# CHAPTER 12: Teratology, Teratogens, and Fetotoxic Agents

*All infectious diseases have a tendency to bring about death of the child and its subsequent expulsion from the uterus. The fatal result is usually due to the transmission of toxins, and occasionally the specific micro-organisms from the mother to the child. Poisoning with phosphorus, lead, illuminating gas, and other substances may lead to similar results.*

—J. Whitridge Williams (1903)

## INTRODUCTION

Other than referring to fetal deformities that might impede vaginal delivery, little is written in the first edition of this book regarding teratogens and fetal malformations. This is despite the fact that birth defects are common, and 2 to 3 percent of all newborns have a major congenital abnormality detectable at birth (Cragan, 2009; Dolk, 2010). There are undoubtedly medications that pose significant risk to the developing embryo or fetus (Table 12-1). However, 80 percent of birth defects do not have an obvious etiology, and of those with an identified cause, nearly 95 percent of cases have chromosomal or genetic origins (Feldkamp, 2017). The Food and Drug Administration (FDA) (2005) estimates that less than 1 percent of all birth defects are caused by medications. Their remarkably small contribution to congenital abnormalities is shown in Figure 12-1.

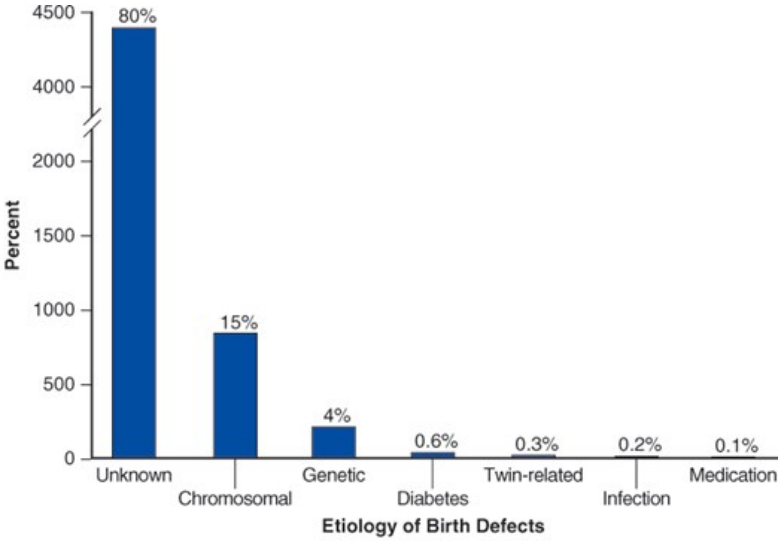
TABLE 12-1

**Selected Teratogens and Fetotoxic Agents**

| | |
|---|---|
| Acitretin | |
| Alcohol | Lithium |
| Ambrisentan | Macitentan |
| Angiotensin-converting enzyme inhibitors | Methimazole |
| Angiotensin-receptor blockers | Mercury |
| Androgens | Methotrexate |
| Bexarotene | Misoprostol |
| Bosentan | Mycophenolate |
| Carbamazepine | Paroxetine |
| Chloramphenicol | Phenobarbital |
| Cocaine | Phenytoin |
| Corticosteroids | Radioactive iodine |
| Cyclophosphamide | Ribavirin |
| Danazol | Tamoxifen |
| Diethylstilbestrol (DES) | Tetracycline |
| Efavirenz | Thalidomide |
| Fluconazole | Tobacco |
| Isotretinoin | Toluene |
| Lamotrigine | Topiramate |
| Lead | Trastuzumab |
| Leflunomide | Tretinoin |
| Lenalidomide | Valproic acid |
| | Warfarin |

**FIGURE 12-1**

Etiology of birth defects. Known and unknown causes of 5504 birth defects from a population-based review of 270,878 births.




Source: F. Gary Cunningham, Kenneth J. Leveno, Steven L. Bloom, Catherine Y. Spong, Jodi S. Dashe, Barbara L. Hoffman, Brian M. Casey, Jeanne S. Sheffield: *Williams Obstetrics*, 25th Edition

That said, significant concern surrounds medication use in pregnancy. This is because so many pregnant women are prescribed medications and because safety data are often lacking. Investigators from the National Birth Defects Prevention Study found that women take an average of two to three medications per pregnancy and that 70 percent use medication in the first trimester (Mitchell, 2011). And, in one review of medications approved by the FDA between 2000 and 2010, the Teratogen Information System (TERIS) advisory board deemed the pregnancy risk "undetermined" for more than 95 percent of these agents (Adam, 2011).

## TERATOLOGY

The study of birth defects and their etiology is termed teratology, derived from the Greek *teratos,* meaning monster. A *teratogen* may be defined as any agent that acts during embryonic or fetal development to produce a permanent alteration of form or function. Thus, a teratogen may be a medication or other chemical substance, a physical or environmental factor such as heat or radiation, a maternal metabolite as in diabetes or phenylketonuria, or an infection such as cytomegalovirus. Even obesity is considered a teratogen (Stothard, 2009; Waller, 2007).

Strictly defined, a teratogen causes only structural abnormalities. A *hadegen*—after the god Hades—is an agent that interferes with organ maturation and function, and a *trophogen* alters growth. Substances in the latter two groups typically affect development in the fetal period or after birth, when exposures are often more difficult to document. In most circumstances, the term teratogen is used to refer to all three types of agents.

### Criteria for Determining Teratogenicity

The guidelines shown in Table 12-2 were proposed by Shepard (1994) as a framework for discussion and have proven useful for more than 25 years. Although each individual criterion is not required to establish teratogenicity, the following tenets must be considered (Shepard, 2002a):

TABLE 12-2

**Criteria for Determining Teratogenicity**

**Essential Criteria:**

1. Careful delineation of clinical cases, particularly if there is a specific defect or syndrome
2. Proof that exposure occurred at critical time during development (see Fig. 12-2)
3. Consistent findings by at least two epidemiological studies with:
    a. exclusion of bias,
    b. adjustment for confounding variables,
    c. adequate sample size (power),
    d. prospective ascertainment if possible, and
    e. relative risk (RR) of 3.0 or greater, some recommend RR of 6.0 or greater

***or***

For a rare environmental exposure associated with a rare defect, at least three reported cases. This is easiest if defect is severe

**Ancillary Criteria:**

4. The association is biologically plausible
5. Teratogenicity in experimental animals is important but not essential
6. The agent acts in an unaltered form in an experimental model

Data from from Shepard 1994, 2002a.

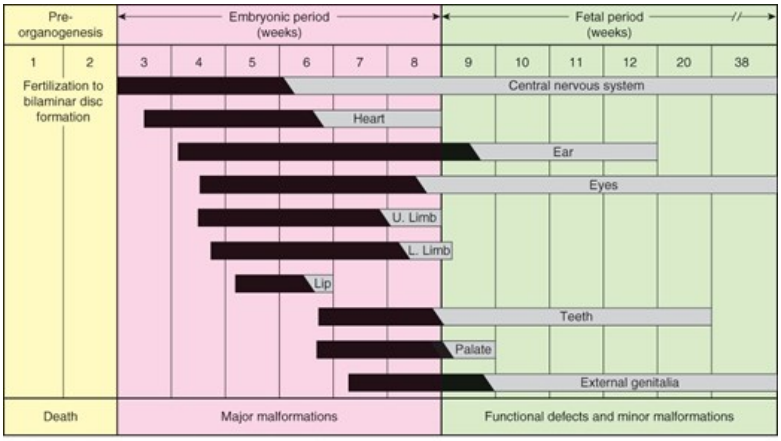
- The defect has been completely characterized. This is preferably done by a geneticist or dysmorphologist because various genetic and environmental factors may produce similar anomalies. It is easiest to prove causation when a rare exposure produces a rare defect, when at least three cases with the same exposure have been identified, and when the defect is severe.
- The agent must cross the placenta. Although almost all drugs cross the placenta, transport must be of sufficient quantity to directly influence

embryonic or fetal development or to alter maternal or placental metabolism to exert an indirect effect. Placental transfer depends on maternal metabolism; on specific characteristics of the drug, such as protein binding and storage, molecular size, electrical charge, and lipid solubility; and on placental metabolism, such as by the cytochrome $P_{450}$ enzyme system. In early pregnancy, the placenta also has a relatively thick membrane that slows diffusion.

- Exposure must occur during a critical developmental period.
  - The *preimplantation period* is the 2 weeks between fertilization and implantation and is known as the "all or none" period. As the zygote undergoes cleavage, an insult damaging a large number of cells typically causes embryonic death. However, if only a few cells are injured, compensation may be possible and allow normal development (Clayton-Smith, 1996). From animal data, insults that appreciably diminish the cell number in the inner cell mass may produce a dose-dependent diminution in body length or size (Iahnaccone, 1987).
  - The *embryonic period* extends from the second through the eighth week postconception. It encompasses organogenesis and is thus the most crucial period with regard to structural malformations. Critical developmental periods for each organ system are illustrated in Figure 12-2.
  - The *fetal period*, which is beyond 8 weeks postconception, is characterized by continued maturation and functional development. During this time, certain organs remain vulnerable.
- A biologically plausible association is supportive. Because birth defects and medication exposures are both common, they may be temporally but not causally related.
- Epidemiological findings must be consistent. Because initial evaluation of teratogen exposure is often retrospective, it may be hampered by recall bias, inadequate reporting, and incomplete assessment of the exposed population. Potential confounding factors include varying dosages, concomitant drug therapy, and comorbid maternal disease(s). Familial and environmental variables can also influence development of birth defects. Thus, an important criterion for teratogenicity is that two or more high-quality epidemiological studies report similar findings. Finally, a relative risk of *3.0 or greater* is generally considered necessary to support the hypothesis, whereas a lesser risk is interpreted with caution (Khoury, 1992).
- The suspected teratogen causes a defect in animal studies. This criterion is not obligatory. In fact, the Teratology Society (2005) states that establishment of causation in teratology-related litigation requires human data.

