause or suspected of causing developmental toxicity is critical, and providing women of reproductive age with the basis for interpreting reproductive data is important. Moreover, pharmacists can make a difference by ensuring that women of reproductive age are taking adequate vitamins, especially folic acid, before and during pregnancy and are avoiding potentially toxic social drugs if they are pregnant. For example, folic acid 0.4 mg daily (4–5 mg daily for women taking anticonvulsants or who have a history of delivering an infant with an NTD) started before conception significantly reduces the incidence of NTDs. Any amounts of alcohol or cocaine use or tobacco smoking during pregnancy can cause structural defects, neurobehavioral deficits, or death in the offspring. To make a difference, pharmacists need a general understanding of the principles of teratology, knowledge of the drugs known to cause or suspected of causing disrupted development, and access to current sources of information. This knowledge base is critical to ensure that a woman receives accurate and appropriate counseling. Moreover, pharmacists possessing this knowledge can estimate the risk from any drug exposure in pregnancy and convey this in a confident manner to the woman or her health care provider. This knowledge transfer can markedly decrease the anxiety that women commonly experience after taking a drug in pregnancy. Sadly, there are incidences when women have terminated wanted pregnancies because of an unwarranted fear of a low-risk exposure causing a birth defect. Thus, pharmacists can make a difference if they acquire the necessary tools and are willing to apply them.

Conclusion

The effect of drugs on the embryo and fetus is a complex topic. Because of the relative genetic diversity of humans, every drug exposure during pregnancy has the potential to cause harm to the developing human. Consequently, few drugs can be called safe in pregnancy, even though it appears that few drugs cause harm. The best approach is to categorize drugs by their estimated degree of risk: low risk, moderate risk, risk, or high risk.

Annotated Bibliography

1. Brent RL. Environmental causes of human congenital malformations: the pediatrician's role in dealing with these complex clinical problems caused by a multiplicity of environmental and genetic factors. *Pediatrics* 2004;113:957–68.

This review summarizes some of the advances made during the past 50 years, as well as the challenges that remain. There are six important clinical rules to follow when determining the cause of a congenital malformation: (1) a teratogenic agent cannot be described qualitatively as a teratogen because dose and timing are critical; (2) teratogenic agents cannot produce every type of malformation but typically produce a spectrum of defects; (3) teratogenic agents follow a dose-response curve and have a threshold dose, below which there is no toxicity; (4) evaluation of an infant with a birth defect requires the same intensity and scholarship as any other complex medical problem; (5) there are adverse consequences to providing erroneous information about the risk of a drug exposure in pregnancy or inaccurately alleging that a particular exposure caused the defect; and (6) there must be more emphasis on clinical teratology and genetics in medical schools and residency programs. Also discussed are the basic principles of teratology, factors that affect the susceptibility to developmental toxicants, and a list of substances and/or conditions (i.e., drugs, chemicals, infections, and maternal disease states) that are known to cause or suspected of causing congenital malformations or embryotoxicity. The background rate of congenital malformations is 3% to 6% and includes those recognized at birth and later in life. In addition, 15% of clinically recognized pregnancies will abort spontaneously. The review concludes with a series of clinical cases to demonstrate methods of evaluating adverse pregnancy outcomes.

2. Briggs GG, Freeman RF, Yaffe SJ. *Drugs in Pregnancy and Lactation*, 8th ed. Philadelphia: Lippincott, Williams & Wilkins, 2008.

First published in 1983, the eighth edition contains almost 1200 individual agents, arranged alphabetically. The format of each monograph is consistent throughout: generic name, pharmacological class, FDA risk factor, fetal risk summary and recommendation, breastfeeding summary and recommendation, and references. Many reviews have a summary paragraph that highlights the published findings. The 16 pregnancy and 6 breastfeeding recommendations are an attempt to provide the clinician with some indication of the risk level from exposure to the drug or agent. For pregnancy and breastfeeding, the levels of risk change continuously, and this is reflected in the recommendations.

