

# Teratogenesis and Environmental Exposure

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A *teratogenic exposure* is defined as one that has the potential to interfere with the normal functional or structural development of an embryo or fetus. An exposure includes an agent (e.g., chemical) and an exposure level (e.g., dose). Although teratogenic exposures typically increase the risk of major congenital anomalies, they also increase the risk of a spectrum of adverse pregnancy outcomes, including spontaneous abortion, stillbirth, minor structural anomalies, shortened gestational age, growth restriction, and behavioral or cognitive deficits. Excess risks for the latter events may be much more difficult to recognize.

Known teratogenic exposures comprise a wide range of doses and agents, including some prescription and over-the-counter medications, recreational drugs and alcohol, chemicals, physical agents, and maternal diseases. Although studies specifically evaluating human teratogenicity are lacking for most environmental agents, including prescription medications, it is estimated that about 10% of major birth defects are attributable to environmental exposures and are therefore preventable to some extent.

## Historical Perspective

Before the 1940s, it was somewhat naively thought by clinicians that the placenta provided a protective barrier for the developing embryo and fetus and that agents to which the mother was exposed could not interfere with normal prenatal development. The revolutionary concept that a maternal exposure could pose a risk to the developing embryo or fetus was first raised in the clinical literature by an Australian ophthalmologist, Norman Gregg, who observed in his clinical practice an unusual number of children diagnosed with congenital cataracts shortly after a rubella epidemic. Gregg's work led to investigations that identified additional features of a variable but characteristic pattern of developmental abnormalities associated with fetal rubella infection, including congenital heart defects, hearing deficits, poor growth, and thrombocytopenia, which came to be known as the congenital rubella syndrome.<sup>1</sup>

In the early 1960s, an Australian obstetrician and a German geneticist independently recognized that first-trimester maternal use of thalidomide, a sedative-hypnotic drug, was associated with the appearance of a characteristic pattern of limb reduction anomalies and other defects.<sup>2,3</sup> Although the drug had undergone premarket testing in rodents, it had not shown the characteristic limb defects in these species. In the United States, subsequent recognition that therapeutic agents could induce malformations was a major stimulus for the implementation of the Kefauver-Harris Amendment to the Food, Drug, and Cosmetic Act, which expanded the role of the U.S. Food and Drug

Administration (FDA) as a regulatory agency charged with ensuring the efficacy and safety of products.<sup>4</sup>

Although the thalidomide experience raised public awareness of the potential risks of prenatal exposures, the thalidomide episode was accompanied by misunderstandings about how to differentiate exposures that cause birth defects from coincidental exposures occurring in women whose pregnancy outcome is abnormal for other, unrelated reasons. A classic example is doxylamine succinate and pyridoxine hydrochloride with or without dicyclomine hydrochloride (Bendectin), a once-popular antiemetic medication used by as many as 30% of American women for the treatment of nausea and vomiting of pregnancy. In 1983, this agent was voluntarily withdrawn from the market after an onslaught of litigation claiming teratogenicity despite voluminous scientific evidence to the contrary.<sup>5</sup>

Within the past 40 years, research in the field of teratology has advanced, and several new human teratogenic exposures have been identified, including several anticonvulsants, selected antineoplastic agents, inhibitors of enzymes in the renin-angiotensin system, methylmercury, ethanol, hyperthermia, tetracycline, warfarin, and isotretinoin. Work continues to better define the range of adverse outcomes associated with these exposures, the magnitude of the risk for a given dose at a specific gestational age, and the subpopulations of mothers and infants who may be at particularly increased risk because of their genotype. However, major knowledge gaps exist for most agents, few of which have been adequately evaluated in human pregnancy.

Drug exposure during pregnancy is extremely common. In one U.S. health care system sample of 98,182 deliveries, 64% of women were prescribed at least one medication during their pregnancy other than a vitamin or mineral supplement.<sup>6</sup> In another U.S. population-based sample of women, more than 65% reported the use of one or more over-the-counter medications during pregnancy.<sup>7</sup> In many cases, these medications are necessary for the health of the mother or fetus, but in other cases, the exposures could have been avoided. A theoretical and practical framework is necessary to aid clinicians in advising patients, who are likely to have experienced several exposures by the time their pregnancy is recognized, and to support clinical decision making in the common situations in which treatment during pregnancy is recommended.