**FIGURE 12-2**

Timing of organogenesis during the embryonic period. (Reproduced with permission from Salder TW: Langman's Medical Embryology, 6th ed. Baltimore, Williams & Wilkins; 1990.)






Failure to employ these tenets and criteria has contributed to erroneous conclusions regarding the safety of some widely used drugs. The poster child for this is the medicolegal fiasco surrounding Bendectin. This antiemetic was a combination of doxylamine and pyridoxine, with or without

dicyclomine, and was safe and effective for nausea and vomiting in early pregnancy. More than 30 million women used this drug worldwide, and the 3-percent congenital anomaly rate among exposed fetuses was not different from the background rate (McKeigue, 1994). Despite considerable evidence that this combination of an antihistamine and a B-vitamin is not teratogenic, Bendectin was the target of numerous lawsuits, and the financial burden of defending these forced its withdrawal from the marketplace. As a consequence, hospitalizations for hyperemesis doubled (Koren, 1998). Ironically, the combination of doxylamine and pyridoxine was subsequently remarketed under the brand name Diclegis and was approved by the FDA in 2013.

## Studies in Pregnant Women

The study of medication safety—or teratogenicity—in pregnant women is fraught with complications. First, animal studies are considered necessary but insufficient. For example, thalidomide is harmless in several animal species but resulted in phocomelia in thousands of children born across Europe in the late 1950s and early 1960s. Second, medications are rarely approved by the FDA for a pregnancy-related indication. Instead, pregnant women are considered a special population and summarily excluded from medication trials. Last, drug concentration and thus embryo-fetal exposure are affected by pregnancy physiology. These include changes in volume of distribution, cardiac output, gastrointestinal absorption, hepatic metabolism, and renal clearance. In the absence of research trials, counseling is based on case reports or series, case-control studies, cohort studies, and pregnancy registry data.

## Case Reports and Series

Many, if not most, major teratogens were first described by clinicians who observed a rare defect occurring after a rare exposure. This has been termed the “astute clinician model” (Carey, 2009). Congenital rubella syndrome was identified in this way by Gregg (1941), an Australian ophthalmologist whose observations challenged the view that the uterine environment was impervious to noxious agents. Other teratogens identified through case series include thalidomide and alcohol (Jones, 1973; Lenz, 1962). Shepard (2002a) recommended that establishment of teratogenicity in this way requires proven exposure at a critical time in development and probably at least three such cases, each carefully delineated. Unfortunately, teratogens are less likely to be identified if the exposure is uncommon, if the defects are relatively nonspecific, or if abnormalities develop in only a small proportion of exposed fetuses. A major limitation of case series is their lack of a control group.

## Case-Control Studies

These studies begin with groups of affected infants (cases) and unaffected controls and are structured to allow retrospective assessment of prenatal exposure to particular substances. Case-control studies are an efficient way to study rare outcomes (Alwan, 2015). These permit investigators to evaluate associations and generate useful hypotheses. However, case-control studies have inherent potential for *recall bias.* Namely, parents of an affected infant are often more likely to recall exposure than those whose child is not ill. Confounding by indication is another concern, that is, the indication for the medication may be the cause of the birth defect. And importantly, birth defect registries have statistical power to detect small differences that may not be clinically meaningful. Grimes and Schulz (2012) have cautioned that unless odds ratios in case-control studies are above three- to fourfold, the observed associations may not be correct.

### The National Birth Defects Prevention Study

An excellent example of a population-based case-control study is the National Birth Defects Prevention Study (NBDPS). Funded by Congress and coordinated by the National Center on Birth Defects and Developmental Disabilities, the NBDPS took place between 1997 and 2013 across ten states with active birth defects surveillance programs. Clinical geneticists reviewed each potential case, and standardized telephone interviews were conducted with mothers whose pregnancies were affected or unaffected to obtain information regarding medication exposure and risk factors (Mitchell, 2011; Reefhuis, 2015). Live births, stillbirths, and terminated pregnancies were included and totaled approximately 32,000 cases and nearly 12,000 controls.

The NBDPS has yielded more than 200 scientific manuscripts. It identified novel—although often small—associations between individual birth defects and the following classes of medications: antibiotics, antidepressants, antiemetics, antihypertensives, asthma medications, nonsteroidal antiinflammatory drugs (NSAIDs), and opioids (Ailes, 2016; Broussard, 2011; Fisher, 2017; Hernandez, 2012; Lin, 2012; Munsie, 2011). The NBDPS also found associations between birth defects and exposures such as secondhand smoke, pesticides, and nitrogen oxide, which is a marker of traffic-related air pollution (Hoyt, 2016; Rocheleau, 2015; Stingone, 2017).

The NBDPS did have limitations related to study design. First, interviews were conducted 6 weeks to 2 years following delivery, which raised the likelihood of recall bias. For example, 25 percent of women could not remember which antibiotic they had taken (Ailes, 2016). Another weakness was that only two thirds of women agreed to participate, and there were differences in ethnicity and socioeconomic status between cases and controls. These factors potentially led to selection bias (Reefhuis, 2015). In addition, medical records were not reviewed to verify dosage, and this precluded assessment of dose-response relationships. And a major limitation was that because the NBDPS included only a small number of cases of each birth defect and analyzed them for multiple maternal exposures, it was not possible to adjust for multiple comparisons. As a result, some of the associations observed were likely due to chance (Alwan, 2015). For example, the study of antibiotics and birth defects included 43 comparisons and identified four significant associations, but chance alone predicted that two associations would be identified (Ailes, 2016). Last, the low absolute risk of an abnormality complicates counseling and prenatal management. In many instances, the risk identified by the NBDPS was as low as 1 case per 1000 exposed pregnancies.

### Cohort Studies

These studies begin with cohorts of pregnant women who are exposed or unexposed to a particular medication. The percentage of infants or children affected with birth defects is examined in each cohort. Because individual birth defects are rare, cohort studies require a *very* large sample size. Medicaid datasets and private insurance claims databases are commonly used for cohort studies of teratogenicity in the United States (Ehrenstein, 2010). Inability to adjust for confounding variables—such as the indication for which the medication was needed—may be an important limitation of this study design.

### Pregnancy Registries

Potentially harmful agents may be monitored by clinicians who prospectively enroll exposed pregnancies in a registry. The FDA (2017b) maintains an active list on their webpage titled Pregnancy Registries. As of 2017, this included registries for 100 individual medications and for medication groups used to treat asthma, autoimmune disease, cancer, epilepsy, human immunodeficiency virus (HIV) infection, and transplant rejection. Similar to case series, exposure registries are hampered by lack of a control group. The prevalence of an abnormality identified through a registry requires knowledge of the baseline prevalence of that anomaly in the population. Investigators typically use a birth defect registry to assess population prevalence. One example is the Metropolitan Atlanta Congenital Defects Program, which is an active surveillance program established in 1967 for fetuses and infants with birth defects.

## COUNSELING FOR MEDICATION EXPOSURE

Questions regarding medication and illicit drug use should be part of routine preconceptional and prenatal care. Misinformation is common. Individuals tend to underestimate the background risk for birth defects in the general population and exaggerate potential risks associated with medication exposure. In a recent population-based study of more than 270,000 births from Utah that included 5500 fetuses and infants with major birth defects, only 4 cases were attributed to medication exposure (see Fig. 12-1) (Feldkamp, 2017). And yet, Koren and colleagues (1989) reported that a fourth of women exposed to nonteratogenic drugs thought they had a 25-percent risk for fetal anomalies. Misinformation may be amplified by inaccurate reports in the lay press. Knowledgeable counseling may allay anxiety considerably and may even avert pregnancy termination.

Several sources are available to assist providers with accurate and updated risk information. PubMed is a free tool from the National Center for Biomedical Information that aids rapid search of published research. Online databases, such as Reprotox, TERIS, and Shepard's Online Catalog of Teratogenic Agents, offer reviews of medication risks. They summarize human and animal studies of teratogenicity and fetotoxicity, address the quality of the available evidence, and provide magnitude of risk. Lactmed, a database from the National Library of Medicine, specifically deals with medication use by breastfeeding women. Its entries on specific medications describe levels in breast milk and potential effects on the infant. Finally, with recent changes to the FDA labeling requirements, discussed next, the manufacturer's prescribing information has become increasingly helpful.

### The Food and Drug Administration: Letters and Labels

In 1979, the FDA developed a letter classification system in an effort to provide therapeutic guidance for prescribing medications in pregnancy. Five categories—A, B, C, D, and X—were intended to summarize available evidence from human or animal studies of embryonic–fetal risk. These letters also conveyed benefits of the given medication balanced against its potential risks. The system, shown in Table 12-3, was intended to simplify risk–benefit data.

TABLE 12-3

**Food and Drug Administration Letter Categories for Drugs and Medications (1979–2015)[a]**

| | |
|---|---|
| **Category A:** | Studies in pregnant women have not shown an increased risk for fetal abnormalities if administered during the first (second, third, or all) trimester(s) of pregnancy, and the possibility of fetal harm appears remote. |
| **Category B:** | Animal reproduction studies have been performed and have revealed no evidence of impaired fertility or harm to the fetus. |
| | ***or*** |
| | Animal studies have shown an adverse effect, but adequate and well-controlled studies in pregnant women have failed to demonstrate a risk to the fetus during the first trimester of pregnancy, and there is no evidence of a risk in later trimesters. |
| **Category C:** | Animal reproduction studies have shown that this medication is teratogenic (or embryocidal or has other adverse effect), and there are no adequate and well-controlled studies in pregnant women. |
| | ***or*** |
| | There are no animal reproduction studies and no adequate and well-controlled studies in humans. |
| **Category D:** | This medication can cause fetal harm when administered to a pregnant woman. If this drug is used during pregnancy or if a woman becomes pregnant while taking this medication, she should be apprised of the potential hazard to the fetus. |
| **Category X:** | This medication is contraindicated in women who are or may become pregnant. It may cause fetal harm. |

[a]Medications approved after June 2015 are not assigned a letter category, whereas older medications will have letter categories phased out after this date.