3. Briggs GG, Wan SR. Drug therapy during labor and delivery. Part 1. *Am J Health Syst Pharm* 2006;63:1038–47; Briggs GG, Wan SR. Drug therapy during labor and delivery. Part 2. *Am J Health Syst Pharm* 2006;63:1131–9.

Part 1 of this review discusses the use of anti-infectives (both therapeutic and prophylactic) and the use of corticosteroids to induce fetal maturity in case of threatened preterm delivery. Anti-infectives are given to prevent and treat maternal infection and to prevent fetal and neonatal disease. Potential pathogens are discussed, as well as the pharmacokinetics of antibiotics during pregnancy. The anti-infectives that should be avoided in pregnancy are briefly discussed. When preterm delivery threatens, corticosteroids (betamethasone [the drug of choice] or dexamethasone) are given to the mother to stimulate the synthesis and release of surfactants in the fetal alveolar spaces. The risks of this therapy are discussed. Part 2 covers the therapy of gestational hypertension, preeclampsia and eclampsia, cervical ripening and labor induction, premature labor, pain control during labor, and postpartum hemorrhage. The benefits and risks of all of these therapies are discussed.

4. Briggs GG. Drug effects on the fetus and breast-fed infant. *Clin Obstet Gynecol* 2002;45:6–21.

This review includes recommendations for counseling women about drugs in pregnancy and in breastfeeding. Counseling women of childbearing age requires a knowledge base that includes agents known or suspected to cause developmental toxicity, the critical periods for the toxicity, an estimate of the magnitude of risk, and the types of potential malformations or toxicity. There are three methods to reduce the risks of embryo/fetal harm from drugs: (1) use only agents considered relatively safe in pregnancy; (2) if a drug known to cause developmental toxicity must be used, avoid the critical period if possible; and (3) use new drugs with no human pregnancy experience only when necessary and only after careful review of all available information. The review briefly covers the criteria for establishing teratogenicity, interpretation of animal reproduction studies, and placental transfer of drugs. Known human teratogens are covered, and the critical exposure period, magnitude of risk, mechanisms if known, and reported defects and toxicity are discussed. Some of these data are shown in Table 1-1.

5. Chambers CD, Braddock SR, Briggs GG, Einarson A, Johnson VR, Miller RK, et al. Postmarketing surveillance for human teratogenicity: a model approach. *Teratology* 2001;64:252–61.

The authors, all members of OTIS, describe a new research method to assist in the identification of drug-induced teratogenicity. Traditional methods, such as case reports, manufacturers' registries, cohort studies, and retrospective surveillance programs and case-control studies, often have difficulty in finding associations between drugs and developmental toxicity because of the relatively high background risk of a defect, small sample size, or subtle nature of many drug-induced malformations. Recognizing that most malformations are notable for a pattern of minor and major defects, the new method involves multicenter prospective cohort studies with structured interviews during and after gestation and examinations by a dysmorphologist of all live-born infants. If the drug exposure has a higher probability than others of affecting fetal brain development, neurobehavioral testing of the offspring is conducted. The control groups are formed from pregnant women with exposures known not to cause developmental toxicity. A table

lists defects, classified by body system, that are considered minor malformations. Statistical methods and sample size are also discussed. Another table provides the number of subjects required to detect various risks for a single major malformation with a specified baseline prevalence. For example, to document a relative risk of 3 for cleft lip with a baseline prevalence of 1/1000, a cohort study would need about 8800 subjects and a similar number of controls using a two-tailed test, power of 80%, and an α of 0.05. Few studies are able to generate these numbers and, thus, these should be viewed only as hypotheses-generating for specific major malformations. The major strength of the described method is its ability to detect all of the elements of developmental toxicity, including major and minor structural defects, pre- and postnatal growth deficiency, perinatal complications, and cognitive impairment.

6. Cunningham FG, Leveno KJ, Bloom SL, Hauth JC, Gilstrap LC 3rd, Wenstrom KD. *Williams Obstetrics*, 22nd ed. New York: McGraw-Hill, 2005.