## Principles of Teratology

James G. Wilson<sup>8</sup> outlined the basic principles of teratology in the early 1970s. These six principles, given in Wilson's own words, were based on experience with experimental animal studies, but they can be applied equally well to human pregnancy.

1. *Susceptibility to teratogenesis depends on the genotype of the conceptus and the manner in which this interacts with environmental factors.*

Exposures do not occur in a vacuum; women and their fetuses bring different genetic makeups to the exposure scenario. Different genetic characteristics may alter the way a drug or chemical is metabolized or may alter the susceptibility of a developmental process to disturbance by an exposure. For example, women with infants who have cleft lip with or without cleft palate or isolated cleft palate are approximately twice as likely to report heavy first-trimester tobacco use than are mothers of normal newborns. However, women who have a certain transforming growth factor- $\alpha$  (TGF- $\alpha$ ) polymorphism and who smoke heavily have a 3 to 11 times higher risk of having a child with an oral cleft, suggesting an interaction of the genetic characteristics of the mother with the tobacco smoke exposure. This risk appears to be lessened by maternal multivitamin use.<sup>9,10</sup> Similarly, a low level of epoxide hydrolase enzyme activity influenced by epoxide hydrolase polymorphisms has been implicated as a risk factor for fetal hydantoin syndrome in children whose mothers have taken phenytoin for the treatment of a seizure disorder during pregnancy.<sup>11</sup>

2. *Susceptibility to teratogenic agents varies with the developmental stage at the time of exposure.*

The principle of *gestational timing*, or critical developmental windows of exposure, requires that the exposure occur during the stage in development when the targeted developmental process is most susceptible. For example, the critical window for an agent that interferes with closure of the neural tube in the human embryo is approximately 21 to 28 days after conception. Carbamazepine, an anticonvulsant linked to a 10-fold increased risk of neural tube defects, does not produce the defect if maternal exposure occurs after the second month of pregnancy.<sup>12,13</sup>

Depending on the gestational timing of exposure, different outcomes may be induced. For example, warfarin therapy is associated with a pattern of nasal hypoplasia and skeletal abnormalities when prenatal exposure occurs during the latter portion of the first trimester, whereas later gestational exposure is associated with central nervous system (CNS) abnormalities.<sup>14</sup> The first-trimester effects likely reflect vitamin K deficiency, and later effects are a complication of fetal bleeding.

Consistent with this concept, very early gestational exposure, usually limited to the first 2 weeks after conception, poses little potential for teratogenicity, because pluripotent cells of the early embryo are able to replace one another if there is exposure-induced damage, or if the magnitude of cell loss is too great, the conceptus is lost, resulting in spontaneous abortion.<sup>8</sup>

3. *Teratogenic agents act in specific ways (mechanisms) on developing cells and tissues to initiate abnormal embryogenesis (pathogenesis).*

There is no teratogenic exposure that increases the risk of all adverse outcomes; rather, teratogenic exposures act on specific developmental processes to produce a characteristic pattern of effects. This principle underlies the methods by which many human teratogens have been suspected. The pattern of abnormalities associated with a particular teratogenic exposure helps to identify the exposure as the cause of an outcome. For example, the characteristic pattern of abnormalities comprising the fetal alcohol syndrome includes minor craniofacial features (i.e.,

short palpebral fissures, smooth philtrum, and thin vermilion of the upper lip) accompanied by microcephaly, growth deficiency, and cognitive and behavioral deficits. The prenatal effects of ethanol, although pervasive, nevertheless represent a constellation of features that is unlikely to randomly occur without exposure to alcohol in substantial doses and during certain gestational weeks.

There are a few general mechanisms that lead to abnormal development. For example, a teratogenic agent can interact with a receptor, bind to DNA or protein, degrade cell membranes, inhibit proteins, inhibit an enzyme, or modify proteins. These mechanisms manifest as excessive or reduced cell death, failed cell interactions, reduced biosynthesis, impeded morphogenetic movement, or mechanical disruption of tissues. For this reason, some teratogenic exposures have the same end result because they act through a common pathway. For example, some anticonvulsants may increase the risk for neural tube defects through folate antagonism.<sup>15</sup> Angiotensin I-converting enzyme inhibitors (ACEIs) such as enalapril and lisinopril may induce ACEI fetopathy, which consists of renal tubular dysplasia and hypocalvarium, possibly through drug-induced fetal hypotension that leads to hypoperfusion and oligohydramnios.<sup>16</sup>