Unfortunately, information regarding medication risk was very often incomplete and led to an overreliance on the definition of the letter category alone. However, a higher letter grade did not necessarily mean greater risk, and drugs in the same category often had very different risks. Very few medications—fewer than 1 percent—had demonstrated safety in human pregnancy (category A), and most had no safety data in human or animal studies (category C). Another difficulty was that the classification system did not address inadvertent exposure, a common reason for counseling. Ultimately, it is the responsibility of the clinician to interpret letter category information in the context of medication dosage and route, timing of exposure during pregnancy, other medications used, and underlying medical condition(s).

To address these deficiencies, new labeling requirements were created and went into effect in 2015. Updates to older medications will be phased in over time (Food and Drug Administration, 2014). With the new requirements, the FDA letter categories have been (or will be) removed from all prescription drug and biological product labeling. The format for providing information includes a summary of risks, clinical considerations, and available data. The pregnancy subsection has registry information, if available, as well as labor and delivery information. For each medication, a lactation subsection—formerly called “nursing mothers”—is included. There is also a section to address potential risks in females and males with reproductive potential.

## Presenting Risk Information

In addition to potential embryonic and fetal risks from drug exposure, counseling should discuss the risks and/or genetic implications of the underlying condition for which the drug is given. Risks associated with not treating the condition are also described. Even the manner in which information is presented affects perception. For example, women given negative information—such as a 2-percent chance of a malformed newborn—are more likely to perceive an exaggerated risk than women given positive information—such as a 98-percent chance of an unaffected infant (Jasper,

2001). Instead of citing a higher odds ratio, it may be helpful to provide the *absolute risk* for a particular defect or the *attributable risk*, which is the difference between prevalence in exposed and unexposed individuals (Conover, 2011). The association between oral corticosteroid medications and cleft lip sounds far more concerning when presented as a tripling or 200-percent increase in risk than when described as an increase from 1 per 1000 to 3 per 1000 or as a 99.7-percent likelihood of no cleft development following exposure.

With a few notable exceptions, most commonly prescribed drugs and medications can be used with relative safety during pregnancy. Many drugs discussed in this chapter are *low-risk teratogens*, which are medications that produce defects in fewer than 10 per 1000 maternal exposures (Shepard, 2002a). Because risks conferred by low-risk teratogens are so close to the population background rate of fetal anomalies, they may not be a major factor in deciding whether to discontinue treatment for an important condition (Shepard, 2002b). *Remember that all women have an approximate 3-percent chance of having a newborn with a birth defect.* Although exposure to a confirmed teratogen may elevate this risk, the magnitude of the increase is usually only 1 or 2 percent or at most, doubled or tripled. The concept of risk versus benefit is often central to counseling. Some untreated diseases pose a more serious threat to both mother and fetus than medication exposure risks.

## KNOWN AND SUSPECTED TERATOGENS

Considering the thousands of compounds available, relatively few medications and other substances are considered to be major human teratogens. The most common examples are listed in Table 12-1. With few exceptions, in every clinical situation potentially requiring therapy with a known teratogen, alternative drugs can be given with relative safety. Realizing limitations in available evidence, pregnant women should be advised to take any medication only when it is clearly needed. In general, targeted sonography is indicated if there has been exposure to any major teratogen during the embryonic period.

### Alcohol

Ethanol is a potent and prevalent teratogen. It is considered the leading cause of preventable developmental disabilities worldwide (Hoyme, 2016). In the United States, 8 percent of pregnant women report drinking alcohol and between 1 and 2 percent admit to binge drinking (Centers for Disease Control and Prevention, 2012).

The fetal effects of alcohol abuse have been recognized since the 1800s. Lemoine (1968) and Jones (1973) and their coworkers are credited with describing the spectrum of alcohol-related fetal defects known as *fetal alcohol syndrome* (Table 12-4). For every child with the syndrome, many more are born with neurobehavioral deficits from alcohol exposure (American College of Obstetricians and Gynecologists, 2013). *Fetal alcohol spectrum disorder* is an umbrella term that includes five conditions attributed to prenatal alcohol damage: (1) fetal alcohol syndrome, (2) partial fetal alcohol syndrome, (3) alcohol-related birth defects, (4) alcohol-related neurodevelopmental disorder, and (5) neurobehavioral disorder associated with prenatal alcohol exposure (Williams, 2015). The birth prevalence of fetal alcohol syndrome is estimated to be as high as 1 percent in the United States (Centers for Disease Control, 2012; Guerri, 2009). But, studies of school children have identified fetal alcohol spectrum disorder in 2 to 5 percent (May, 2009, 2014).

TABLE 12-4

**Criteria for Prenatal Alcohol Exposure, Fetal Alcohol Syndrome, and Alcohol-Related Birth Defects**

**Documented Prenatal Alcohol Exposure—one or more required**

1. ≥6 drinks per week for ≥2 weeks
2. ≥3 drinks per occasion for ≥2 occasions
3. Risk identified with a validated screening questionnaire
4. Laboratory testing indicating alcohol intoxication or positive alcohol-exposure biomarker
5. Documentation of an alcohol-related legal or social problem

**Fetal Alcohol Syndrome Diagnostic Criteria—all required**

1. Dysmorphic facial features (≥2 required)
   a. Short palpebral fissures
   b. Thin vermilion border of the upper lip
   c. Smooth philtrum
2. Prenatal and/or postnatal growth impairment, ≤10th percentile
3. Abnormal brain growth, morphogenesis, or physiology (≥1 required)
   a. Head circumference ≤10th percentile
   b. Structural brain abnormalities
   c. Recurrent nonfebrile seizures
4. Neurobehavioral impairment (defined as >1.5 SD below mean)
   a. Child <3 years: developmental delay
   b. Child ≥3 years: global cognitive impairment, or cognitive deficit in at least 1 neurobehavioral domain, or behavioral deficit in at least 1 domain

**Alcohol-Related Birth Defects**

Cardiac: atrial or ventricular septal defect, aberrant great vessels, conotruncal heart defects

Skeletal: radioulnar synostosis, vertebral segmentation defects, joint contractures, scoliosis

Renal: aplastic or hypoplastic kidneys, dysplastic kidneys, horseshoe kidney, ureteral duplication

Eyes: strabismus, ptosis, retinal vascular abnormalities, optic nerve hypoplasia

Ears: conductive or neurosensory hearing loss

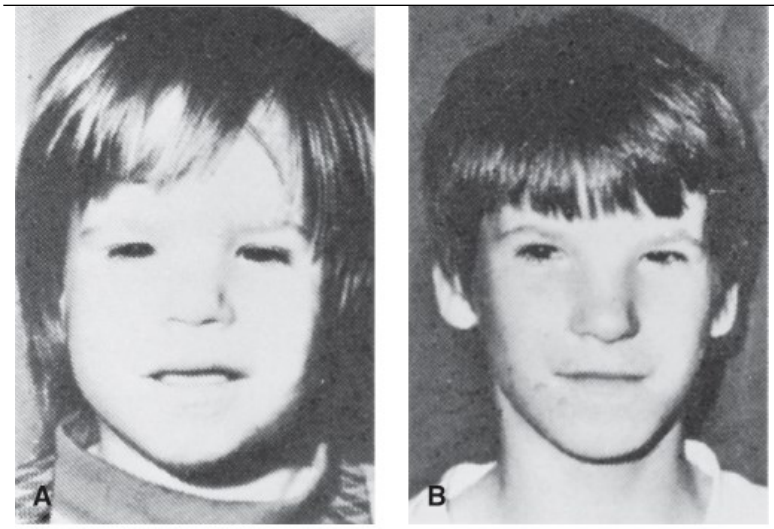
Data from Hoyme, 2016.

## Criteria and Characteristics

Fetal alcohol syndrome has specific criteria (see Table 12-4). These include central nervous system (CNS) abnormalities, pre- or postnatal growth impairment, and a characteristic pattern of minor facial abnormalities (Fig. 12-3). Similar criteria have been established for the other conditions that make up fetal alcohol spectrum disorder (Hoyme, 2016). Prenatal alcohol exposure criteria are also available to assist with assessment.

**FIGURE 12-3**

Fetal alcohol syndrome. **A.** At 2½ years. **B.** At 12 years. Note persistence of short palpebral fissures, epicanthal folds, flat midface, hypoplastic philtrum, and thin upper vermilion border. (Reproduced with permission from Streissguth AP, Clarren, SK, Jones KL. Natural history of fetal alcohol syndrome: a 10-year follow-up of eleven patients, Lancet. 1985 Jul 13;2(8446):85–91.)

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Alcohol-related birth defects include cardiac and renal anomalies, orthopedic problems, and abnormalities of the eyes and ears (see Table 12-4). An association has further been reported between periconceptional alcohol use and omphalocele and gastroschisis (Richardson, 2011). There are no established sonographic criteria for prenatal diagnosis of fetal alcohol syndrome. That said, in some cases, major abnormalities or growth restriction may be suggestive (Paintner, 2012).

### Dose Effect

Fetal vulnerability to alcohol is modified by genetic components, nutritional status, environmental factors, coexisting maternal disease, and maternal age (Abel, 1995). The Centers for Disease Control and Prevention (CDC) and the American Academy of Pediatrics have stressed that *no* amount of alcohol can be considered safe in pregnancy (Williams, 2015). Binge drinking, however, is believed to pose particularly high risk for alcohol-related birth defects and has also been linked to a higher risk for stillbirth (Centers for Disease Control, 2012; Maier, 2001; Strandberg-Larsen, 2008).