This has been the standard text for obstetrics since the first edition appeared in 1930. The newest edition of this classic has been updated and now contains 59 chapters divided among eight major sections that cover all aspects of obstetrics. Although all of the sections are valuable, those that hold special interest for pharmacists planning to provide services to pregnant women are on antepartum, labor and delivery, the fetus and newborn, the puerperium, obstetric complications, and medical and surgical complications. This book is essential for anyone desiring an understanding of obstetrics. Although the chapter on teratology provides an overview and some specific details, other sources, such as the *Teratology Primer* and Schardein, provide a better understanding of teratology, and the eighth edition of Briggs, Freeman, and Yaffe has much more up-to-date information.

7. U.S. Food and Drug Administration. Office of Training and Communication, Division of Drug Information, HFD-240, Center for Drug Evaluation and Research. Reviewer guidance: evaluating the risks of drug exposure in human pregnancies. April 2005. Available at www.fda.gov/cder/guidance/6777fnl.htm. Accessed May 12, 2008.

The purpose of this document was to develop product labels that are helpful to clinicians caring for patients who are pregnant or planning a pregnancy. The guideline evaluates seven critical factors: (1) background prevalence of adverse pregnancy outcomes, (2) combined versus individual rates of birth defects, (3) major versus minor birth defects, (4) timing of exposure, (5) intensity of exposure, (6) variability of response, and (7) class effects. Helpful features of this document are the analysis of pregnancy outcomes, the estimated prevalence of common birth defects, and the range of birth defect rates per 10,000 live births. For pregnancy outcomes (based on 1996 national data, the most recent year these data are available), only 62% of clinically recognized pregnancies resulted in a live birth. The remaining outcomes were elective terminations (22%) and spontaneous abortions (20 weeks or less of gestation) or fetal death (20 weeks or more) (16%). Among the live births, 12.5% ended in a birth before 35 weeks of gestation, and 8.3% involved a low-birth-weight (less than 2500 g) infant. The most common category of birth defects involved the heart and circulation; this was followed by muscles and skeleton, genitourinary tract, nervous system and eye, respiratory tract, and metabolic disorders. The approximate prevalence of a few common defects (per 1000 live births) was atrial septal defects (1.05–7.03), ventricular septal defects 0.84–7.92, oral clefts (0.8–3.23), gastroschisis

(0.09–0.66), hydrocephalus without spina bifida (0.06–1.93), spina bifida without anencephalus (0.14–0.81), hypospadias (0.16–66), omphalocele (0.05–0.35), rectal and large intestine atresia/stenosis (0.10–0.90), limb reduction defects (0.15–1.04), tetralogy of Fallot (0.15–0.81), and transposition of the great heart vessels (0.10–0.67). The data provide the means to calculate the absolute risk of specific defects. The guideline also lists resources for more information and the assessment of postmarketing data.

8. Fisk Green R, Stoler JM. Alcohol dehydrogenase 1B genotype and fetal alcohol syndrome: a HuGE minireview. *Am J Obstet Gynecol* 2007;197:12–25.

This review, containing 135 references, describes the growing genetic evidence behind the current hypothesis that susceptibility to FAS is genetically determined. Also cited are some of the problems in analyzing the published evidence, including the level of alcohol exposure, demographic factors, inconsistent case definitions, and other factors. The prevalence of FAS is 0.5–2.0 per 1000 live births, making it one of the most common defects in the United States. Two helpful tables on FAS are included in the review, one citing case-control studies and the other citing cohort studies. Although the genetic data are complex, this review provides the reader with a basic understanding of how many different processes are involved in a common birth defect.