## Antiepileptic Medications

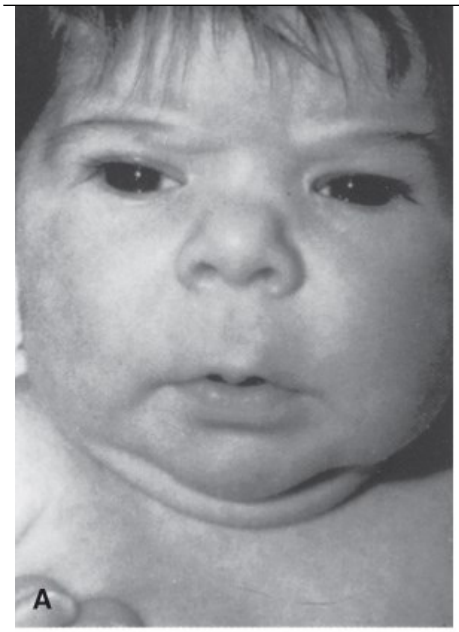
Traditionally, women with epilepsy requiring treatment with medication were informed that their risk for fetal malformations was increased. More recent data suggest that the risk may not be as great as once thought, particularly for newer agents. The most frequently reported anomalies are orofacial clefts, cardiac malformations, and neural-tube defects.

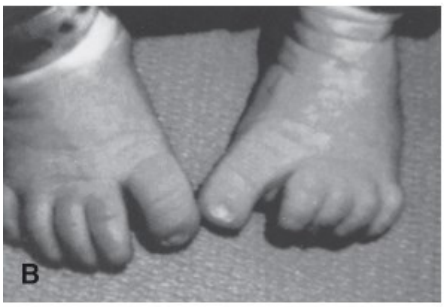
Of agents in current use, valproic acid confers the greatest risk (Vajda, 2014). The North American Antiepileptic Drug (NAAED) Pregnancy Registry reported that major malformations developed in 9 percent of fetuses with first-trimester valproate exposure. This included a 4-percent risk for neural-tube defects (Hernandez-Diaz, 2012). School-aged children with in utero exposure to valproic acid have poorer cognitive development—including significantly lower intelligence quotient (IQ) scores—than children exposed to other antiepileptic drugs (Bromley, 2014; Meador, 2009).

Regarding other specific anticonvulsants, one recent metaanalysis identified higher malformation rates among exposed children compared with rates among children born to women with untreated epilepsy. Rates were twofold higher among children exposed to carbamazepine or phenytoin, threefold higher among those exposed to phenobarbital, and fourfold higher among those exposed to topiramate as monotherapy (Weston, 2016). The risk for fetal malformations is approximately doubled if multiple agents are required (Vajda, 2016). Several older anticonvulsants also produce a constellation of malformations similar to the fetal hydantoin syndrome, which is described in Figure 12-4.

**FIGURE 12-4**

Fetal hydantoin syndrome. **A.** Facial features including upturned nose, mild midfacial hypoplasia, and long upper lip with thin vermilion border. **B.** Distal digital hypoplasia. (Reproduced with permission from Buehler BA1, Delimont D, van Waes M, et al: Prenatal prediction of risk of the fetal hydantoin syndrome, N Engl J Med. 1990 May 31;322(22):1567–1572.)

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These risks do not appear to hold for the newer agents levetiracetam and lamotrigine, although the number of reported pregnancies to date is smaller (Mølgaard-Nielsen, 2011; Weston, 2016). The Motherisk Program reviewed eight studies of levetiracetam and concluded that monotherapy was associated with a 2-percent major malformation rate, which is no different from that for the general population (Chaudhry, 2014).

Providers are encouraged to enroll pregnant women treated with antiepileptic medication in the NAAED Pregnancy Registry. Management of epilepsy in pregnancy is discussed in Chapter 60 (Preconceptional Counseling).

## Angiotensin-Converting Enzyme Inhibitors and Angiotensin-Receptor Blocking Drugs

These medications may result in *ACE-inhibitor fetopathy*. Normal renal development depends on the fetal renin-angiotensin system. ACE-inhibitor medication may cause fetal hypotension and renal hypoperfusion, with subsequent ischemia and anuria (Guron, 2000; Pryde, 1993). Reduced perfusion can result in fetal-growth restriction and calvarium maldevelopment, and oligohydramnios may lead to pulmonary hypoplasia and limb contractures (Barr, 1991). Because angiotensin-receptor blockers have a similar mechanism of action, concerns regarding fetotoxicity have been generalized to include this entire medication class.

Concerns were also raised about ACE-inhibitor embryotoxiciy, although these have largely been disproven. In 2006, a review of 29,000 infants from the Tennessee Medicaid database identified a two- to threefold greater risk for neonatal cardiac and CNS abnormalities among the 209 that had prenatal ACE-inhibitor exposure (Cooper, 2006). Subsequent larger studies have not corroborated these observations. First, in a retrospective cohort study of more than 460,000 pregnancies, risks for birth defects were not greater with ACE inhibitors than with other antihypertensive medications (Li, 2011). Similarly, Bateman and coworkers (2017) reviewed 1.3 million pregnancies from the Medicaid Analytic eXtract and found no higher risk for any malformation with ACE-inhibitor exposure after adjusting for confounding factors such as diabetes. Thus, women with inadvertent first-trimester

exposure to these medications can be reassured. However, given the many therapeutic options for treating hypertension during pregnancy, discussed in Chapter 50 (Management During Pregnancy), it is recommended that ACE inhibitors and angiotensin receptor-blocking drugs be avoided in pregnancy.

## Antifungal Medications

From this class of drugs, fluconazole has been associated with a pattern of congenital malformations resembling the autosomal recessive *Antley-Bixler syndrome*. Abnormalities include oral clefts, abnormal facies, and cardiac, skull, long-bone, and joint abnormalities. Such findings have been reported only with chronic, first-trimester, high-dose treatment at doses of 400 to 800 mg daily.

Regarding low-dose treatment of vulvovaginal candidiasis, the Motherisk Program recently conducted a systematic review of pregnancies with first-trimester fluconazole exposure of 150 or 300 mg in total (Alsaad, 2015). The overall risk for birth defects was not greater, although a small increase in rates of cardiac malformations could not be excluded. A population-based cohort study from Denmark identified a threefold greater risk for tetralogy of Fallot following exposure to low-dose fluconazole (Mølgaard-Nielsen, 2013). The birth prevalence of tetralogy of Fallot rose from 3 to 10 cases per 10,000. This is a risk so low that we would not endorse specialized sonography for this indication. Notably, investigators did not identify increased risks for 14 other birth defects previously associated with exposure to high-dose azole antifungal agents (Mølgaard-Nielsen, 2013).

## Antiinflammatory Agents

### Nonsteroidal Antiinflammatory Drugs

This drug class includes both aspirin and traditional NSAIDs such as ibuprofen and indomethacin. They exert their effects by inhibiting prostaglandin synthesis. In a report from the NBDPS, at least 20 percent of pregnant women recall first-trimester NSAID use, particularly ibuprofen and aspirin, and such exposure is not a major risk factor for birth defects (Hernandez, 2012).

However, when taken in late pregnancy, indomethacin may cause constriction of the fetal ductus arteriosus and subsequent pulmonary hypertension. Fetal ductal constriction is more likely when the drug is taken in the third trimester for longer than 72 hours. The risk is 15-fold higher among indomethacin-exposed pregnancies (Koren, 2006). The drug also may decrease fetal urine production and amnionic fluid volume (Rasanen, 1995; van der Heijden, 1994; Walker, 1994). In one systematic review, indomethacin tocolysis was associated with neonatal morbidity (Hammers, 2015a,b). Specifically, the risk for bronchopulmonary dysplasia, severe intraventricular hemorrhage, and necrotizing enterocolitis was increased approximately 50 percent (odds ratio 1.5).

With aspirin, a low dosage of 100 mg daily or less does *not* confer a greater risk for constriction of the ductus arteriosus or for adverse infant outcomes (Di Sessa, 1994; Grab, 2000). As with other NSAIDs, however, high-dose aspirin use should be avoided, particularly in the third trimester.

### Leflunomide

This is a pyrimidine-synthesis inhibitor used to treat rheumatoid arthritis but is contraindicated in pregnancy. In several animal species, it results in fetal hydrocephalus, eye anomalies, skeletal abnormalities, and embryo death when given at or below human-equivalent doses (Sanofi-Aventis, 2016). The active metabolite, teriflunomide, is detectable in plasma for up to 2 years following discontinuation of the medication. Women who become pregnant while taking leflunomide, and even those of childbearing potential who have discontinued it, are recommended to undergo an accelerated drug elimination procedure with either cholestyramine or activated charcoal (Sanofi-Aventis, 2016). Reassuringly, in a cohort of 60 women with first-trimester leflunomide exposure who completed cholestyramine washout, the rate of birth defects was not increased (Chambers, 2010).

## Antimicrobial Drugs

Medications used to treat infections are among those most frequently administered during pregnancy. Over the years, experience has accrued regarding their general safety. With a few exceptions cited below, most of the commonly used antimicrobial agents are considered safe for the embryo-fetus.

### Aminoglycosides

Some preterm neonates treated with gentamicin or streptomycin have developed nephrotoxicity and ototoxicity. Despite theoretical concern for potential fetal toxicity, no adverse effects have been demonstrated, and no congenital defects resulting from prenatal exposure have been identified.

### Chloramphenicol

This antimicrobial is not considered teratogenic and is no longer routinely used in the United States. More than 50 years ago, a constellation of findings termed the *gray baby syndrome* was described in neonates who received the medication. Preterm newborns were unable to conjugate and excrete the drug and manifested abdominal distention, respiratory abnormalities, an ashen-gray color, and vascular collapse (Weiss, 1960). Chloramphenicol was subsequently avoided in late pregnancy due to theoretical concerns.