9. Garland M. Pharmacology of drug transfer across the placenta. *Obstet Gynecol Clin North Am* 1998;25:21–42.

As stated in this review, there are no clinical methods to determine the amount of fetal exposure. Percutaneous umbilical blood sampling can determine fetal drug concentrations, but this procedure is not used because of the potential risks of hemorrhage and membrane rupture. Quantification of fetal drug exposure can be made by observing the effects on the embryo and fetus. Maternal drug history and urine toxicology screens are used to provide qualitative information of drug exposure. Newborn urine screening can detect recent in utero drug exposure, and analysis of hair and meconium (the first intestinal discharges of the newborn infant) is used to detect exposure earlier in gestation. The major determinant of fetal drug concentration is maternal concentration, which is based on absorption, distribution, and elimination pharmacokinetics, all of which can undergo constant change throughout pregnancy. Other factors (e.g., molecular weight, solubility, ionization, protein binding) determine how readily the drug will cross the placenta. In addition, direct fetal clearance of the drug will decrease the concentration in the fetal plasma and will alter fetal-maternal plasma ratios. There is an extensive discussion of the pharmacokinetics of drug transfer across the placenta using a two-compartment model, but almost all of the discussion is based on computer models or, because of the lack of human data, on animal studies. There are also discussions on passive diffusion, changes in placental permeability, protein binding, ionization, placental blood flow, facilitated diffusion, active transfer, and pinocytosis. The review concludes with a discussion on the role of the fetus in drug disposition. This involves direct fetal clearance; the relatively unknown developmental time for regulation of fetal drug metabolism; and drug metabolites, both active and inactive. However, placental metabolizing enzymes are an important determinant of the amount of active drug reaching the fetal compartment, and this component is not discussed in this review.

10. Guidelines for developmental toxicity risk assessment. U.S. Environmental Protection Agency. Risk Assessment Forum, Washington, DC: EPA/600/FR-91/001, 1991. Available at cfpub.epa.gov/ncea/cfm/recordisplay.cfm?deid=23162. Accessed February 3, 2008.

The focus of this dated but still relevant 70-page guideline is on environmental exposures such as lead, mercury, ionizing radiation, and polychlorinated biphenyls. It also contains important basic tenants that are crucial to the understanding of developmental toxicity and, therefore, can be applied to drug exposures in pregnancy. In this regard, it provides the pharmacist with knowledge that can be used for human risk assessment. The introductory section discusses these basic tenants, such as the developmental toxicity observed in animals and its relationship to human pregnancy, and the dose-response relationship. In most cases, when the most sensitive species was studied, the minimally effective toxic dose was within 10-fold of the human effective dose. The pregnancy outcomes manifested by adverse developmental end points included spontaneous abortion, stillbirth, structural malformations, reduced birth weight, early postnatal death, mental retardation, sensory loss, and other functional and physical changes observed postnatally. Other sections of the guideline provide detailed, useful information: hazard identification and dose-response evaluation of agents that cause developmental toxicity; and end points of developmental toxicity studies and their interpretation for laboratory animals, maternal toxicity, altered survival, growth, morphologic development, and functional deficits. Although the emphasis is on environmental exposures, the information can be extrapolated to drug exposures in human pregnancy, such as the dose-response relationship and interpretation of the toxic end points. The emphasis in humans is on neurobehavior, but functional deficits can involve competence of one or more organ systems, and the toxic effects can be transient or reversible. Moreover, the deficit may not be apparent until adulthood. There are several tests recommended for neurobehavioral deficits, including tests of sensory systems, neuromotor and locomotor development, learning and memory, reactivity and habituation, and reproductive behavior. However, there is no testing system that addresses all of these functions.

11. Jelinek R. The contribution of new findings and ideas to the old principles of teratology. *Reprod Toxicol* 2005;20:295–300.

Even though the principles of teratology have changed during the past 30–40 years, the five basic principles are still valid today. The modernized principles now number six: (1) genetic component, (2) stage of development at exposure, (3) specific mechanisms of pathogenesis, (4) adverse effects depend on the nature of the agent, (5) developmental toxicity consists of four elements, and (6) toxicity is dose-related. The most important of the new concepts is that most birth defects have a genetic component. This genetic basis can range from single genes with either dominant or recessive roles or, in most cases, multiple genes and environmental triggers interacting in complex mechanisms. Unraveling these mechanisms is extremely difficult because environmental factors, including drugs, can potentially affect a large, perhaps unlimited, number of genes. A two-step approach has been implemented to bring clarity to this issue. Attempts are being made to define the genes involved in the development of the conceptus. The complexity of this step is illustrated by the fact that thousands of genes may be involved in the development of one system, such as orofacial tissues. Researchers are also trying to identify the genes responsible for the pharmacokinetics and

biotransformation of drugs within the mother. Although logical, the task is difficult, and progress has been limited. Molecular mechanisms have been proposed for several human teratogens, including thalidomide, retinoids, valproic acid, and some drug-induced NTDs. For example, there is evidence that genetic differences in folate metabolism, specifically methylene reductase polymorphism, can account for the NTDs observed with anticonvulsants. Moreover, genetic variants have been found in more than 20 drug-metabolizing enzymes. These variants affect the action of a drug in the individual woman and could alter the risk of teratogenicity.

12. Lo WY, Friedman JM. Teratogenicity of recently introduced medications in human pregnancy. *Obstet Gynecol* 2002;100:465–73.

The authors used seven standard clinical teratology resources to evaluate the teratogenic risks of 468 drugs approved by the FDA between 1980 and 2000. The resources used were Teratogen Information System (TERIS), Medline, Toxline, Reprotox, *Catalog of Teratogenic Risks, Drugs in Pregnancy and Lactation*, and *Chemically Induced Birth Defects*. The risk of each drug was classified into one of three categories used by TERIS: (1) no risk, minimal risk, or unlikely to produce an increased risk; (2) associated with a small, moderate, or high risk; or (3) risk undetermined. They found that the teratogenic risk of 91.2% of the drugs marketed between 1980 and 2000 was still undetermined. The authors also compared the three categories used by TERIS with the FDA categories (A through X) for 163 drugs that were in the TERIS database and had an FDA Use-in-Pregnancy category. They combined the TERIS and FDA categories in the following way: TERIS category one, FDA A or B; TERIS category two, FDA D or X; and TERIS category three, FDA C. They then calculated the agreement between the three comparisons and found a statistically poor agreement between the two systems. A table shows the results for each drug.

13. National Perinatal Statistics. Expenditures for perinatal care. March of Dimes. Available at www.marchofdimes.com/aboutus/680_2203.asp. Accessed February 2, 2008.

This short article contains some interesting facts. Birth defects can be expensive, generating high costs in human suffering, medical and rehabilitation services, and special education and other services. In 1992, when the most recent analysis was conducted, the estimated lifetime cost of the 18 most clinically significant birth defects in the United States was \$8 billion. The lifetime costs of specific birth defects ranged from \$75,000 to \$503,000. Examples provided were cerebral palsy (\$503,000), Down syndrome (\$451,000), and spina bifida (\$294,000).

14. Resnik R. Intrauterine growth retardation. *Obstet Gynecol* 2002;99:490–6.

Intrauterine growth retardation is a serious complication. Infants born between 38 and 42 weeks of gestation with weights of 1500–2500 g have a perinatal mortality that is 5–30 times that of infants whose weights are between the 10th and 90th percentiles (not IUGR or large-for-gestational-age). The mortality is even higher if the birth weight is less than 1500 g. Small-for-gestational-age is defined as a birth weight less than the 10th percentile for gestational age. Although some low-birth-weight infants may be constitutionally small (normal for size of parents), infants who are small because of abnormal growth restriction have a markedly increased rate of cerebral palsy. Growth retardation