### Nitrofurantoin

From NBDPS results, first-trimester nitrofurantoin exposure is linked to a twofold risk for cleft lip (Ailes, 2016; Crider, 2009). Considering that the birth prevalence of clefts approximates 1 case per 1000, the likelihood that a nitrofurantoin-exposed fetus would *not* have a cleft would thus be 998 per 1000. For other birth defects, initial associations with this antibiotic did not persist in the final NBDPS cohort (Ailes, 2016).

In one systematic review of nitrofurantoin exposure in pregnancy, results of cohort and case-control studies differed (Goldberg, 2015). Five cohort studies included 9275 exposed pregnancies and nearly 1.5 million unexposed pregnancies, and the review found no higher risk for any malformation. However, among three case-control studies that had nearly 40,000 cases matched with 130,000 controls, the rate of hypoplastic left heart syndrome was threefold greater (Goldberg, 2015). For context, this increase in risk would result in a birth prevalence of fewer than 1 case per 1000 exposed infants. The American College of Obstetricians and Gynecologists (2017e) has concluded that first-trimester nitrofurantoin use is appropriate if no suitable alternatives are available.

### Sulfonamides

These drugs are often combined with trimethoprim and used to treat infections during pregnancy. One indication is treatment of methicillin-resistant *Staphylococcus aureus* (MRSA) infection. The NBDPS, which included 107 pregnancies with periconceptional trimethoprim-sulfamethoxazole exposure and birth defects, identified a fivefold greater risk to have offspring with esophageal atresia or diaphragmatic hernia (Ailes, 2016). Similar to findings with nitrofurantoin exposure, this degree of increase would confer a risk of approximately 1 case per 1000 exposed infants for these selected birth defects. However, these findings have not been corroborated by other reports. One review from the Medication Exposure in Pregnancy Risk Evaluation Program included more than 7500 infants with first-trimester exposure to trimethoprim-sulfamethoxazole (Hansen, 2016). Compared with either unexposed infants or those exposed to penicillins or cephalosporins, no greater risk for any congenital abnormality was identified. The American College of Obstetricians and Gynecologists (2017e) considers sulfonamides appropriate for first-trimester use if suitable alternatives are lacking.

Sulfonamides displace bilirubin from protein-binding sites. Thus, if given near the time of preterm delivery, these agents theoretically might worsen neonatal hyperbilirubinemia. However, a population-based review of more than 800,000 births from Denmark found no association between exposure to sulfamethoxazole in late pregnancy and neonatal jaundice (Klarskov, 2013).

### Tetracyclines

These drugs are no longer commonly used in pregnant women. They are associated with yellowish-brown discoloration of deciduous teeth when used after 25 weeks' gestation. The risk for subsequent dental caries does not appear greater (Billings, 2004; Kutscher, 1966). In contrast, a recent systematic review of doxycycline in pregnancy identified no higher rates of either birth defects or staining of deciduous teeth (Cross, 2016).

## Antineoplastic Agents

Cancer management in pregnancy includes many chemotherapeutic agents generally considered to be at least potentially toxic to the embryo, fetus, or both. For the many novel polyclonal antibody therapies designated as antineoplastics, there are few data concerning their safety. Some risks with these and with other antineoplastic agents are discussed in Chapter 63 (Cancer Therapy in Pregnancy). A few of the more common agents for which experience in pregnancy has accrued are considered next.

### Cyclophosphamide

This alkylating agent inflicts a chemical insult on developing fetal tissues and leads to cell death and heritable DNA alterations in surviving cells. Pregnancy loss rates are increased, and reported malformations include skeletal abnormalities, limb defects, cleft palate, and eye abnormalities (Enns, 1999; Kirshon, 1988). Surviving infants may have growth abnormalities and developmental delays. Environmental exposure among health-care workers is associated with a higher risk for spontaneous abortion (Chap. 18, Paternal Factors).

### Methotrexate

This folic-acid antagonist is a potent teratogen. It is used for cancer chemotherapy, immunosuppression of autoimmune diseases and psoriasis, nonsurgical treatment of ectopic pregnancy, and medical abortion. It is similar in action to aminopterin, which is no longer used clinically, and can cause defects known collectively as the fetal *methotrexate-aminopterin syndrome*. This includes craniosynostosis with a "clover-leaf" skull, wide nasal bridge, low-set ears, micrognathia, and limb abnormalities (Del Campo, 1999). The embryo is thought to be most vulnerable at 8 to 10 weeks postconception and at dosages of at least 10 mg/week. However, this is not universally accepted (Feldkamp, 1993).

The standard 50 mg/m$^2$ dose given to treat ectopic pregnancy or to induce elective abortion exceeds this threshold dose. Some reports have suggested an association with cardiac anomalies, particularly conotruncal defects, in intrauterine pregnancies inadvertently treated with methotrexate for suspected ectopic pregnancy (Dawson, 2014; Hyoun, 2012). Thus, ongoing pregnancies after treatment with methotrexate—especially if used in conjunction with misoprostol—raise serious concerns for fetal malformations (Nurmohamed, 2011).

### Tamoxifen

This nonsteroidal selective estrogen-receptor modulator (SERM) is used as an adjuvant to treat breast cancer. No pattern of birth defects has been described in limited case reports and series (Braems, 2011). However, tamoxifen has been associated with malformations similar to those caused by diethylstilbestrol (DES) exposure in rodents, including vaginal adenosis. Consequently, women who become pregnant on therapy or within 2 months of its discontinuation should be apprised of the potential long-term risks of a DES-like syndrome.

### Trastuzumab

This is a recombinant monoclonal antibody directed to the human epidermal growth factor receptor 2 (HER2) protein. Used to treat breast cancers that express HER2 protein, this drug has not been associated with fetal malformations. However, cases of oligohydramnios sequence resulting in pulmonary hypoplasia, renal failure, skeletal abnormalities, and neonatal deaths have been reported (Genentech, 2017). Surveillance for these complications is recommended for exposed pregnancies and for those treated at any time in the 7 months prior to conception. A trastuzumab pregnancy exposure registry and a pregnancy pharmacovigilance program have been established to monitor pregnancy outcomes. These warnings also apply to those treated with ado-trastuzumab emtansine.

## Antiviral Agents

The number of drugs used to treat viral infections has increased rapidly during the past 20 years. For most, experience in pregnant women is limited.

### Ribavirin

This nucleoside analogue is a component of therapy for hepatitis C infection, discussed in Chapter 55 (Hepatitis D). Ribavirin causes birth defects in multiple animal species at doses significantly lower than those recommended for human use. Reported malformations include skull, palate, eye, skeleton, and gastrointestinal abnormalities. The drug has a half-life of 12 days and persists in extravascular compartments following therapy discontinuation. Treated women must use two forms of contraception and have monthly pregnancy tests while on therapy and for 6 months following drug discontinuation (Genentech, 2015). Ribavirin use is also contraindicated in men whose partners are pregnant.

### Efavirenz

This is a nonnucleoside reverse transcriptase inhibitor used to treat HIV infection (Chap. 65, Delivery Planning). CNS and ocular abnormalities have been reported in cynomolgus monkeys treated with doses comparable to those used in humans. Several case reports also describe neural-tube

defects following human exposure to efavirenz. Reassuringly, the Antiretroviral Pregnancy Registry has identified no increased birth defect rates in more than 800 pregnancies with first-trimester exposure (Bristol-Meyers Squibb, 2017b).

## Endothelin-Receptor Antagonists

Bosentan, ambrisentan, and macitentan are three endothelin-receptor antagonists used to treat pulmonary arterial hypertension (Chap. 49, Cardiomyopathies). The endothelin-receptor signaling pathway is important for neural-crest development. Mice deficient in endothelin receptors develop neural-crest cell defects that include craniofacial and cardiac outflow tract abnormalities (de Raaf, 2015). Each of these three agents has been found to cause similar birth defects in multiple animal species (Actelion, 2017). No human data are available. Endothelin-receptor antagonists may be obtained only through restricted access programs, each of which has stringent requirements that include contraception and monthly pregnancy testing (Actelion, 2016, 2017; Gilead, 2015).

## Sex Hormones

Some of the functions and effects of male and female hormones on the developing fetus are discussed in Chapter 3 (Sexual Differentiation). It is intuitive that exposure of female fetuses to excessive male sex hormones—and vice versa—might be detrimental.

### Testosterone and Anabolic Steroids

Androgen exposure in reproductive-aged women typically stems from anabolic steroid use to accrue lean body mass and muscular strength. Exposure of a female fetus may cause varying degrees of virilization and may result in ambiguous genitalia similar to that encountered in congenital adrenal hyperplasia. Findings can include labioscrotal fusion with first-trimester exposure and phallic enlargement from later fetal exposure (Grumbach, 1960; Schardein, 1980).

### Danazol

This ethinyl testosterone derivative has weak androgenic activity. It is used to treat endometriosis, immune thrombocytopenic purpura, migraine headaches, premenstrual syndrome, and fibrocystic breast disease. In a review of inadvertent exposure during early pregnancy, Brunskill (1992) reported that 40 percent of exposed female fetuses were virilized. There was a dose-related pattern of clitoromegaly, fused labia, and urogenital sinus malformation.

### Diethylstilbestrol

This medication is included for historical context. From 1940 until 1971, between 2 and 10 million pregnant women were given this synthetic estrogen for ill-advised indications. It was removed from the market after Herbst and associates (1971) reported a series of eight women exposed to DES in utero who developed an otherwise rare neoplasm, vaginal clear-cell adenocarcinoma. With no relationship to drug dosage, the absolute cancer risk approximates 1 case per 1000 DES-exposed fetuses. Twofold greater rates of vaginal and cervical intraepithelial neoplasia were also described (Vessey, 1989).