is a manifestation of many possible fetal and maternal disorders, each requiring different management and counseling, and with different outcomes. In about 20% of cases, IUGR is caused by chromosomal abnormalities and multifactorial birth defects. If the growth failure is detected before 26 weeks of gestation or associated with polyhydramnios (excessive amniotic fluid), the percent may be in the 90% range. Other risk factors for IUGR are multiple gestations and infections. Placental risk factors include small placenta and other placenta abnormalities. Maternal risk factors include extremes of malnutrition, vascular or renal disease (e.g., hypertension), congenital or acquired thrombophilia disorder, drug use or lifestyle, and high altitude or significant hypoxic disorder. Maternal vascular disease accounts for 25% to 30% of IUGR cases and is the most common cause in infants without birth defects. Drugs (therapeutic and abuse) and viral infections (primarily cytomegalovirus but also rubella and parvovirus) can cause growth restriction. Management consists of increased ultrasound surveillance and fetal testing and, if necessary, early delivery.

15. Samuelsen GB, Pakkenberg B, Bogdanovic N, Gundersen HJG, Falck Larsen J, Graem N, et al. Severe cell reduction in the future brain cortex in human growth-restricted fetuses and infants. *Am J Obstet Gynecol* 2007;197:56.e1–56.e7.

Because long-term studies of infants with IUGR have shown decreased academic and professional ability, the authors used an optical fractionator to make direct estimates of cell numbers in the brains of fetuses with IUGR compared with controls. This was the first study to estimate cell numbers in the brains of fetuses with growth restriction. Both groups of fetuses had undergone autopsies after intrauterine death. Four developmental zones were studied: (1) ventricular and subventricular zones (zones of proliferation); (2) intermediate zone (the future white matter); (3) subplate (a transient zone formed by the earliest formed neurons, which ultimately connect to incoming fibers); and (4) cortical plate and marginal zone (representing the future cortex). In the cortical plate and marginal zone samples, controls had significantly more cells than did fetuses with IUGR ($p=0.005$). There were no significant differences in the other three groups. The results of this study confirmed the findings of an earlier study that had used DNA quantification as an indirect measure of total cell number, and these results also confirmed the belief that head circumference is an indirect measure of brain size because subject fetuses had significantly smaller head circumferences than controls. Based on their results, the authors concluded that IUGR primarily damages the cortex.

16. Schardein JL. *Chemically Induced Birth Defects*, 3rd ed. New York: Marcel Dekker, 2000:1–65.

The first chapter discusses three basic principles of teratogenesis. First, susceptible species: not all species respond the same way to a teratogen; some are more susceptible or sensitive than others. Thus, a drug can cause birth defects in one species but not another. Second, susceptible stage of development: the timing of exposure is critical and, to cause disrupted development, must occur when the organ or tissue is vulnerable to injury. Third, dose dependency: there is always a NOEL for a drug that causes birth defects or other developmental toxicity. There is no harm below this threshold, but as the dose increases above the threshold, the severity and frequency of the toxicity also increases until the lethal dose is reached. There are also discussions of the manifestations of developmental toxicity, other factors to assess developmental effects, the use of animal models to assess human risk, and the evaluation of human risk. Three important tables

describe the periods of organogenesis in various species, the incidence rate of selected birth defects, and the timing of various malformations in humans. The last table lists 22 defects and the period in which the defect is induced, given in days from the first day of the last menstrual period (e.g., cleft lip must be induced before 50 days; anencephaly and other NTDs, 40 days; ventricular septal defect, 56 days; cleft palate, 70–77 days). Exposures after these times could not cause the defects. There are 32 other chapters in this book, arranged by pharmacological class; these chapters discuss animal and human reproductive toxicology caused by drug and chemical exposure. Although the edition is dated and, as with any book, lacks the most recent findings, it remains an excellent resource.

17. Scialli AR, Buelke-Sam JL, Chambers CD, Friedman JM, Kimmel CA, Polifka JE, et al. Communicating risks during pregnancy: a workshop on the use of data from animal developmental toxicity studies in pregnancy labels for drugs. *Birth Defects Res Clin Mol Teratol* 2004;70:7–12.

This paper summarizes a workshop organized by the Teratology Society and sponsored by the Centers for Disease Control and Prevention, FDA's Office of Women's Health, March of Dimes, Merck Research Laboratories, National Institute of Environmental Health Sciences, Neurobehavioral Teratology Society, OTIS, and Pfizer. The background leading up to the workshop included a general dissatisfaction with the present FDA risk factors and the intent of the FDA to replace them with text. The primary objective of the workshop was to recommend a method to describe developmental toxicity observed in animal tests so that this information could be used by the clinician in assessing human pregnancy risk. This reference provides an excellent summary of current limitations of drug labeling in terms of pregnancy, including its simplistic approach, lack of sufficient detail to guide clinicians in the interpretation of animal data, absence of information on the full range of potential developmental toxicities, need for guidance in responding to inadvertent exposures in pregnancy (a common event), and lack of information on the risk of developmental toxicity from untreated maternal disease. One of the workshop's key recommendations was that if a drug did not cause developmental toxicity in a species at doses that were 10 times or less than the human dose, based on body surface area or area under the curve and in the absence of maternal toxicity, then this was predictive of low risk for a human pregnancy.

18. Shepard TH, Lemire RJ. *Catalog of Teratogenic Agents*, 12th ed. Baltimore: The Johns Hopkins University Press, 2007.

This book is one of the sources used for Table 1-1. The introductory sections contain a list of seven factors required to prove human teratogenicity; a table of human teratogens subdivided into radiation, infections, maternal and metabolic imbalance, and drugs and environmental chemicals; and a table of possible and unlikely teratogens. Four of the seven factors were considered essential: exposure at the critical time, consistent findings of two or more epidemiologic studies, clinical cases (especially if there is a specific defect or syndrome), and a rare exposure associated with a rare defect. Three other factors were classified as helpful but nonessential: teratogenicity in experimental animals, biologic plausibility, and proof that the agent acts in an unaltered way and not through a metabolite. In addition to the agents listed in Table 1-1 and radiation, other therapeutic agents that are possible teratogens are colchicine, disulfiram, ergotamine, streptomycin, zidovudine, and zinc deficiency. Maternal and metabolic imbalances classified as teratogenic were those

caused by early amniocentesis and chorionic villus sampling (before day 60), endemic cretinism, diabetes mellitus, folic acid deficiency, hyperthermia, myasthenia gravis, phenylketonuria, rheumatic disease and congenital heart block, Sjögren's syndrome, and virilizing tumors. A useful table, encompassing four pages divided between the front and back of book, lists the comparative periods of embryonic and fetal development in humans and seven experimental animal species. The book is arranged alphabetically and contains short summaries of relevant literature on more than 3000 drugs, physical factors, and viruses. The primary audience for this portion of the book is individuals working within teratology.

19. Fugh-Berman A, Hales BF, Scialli AR, Tassinari MS, eds. *Teratology Primer*. Reston, VA: The Teratology Society, 2005.

The Primer contains concise information regarding the discipline of teratology. The 36 authors represent some of the most well-known researchers in the field. The Primer is divided into three broad sections of 9–11 short chapters, each no more than a few pages in length. Although the discussions do not cite specific references, each of the 30 chapters contains a list of recommended readings. In the first section, “The What, How and When: Basic Principles of Teratogen Action,” there are 11 chapters covering topics such as exposure to drugs and chemicals, interactions between genes and drugs as a cause of birth defects, multifactorial inheritance, and the dose-response relationship between drugs and birth defects. The second section, “Identification of Birth Defects and Teratogenic Exposures,” contains nine chapters that discuss ways to determine the birth defect risk associated with an exposure, as well as various sources of information for the clinician. The final section, “What Exposures Should We, or Should We Not, Be Concerned About?,” has 10 chapters that cover various toxic environmental exposures and the legal implications of exposure during gestation. The Primer is not intended to provide an in-depth understanding, and the chapters are brief, touching on only some of the highlights; however, it provides an introduction to a complex discipline. Newcomers to this field would do well to start here.