DES exposure has further been associated with genital tract abnormalities in exposed fetuses of both genders. Women may have a hypoplastic, T-shaped uterine cavity; cervical collars, hoods, septa, and coxcombs; and “withered” fallopian tubes (Goldberg, 1999; Salle, 1996). Some are described and illustrated in Chapter 3 (Diethylstilbestrol Reproductive Tract Abnormalities (Class VII)). Later in life, women exposed in utero have slightly higher rates of earlier menopause and breast cancer (Hoover, 2011). Men may develop epididymal cysts, microphallus, hypospadias, cryptorchidism, and testicular hypoplasia (Klip, 2002; Stillman, 1982).

## Immunosuppressant Medications

Some of the immune functions necessary for pregnancy maintenance are discussed in Chapter 5 (Amnion). Given these important interactions, immunosuppressant drugs logically might affect pregnancy.

### Corticosteroids

These medications include glucocorticoids and mineralocorticoids, which have antiinflammatory and immunosuppressive actions. They are frequently used to treat serious disorders such as asthma and autoimmune disease. Corticosteroids have been associated with clefts in animal studies. In one metaanalysis of case-control studies by the Motherisk Program, systemic corticosteroid exposure was associated with a threefold increase in the rate of clefts. This is an absolute risk of 3 cases per 1000 exposed fetuses (Park-Wyllie, 2000). A 10-year prospective cohort study by the same group, however, did not identify higher risks for major malformations. Based on these findings, corticosteroids are not considered to represent a major teratogenic risk.

Unlike other corticosteroids, the active metabolite of prednisone, which is prednisolone, is inactivated by the placental enzyme 11β-hydroxysteroid dehydrogenase 2. Thus, it may not effectively reach the fetus.

### Mycophenolate Mofetil

This inosine monophosphate dehydrogenase inhibitor, and a related agent, mycophenolic acid, are immunosuppressants. They are used to prevent rejection in organ-transplant recipients and to treat autoimmune disease (Chap. 59, Perinatal Mortality and Morbidity). Mycophenolate is a potent teratogen. From the National Transplantation Pregnancy Registry, of pregnancies in which mycophenolate was not discontinued until after the first trimester, birth defects complicated 30 percent, and another 30 percent spontaneously aborted (King, 2017). One prospective review by the European Network of Teratology Information Services similarly identified a spontaneous loss rate of nearly 30 percent in exposed pregnancies. More than 20 percent of liveborn infants had major anomalies (Hoeltzenbein, 2012).

Many affected infants have a pattern of defects termed *mycophenolate embryopathy*. This includes microtia, auditory canal atresia, clefts, coloboma and other eye anomalies, short fingers with hypoplastic nails, and cardiac defects (Anderka, 2009; Merlob, 2009). A Risk Evaluation and Mitigation Strategy (REMS) has been developed for mycophenolate prescribers who treat women with reproductive potential. REMS are safety strategies mandated by the FDA to help manage known risks associated with a medicine yet still allow patients to have access to the benefits of a given drug.

## Radioiodine

Radioactive iodine-131 is used for treatment of thyroid cancer and thyrotoxicosis and for diagnostic thyroid scanning. It is also a component of iodine-131 tositumomab therapy, which is employed to treat a type of non-Hodgkin lymphoma. Radioiodine is contraindicated during pregnancy because it readily crosses the placenta and is then concentrated in the fetal thyroid gland by 12 weeks' gestation. It may cause severe or irreversible fetal and neonatal hypothyroidism, which can lead to decreased mental capacity and delayed skeletal maturation (Jubilant DraxImage, 2016). Pregnancy testing should be performed before administration of radioiodine-131.

## Lead

Prenatal lead exposure is associated with fetal-growth abnormalities and with childhood developmental delay and behavioral abnormalities. According to the CDC (2010), no level of lead exposure is considered safe in pregnancy. Care and testing for at-risk pregnancies is discussed in Chapter 9 (Common Concerns).

## Mercury

Environmental spills of methyl mercury in Minamata Bay, Japan, and rural Iraq demonstrated that the developing nervous system is particularly susceptible to this heavy metal. Prenatal exposure causes disturbances in neuronal cell division and migration. This leads to a range of defects from developmental delay to microcephaly and severe brain damage (Choi, 1978).

The principal concern for prenatal mercury exposure is the consumption of certain species of large fish (Chap. 9, Common Concerns). The FDA (2017a) advises that pregnant women and breastfeeding mothers avoid consumption of king mackerel, marlin, orange roughy, shark, swordfish, tilefish, and bigeye tuna.

## Psychiatric Medications

Treatment of psychiatric illness in pregnancy, including a discussion of the risks and benefits of various psychiatric medications, is described in Chapter 61 (Psychological Adjustments to Pregnancy). Selected birth defects and adverse effects associated with specific medications are presented

here.

### Lithium

This medication has been associated with Ebstein anomaly, a rare cardiac abnormality that otherwise complicates only 1 per 20,000 births. Ebstein anomaly is characterized by apical displacement of the tricuspid valve, often resulting in severe tricuspid regurgitation and marked right atrial enlargement that confer significant morbidity. A report from the Lithium Baby Registry initially suggested that the risk for Ebstein anomaly was as high as 3 percent. However, subsequent series have identified an attributable risk for Ebstein anomaly and co-occurring right-sided cardiac anomalies of only 1 to 4 per 1000 exposed pregnancies (Patorno, 2017; Yacobi, 2008). In a review of four case-control studies that included more than 200 infants with Ebstein anomaly, no cases were attributed to lithium exposure (Cohen, 1994).

*Neonatal lithium toxicity* stems from exposure near delivery. The manufacturer recommends that if possible, the dosage should be decreased or drug discontinued 2 to 3 days prior to delivery to reduce this risk (West-Ward, 2016). Findings typically persist for 1 to 2 weeks and may include neonatal hypothyroidism, diabetes insipidus, cardiomegaly, bradycardia, electrocardiogram abnormalities, cyanosis, and hypotonia (American College of Obstetricians and Gynecologists, 2016).

### Selective Serotonin- and Norepinephrine-Reuptake Inhibitors

As a class, these medications are not considered major teratogens (American College of Obstetricians and Gynecologists, 2016). The one exception is paroxetine, which has been associated with a higher risk for cardiac anomalies, particularly atrial and ventricular septal defects. Three large databases—a Swedish national registry, a United States insurance claims database, and the Motherisk Program—each identified a 1.5- to twofold greater risk for cardiac malformations following first-trimester paroxetine exposure (Bar-Oz, 2007; Sebela, 2017). For these reasons, the American College of Obstetricians and Gynecologists (2016) recommends that paroxetine be avoided in women planning pregnancy. Fetal echocardiography should be considered for those with first-trimester paroxetine exposure.

Neonatal effects have been associated with prenatal exposure to selective serotonin-reuptake inhibitors (SSRIs) and selective norepinephrine-reuptake inhibitors (SNRIs). Approximately 25 percent of neonates exposed to SSRIs in late pregnancy manifest one or more nonspecific findings considered to represent poor neonatal adaptation (Chambers, 2006; Costei, 2002; Jordan, 2008). Collectively termed the *neonatal behavioral syndrome*, findings can include jitteriness, irritability, hyper- or hypotonia, feeding abnormalities, vomiting, hypoglycemia, thermoregulatory instability, and respiratory abnormalities. Fortunately, these neonatal behaviors are typically mild and self-limited and last approximately 2 days. Jordan and coworkers (2008) reported that affected newborns were not more likely to require a higher level of care, to experience respiratory abnormalities, or to have prolonged hospitalization. Rarely, neonates exposed to SSRIs in late pregnancy demonstrated more severe adaptation abnormalities (Ornoy, 2017).

Another concern with late-pregnancy exposure is the possible association of SSRI medications with *persistent pulmonary hypertension of the newborn (PPHN)*. The baseline incidence approximates 2 cases per 1000 term newborns. PPHN is characterized by elevated pulmonary vascular resistance with right-to-left shunting and resultant hypoxemia. Two recent population-based cohort studies—together involving more than 5 million pregnancies—identified an attributable risk of only 1 to 2 cases per 1000 births (Huybrechts, 2015; Kieler, 2012). Not only is the risk for this condition quite low, but cases associated with SSRI medication have not been severe (Ornoy, 2017).

### Antipsychotic Medications

No antipsychotic medications are considered teratogenic. Exposed neonates can manifest abnormal extrapyramidal muscle movements and withdrawal symptoms that include agitation, abnormally enhanced or diminished muscle tone, tremor, sleepiness, feeding difficulty, and respiratory abnormalities. These findings are nonspecific and transient, similar to the neonatal behavioral syndrome that can follow SSRI exposure. An FDA (2011) alert cites all medications in this class. These include older drugs such as haloperidol and chlorpromazine, as well as newer medications such as aripiprazole, olanzapine, quetiapine, and risperidone.

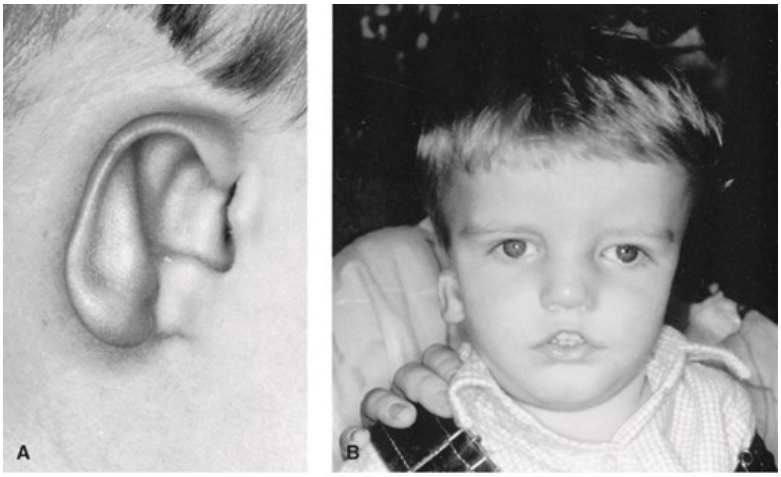
## Retinoids

These vitamin A derivatives are among the most potent human teratogens. Three retinoids available in the United States are highly teratogenic when orally administered—isotretinoin, acitretin, and bexarotene. By inhibiting neural-crest cell migration during embryogenesis, they create a pattern of

cranial neural-crest defects—termed *retinoic acid embryopathy*—that involve the CNS, face, heart, and thymus (Fig. 12-5). Specific anomalies may include ventriculomegaly, maldevelopment of the facial bones or cranium, microtia or anotia, micrognathia, cleft palate, conotruncal heart defects, and thymic aplasia or hypoplasia.

FIGURE 12-5

Isotretinoin embryopathy. **A.** Bilateral microtia or anotia with stenosis of external ear canal. **B.** Flat, depressed nasal bridge and ocular hypertelorism. (Used with permission from Dr. Edward Lammer.)






### Isotretinoin

13-*cis*-Retinoic acid is a vitamin A isomer that stimulates epithelial cell differentiation and is used for dermatological disorders, especially cystic nodular acne. First-trimester exposure is associated with a high rate of pregnancy loss, and up to a third of fetuses have malformations (Lammer, 1985). The iPLEDGE program is an FDA-mandated REMS for isotretinoin and is found at: www.ipledgeprogram.com. This web-based, restricted-distribution program requires participation for all patients, physicians, and pharmacies to help eliminate embryonic–fetal exposure. Although other countries have instituted similar programs, inadvertent exposure remains a global concern (Crijns, 2011).

### Acitretin

This retinoid is used to treat severe psoriasis and was introduced to replace etretinate. The latter is a lipophilic retinoid with such a long half-life (120 days) that birth defects resulted more than 2 years after therapy was discontinued. Although acitretin has a short half-life, it is metabolized to etretinate, and thus remains in the body for prolonged periods (Stiefel Laboratories, 2015). To obviate exposure, the manufacturer of acitretin has developed a pregnancy risk management program. Called "Do Your P.A.R.T"—Pregnancy prevention Actively Required during and after Treatment, this program promotes a delay of conception for at least 3 years following therapy discontinuation.

### Bexarotene

This retinoid is used to treat cutaneous T-cell lymphoma. When given to rats in doses comparable to those for human therapy, fetuses developed eye and ear abnormalities, cleft palate, and incomplete ossification. For a woman to receive this medication, the manufacturer requires two forms of contraception that are initiated 1 month before therapy and are continued for 1 month after bexarotene discontinuation. This is coupled with monthly pregnancy testing during treatment (Valeant Pharmaceuticals, 2015). Males who have partners who could become pregnant are advised to use condoms during sexual intercourse while taking bexarotene and for 1 month after discontinuing therapy.

### Topical Retinoids

These compounds, initially used to treat acne, have become so popular for the treatment of sun damage that they are called *cosmeceuticals*

(Panchaud, 2012). The most commonly used topical agents are tretinoin, isotretinoin, and adapalene. Systemic absorption is low, and this argues against plausible teratogenicity.

Isolated case reports have described malformations following topical tretinoin, and it is unknown whether this is due to variability in absorption or perhaps potential individual susceptibility (Kaplan, 2015). A prospective study by the European Network of Teratology Information Services found no higher rates of birth defects or spontaneous losses, and no case of retinoid embryopathy (Panchaud, 2012). One systematic review by the Motherisk Program included 635 pregnancies with exposure to topical retinoids. Investigators similarly identified no higher risk for congenital malformations, spontaneous abortion, stillbirth, low birthweight, or preterm delivery (Kaplan, 2015). These results may be reassuring to pregnant women with inadvertent exposure.

Notably, the manufacturer of tazarotene cautions that application over a sufficient body surface area could be comparable to oral treatment. Accordingly, its use in pregnancy is not recommended (Allergan, 2017).

### Vitamin A

There are two natural forms of vitamin A. Beta-carotene, which is a precursor of provitamin A, is found in fruits and vegetables and has never been shown to cause birth defects (Oakley, 1995). Retinol is preformed vitamin A, which has been associated with cranial neural-crest defects when more than 10,000 IU per day is consumed in the first trimester (Rothman, 1995). It seems reasonable to avoid doses of preformed preparations that exceed the recommended 3000 IU daily allowance (American Academy of Pediatrics, 2017).

## Thalidomide and Lenalidomide

Possibly the most notorious human teratogen, thalidomide causes malformations in 20 percent of fetuses exposed between 34 and 50 days menstrual age. The characteristic malformation is *phocomelia*—an absence of one or more long bones. As a result, hands or feet are attached to the trunk, occasionally by a small rudimentary bone. Cardiac malformations, gastrointestinal abnormalities, external ear malformations, eye anomalies, and other limb-reduction defects are also common following thalidomide exposure. The manufacturer reports that up to 40 percent of affected newborns do not survive the neonatal period (Celgene, 2017a).

Thalidomide was marketed outside the United States from 1956 to 1960, before its teratogenicity was appreciated. The ensuing disaster, with thousands of affected children, was instructive of several important teratological principles. First, the placenta is not an effective barrier to the transfer of toxic substances from mother to embryo (Dally, 1998). Second, different species show extreme variability in their susceptibility to drugs and chemicals. Namely, thalidomide produced no defects in multiple rodent species and was assumed to be safe for humans. Last, exposure timing and defect type are often closely related (Vargesson, 2015). For example, upper-limb amelia may develop with thalidomide exposure during days 24 to 30 postconception, upper-limb phocomelia with exposure during days 24 to 33, and lower-limb phocomelia with exposure during days 27 to 33.

Thalidomide was first approved in the United States in 1999 and currently is used to treat erythema leprosum nodosum and multiple myeloma (Celgene, 2017a). The FDA has mandated a web-based, restricted-distribution program for thalidomide, called THALOMID REMS, which is required before patients, physicians, and pharmacies can access the medication.

Lenalidomide is an analogue of thalidomide that is used to treat some types of myelodysplastic syndrome and multiple myeloma. It crosses the placenta in multiple animal species, and it causes thalidomide-like limb abnormalities in monkeys (Celgene, 2017b). Because of obvious teratogenicity concerns, a restricted-distribution program similar to that used for thalidomide has been developed.

## Warfarin

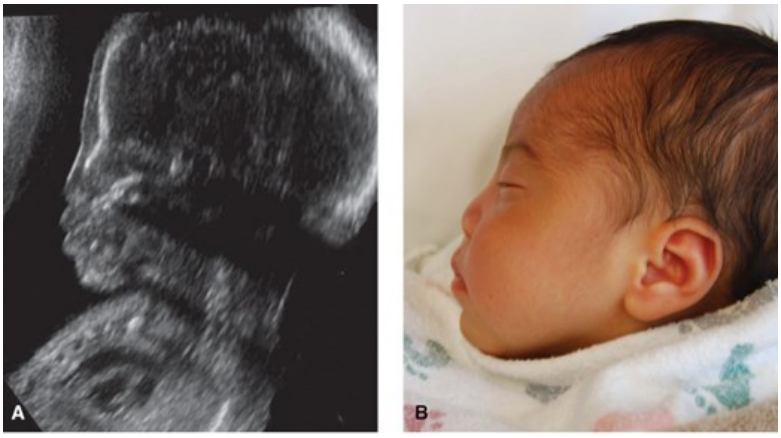
This anticoagulant is a vitamin K antagonist with a long half-life. Because of its low molecular weight, it readily crosses the placenta and may cause embryotoxic and fetotoxic effects. Warfarin analogues, such as Coumadin, are considered contraindicated in pregnancy. An exception, as discussed in Chapter 49 (Surgically Corrected Heart Disease), is treatment of women with mechanical heart valves who are at high risk for thromboembolism (Bristol-Myers Squibb, 2017a).

*Warfarin embryopathy* is characterized by stippled epiphyses and nasal hypoplasia (Fig. 12-6). In one review of 63 cases attributed to warfarin exposure, 80 percent displayed characteristic findings, which include depressed nasal bridge with nasal hypoplasia and choanal atresia, along with

stippled epiphyses of the femur, humerus, calcanei, and distal phalanges (Van Driel, 2002). It may result from exposure between the 6th and 9th weeks' gestation (Hall, 1980). The prevalence of the warfarin embryopathy following exposure during this critical period is estimated to be 6 percent (van Driel, 2002). One metaanalysis of cases in which the warfarin dosage was ≤5 mg/d identified embryopathy in 1 percent of exposed fetuses. This suggests that risk may be dose dependent (Hassouna, 2014).

**FIGURE 12-6**

Warfarin embryopathy or fetal warfarin syndrome: nasal hypoplasia and depressed nasal bridge seen in a fetal sonographic image **(A)** and in the same newborn **(B)**.






If used beyond the first trimester, warfarin may lead to hemorrhage into fetal structures, which can cause abnormal growth and deformation from scarring (Warkany, 1976). Nearly 50 percent of reported embryopathy cases also have CNS anomalies (van Driel, 2002). Abnormalities can include agenesis of the corpus callosum; cerebellar vermian agenesis, which is the Dandy-Walker malformation; microphthalmia; and optic atrophy (Hall, 1980). Affected infants are also at risk for blindness, deafness, and developmental delays.

## Herbal Remedies

With various herbal remedies, associated risks are more challenging to estimate because studies are few and because these compounds are not FDA-regulated. The European Committee of Herbal Medicinal Products provides assessment reports and monographs on selected herbal substances and preparations, but safety data are generally limited (Wiesner, 2017). Animal studies have not been conducted, and thus knowledge of complications often derives from reports of acute toxicity (Hepner, 2002; Sheehan, 1998). Further, the identity, quantity, and purity of each ingredient are usually unknown. Given these uncertainties, it seems prudent to counsel pregnant women to avoid these substances. A list of selected herbal compounds and their potential effects is shown in Table 12-5.

TABLE 12-5

**Pharmacological Actions and Adverse Effects of Some Herbal Medicines**

| Herb and Common Name | Relevant Pharmacological Effects | Concerns |
|---|---|---|
| Aloe (oral ingestion) | Smooth-muscle stimulant | May cause uterine contractions |
| Black cohosh | Smooth-muscle stimulant | Causes uterine contractions; also has an estrogenic compound |
| Blue cohosh | Smooth-muscle stimulant | Causes uterine contractions; contains compounds teratogenic in multiple animal species |
| Echinacea: *purple coneflower root* | Activates cell-mediated immunity | Allergic reactions; decreases immunosuppressant effectiveness; possible immunosuppression with long-term use |
| Ephedra: *ma huang* | Direct and indirect sympathomimetic; tachycardia and hypertension | Hypertension, arrhythmias, myocardial ischemia, stroke; depletes endogenous catecholamines; life-threatening interaction with monoamine oxidase inhibitors |
| Evening primrose oil | Contains linoleic acids, a prostaglandin precursor | Possible complications if used for labor induction |
| Garlic: *ajo* | Inhibits platelet aggregation; increased fibrinolysis; antihypertensive activity | Risk of bleeding, especially when combined with other platelet aggregation inhibitors |
| Ginger | Cyclooxygenase inhibitor, thromboxane synthetase inhibitor | Increased risk of bleeding |
| Ginkgo biloba | Anticoagulant | Risk of bleeding; interferes with monoamine oxidase inhibitors |
| Ginseng | Lowers blood glucose; inhibition of platelet aggregation | Hypoglycemia; hypertension; risk of bleeding |
| Kava: *awa, intoxicating pepper, kawa* | Sedation, anxiolysis | Sedation; tolerance and withdrawal |
| Valerian: *all heal, garden heliotrope, vandal root* | Sedation | Sedation; hepatotoxicity, benzodiazepine-like acute withdrawal |
| Yohimbe | | Hypertension, arrhythmias |

Data from Ang-Lee, 2001; Briggs, 2015; Hall, 2012; Wiesner, 2017.

## Recreational Drugs

Not uncommonly, fetuses are exposed to one or more illicit drugs. Assessment of outcomes attributable to these drugs may be confounded by factors such as poor maternal health, malnutrition, infectious disease, and polysubstance abuse. Moreover, illegal substances may contain toxic contaminants such as lead, cyanide, herbicides, and pesticides. Impurities added as diluents may independently have serious adverse perinatal effects. As noted in Known and Suspected Teratogens, alcohol is a significant teratogen. Because it is legally obtained and ubiquitous, its use also confounds the study of

illicit drug teratogenicity.

### Amphetamines

These sympathomimetic amines are not considered to be major teratogens. Methamphetamine enhances dopamine release and blocks its reuptake. It is prescribed to treat attention-deficit/hyperactivity disorder and narcolepsy. Methamphetamine abuse has been rising in the United States since the late 1980s (American College of Obstetricians and Gynecologists, 2017b). In utero exposure has been consistently associated with higher rates of small-for-gestational age newborns (Gorman, 2014; Smith, 2006). Hypertensive complications, placental abruption, preterm birth, and stillbirth are other associated complications (Gorman, 2014). Behavioral abnormalities have been described in both infants and school-aged children (Eze, 2016).

### Cocaine

With this CNS stimulant, most adverse outcomes result from its vasoconstrictive and hypertensive effects. Serious potential maternal complications are cerebrovascular hemorrhage, myocardial damage, and placental abruption. Studies of congenital abnormalities and cocaine exposure have yielded conflicting results, but associations with cleft palate, cardiovascular abnormalities, and urinary tract anomalies have been reported (Chasnoff, 1988; Lipshultz, 1991; van Gelder, 2009). Cocaine use is also associated with fetal-growth restriction and preterm delivery. Children exposed as fetuses have risks for behavioral abnormalities and cognitive impairments (Bada, 2011; Gouin, 2011).

### Opioids–Narcotics

The dramatic rise in narcotic use among non-pregnant and pregnant individuals has been aptly termed an epidemic. Opioids are not considered to be major teratogens. The NBDPS did identify a slightly greater risk for spina bifida, gastroschisis, and cardiac abnormalities with periconceptional opioid exposure (Broussard, 2011). The American College of Obstetricians and Gynecologists (2017c) stresses that this potential, small increase in birth defects with maintenance therapy should be weighed against the risks associated with uncontrolled opioid abuse. Heroin addiction is associated with adverse pregnancy outcomes from the effects of repeated narcotic withdrawal on the fetus and placenta (American College of Obstetricians and Gynecologists, 2017c). These include preterm birth, placental abruption, fetal-growth restriction, and fetal death.

Neonatal narcotic withdrawal, called the *neonatal abstinence syndrome*, may manifest in 40 to 90 percent of exposed newborns (Blinick, 1973; Creanga, 2012; Dashe, 2002; Zelson, 1973). As discussed in Chapter 33 (Neonatal Abstinence Syndrome), CNS irritability may progress to seizures if untreated and may be accompanied by tachypnea, apneic episodes, poor feeding, and failure to thrive. At-risk neonates are closely monitored using a scoring system, and those severely affected are treated with opioids (Finnegan, 1975). The proportion of exposed newborns developing neonatal abstinence syndrome has risen significantly in recent years (Creanga, 2012; Lind, 2015).

The American College of Obstetricians and Gynecologists (2017c) recommends that pregnant women with opioid-use disorder be maintained on opioid-agonist therapy to reduce the risks associated with illicit opioid abuse and associated behaviors. Treatment includes either methadone, usually through a licensed outpatient opioid treatment program, or buprenorphine, which may be given in an office-based setting by a licensed buprenorphine prescriber. A multidisciplinary treatment program is recommended to reduce the likelihood of additional opioid abuse while on maintenance therapy. The College (2017c) discourages withdrawal from methadone during pregnancy because of high relapse rates. At Parkland Hospital, pregnant opioid users who decline maintenance therapy are offered inpatient hospitalization for controlled methadone taper, with the goal of reducing the likelihood of neonatal abstinence syndrome (Dashe, 2002; Stewart, 2013).

### Marijuana

This is the illicit drug most commonly used in pregnancy (American College of Obstetricians and Gynecologists, 2017a). Based on data from the National Survey on Drug Use and Health, the prevalence of marijuana use in pregnancy was nearly 4 percent in 2014 (Brown, 2017). Cannabinoids are not considered to be major teratogens, but there is concern because endogenous cannabinoids play key roles in human brain development. In one metaanalysis of nearly 8000 exposed pregnancies, adverse outcomes such as preterm birth and low birthweight were increased only in the presence of concomitant tobacco use (Conner, 2016).

### Miscellaneous Drugs

*Phencyclidine (PCP)* or angel dust is not associated with congenital anomalies. More than half of exposed newborns, however, experience withdrawal

symptoms characterized by tremors, jitteriness, and irritability. *Toluene* is a common solvent used in paints and glue. Occupational exposure is reported to have significant fetal risks (Wilkins-Haug, 1997). When abused by women in early pregnancy, it is associated with *toluene embryopathy*, which is phenotypically similar to fetal alcohol syndrome. Abnormalities include pre- and postnatal growth deficiency, microcephaly, midface hypoplasia, short palpebral fissures, and wide nasal bridge (Pearson, 1994). Up to 40 percent of exposed children have developmental delays (Arnold, 1994).

### Tobacco

Cigarette smoke contains a complex mixture of nicotine, cotinine, cyanide, thiocyanate, carbon monoxide, cadmium, lead, and various hydrocarbons (Stillerman, 2008). In addition to being fetotoxic, many of these substances have vasoactive effects or reduce oxygen levels. Tobacco is not considered a major teratogen, although selected birth defects have been reported to occur with greater frequency among newborns of women who smoke. It is plausible that the vasoactive properties of tobacco smoke could produce congenital defects related to vascular disturbances. For example, the prevalence of Poland sequence, which is caused by an interruption in the vascular supply to one side of the fetal chest and ipsilateral arm, is twofold greater in smokers (Martinez-Frias, 1999). A small increased risk for cardiac anomalies has also been reported and may be dose related (Alverson, 2011; Malik, 2008; Sullivan, 2015). One study analyzing more than 6 million births found an association between maternal smoking and hydrocephaly, microcephaly, omphalocele, gastroschisis, cleft lip and palate, and hand abnormalities (Honein, 2001). Electronic nicotine delivery systems are not considered safe, as nicotine may have adverse effects on fetal brain and lung development (American College of Obstetricians and Gynecologists, 2017d).

The best-documented adverse reproductive outcome from smoking is a dose-response reduction in fetal growth. Newborns of mothers who smoke weigh on average 200 g less than newborns of nonsmokers (D'Souza, 1981). Smoking doubles the risk of low birthweight and raises the risk of fetal-growth restriction two- to threefold (Werler, 1997). Even secondhand smoke increases the risk for low birthweight (Hegaard, 2006). Women who stop smoking early in pregnancy may have neonates with normal birthweights (Cliver, 1995). Other adverse outcomes associated with cigarette smoking include preterm birth, placenta previa, placenta abruption, spontaneous abortion, and sudden infant death syndrome (American College of Obstetricians and Gynecologists, 2017d). Risks of childhood asthma and obesity are also increased.

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