4. *The final manifestations of abnormal development are developmental malformation, growth retardation, and functional disorder.*

Depending on the nature of the exposure and timing during gestation, adverse outcomes may encompass effects ranging from spontaneous abortion or stillbirth to major and minor structural defects, prenatal or postnatal growth deficiency, preterm delivery, and functional deficits or learning disabilities. For example, moderate to heavy maternal ethanol intake, particularly if consumed in a binge pattern, increases the risk for spontaneous abortion; stillbirth; a characteristic pattern of minor craniofacial abnormalities; selected major structural defects, including atrial and ventricular septal defects and oral clefts; prenatal and postnatal growth deficiency; deficits in global IQ; and specific behavioral and learning abnormalities. Experimental animal and human studies support the notion that the entire spectrum of outcomes associated with ethanol may not manifest in any single affected pregnancy; rather, the results vary by dose and pattern of drinking, may correlate with gestational timing of exposure, and may be influenced by genetic susceptibility and other modifying factors such as maternal nutrition.

5. *The access of adverse environmental influences to developing tissues depends on the nature of the influences (agents).*

The effective dose of an agent is that dose biologically available to the embryo or fetus. This principle can be applied to human exposures by oral dosing compared with topical application. For example, therapy with oral retinoids increases the risk of malformations in human pregnancy. Isotretinoin (13-*cis*-retinoic acid) taken as an oral medication for only a few days in early pregnancy is associated with an approximately 20% risk of a pattern of brain, conotruncal heart, ear, and thymus abnormalities and mental deficiency in liveborn children.<sup>18</sup> In contrast, topical tretinoin (all-*trans*-retinoic acid) used for acne or to reduce signs of skin aging has not been associated with an increased risk of the same pattern of adverse effects.<sup>19,20</sup> These findings are attributed to the much lower blood concentration of retinoic acids from topical than from oral therapy.



6. Manifestations of deviant development increase in degree as dose increases from the no-effect level to the totally lethal level. The principle of dose response suggests that for all exposures, there is a threshold dose below which no effect is detected, higher doses produce stronger effects compared with lower doses, and the highest dose often is lethal. When the anticonvulsant and mood stabilizer valproic acid is taken by a pregnant woman during the critical window for neural tube closure, the risk for that defect increases by approximately 10- to 20-fold, from a baseline risk of 0.1% to a risk of 1% to 2%. However, there is evidence that the risk is dose related, because valproate-treated mothers who deliver infants with spina bifida on average have taken significantly higher doses than valproate-treated mothers of normal newborns.<sup>21</sup>

## Sources of Safety Data on Exposures in Pregnancy

For most medications, information on pregnancy effects comes exclusively from experimental animal studies. These studies are useful in indicating the exposure level at which adverse effects are seen, the nature of those effects, and associated effects on the mother. Interpretation of this information for counseling women requires an understanding of similarities and differences in the pharmacokinetics of the drug in the experimental model and in humans, information that may not be readily available. Although precautions may appear in the product labeling solely on the basis of experimental animal data, it is desirable that experimental animal data be supplemented by data obtained in humans.

## CASE REPORTS OF ADVERSE EVENTS

Reports of pregnancy exposures with adverse outcomes may appear as case reports in the literature, through safety data provided to the FDA by manufacturers, or in voluntary reports by clinicians or patients. Individual adverse outcome reports have the potential to generate hypotheses regarding teratogenicity, but case reports lack critical information about the number of exposed pregnancies with normal outcomes and cannot be used to determine whether the adverse event reports represent an excess risk over the baseline for that event or simply coincidence.

## PREGNANCY REGISTRIES

Pregnancy registries retrospectively and prospectively collect data regarding exposures to a specific drug or group of drugs. The outcome of primary interest in traditional pregnancy registries is major birth defects. Registry data are periodically summarized and reviewed for signals that may lead to recommendations for initiation of a hypothesis-testing study. Strengths of registries include their potential for gathering early information about a new drug and the possibility of identifying a unique pattern of malformation that is associated with exposure to the drug of interest. However, traditional registries lack formal comparison groups and typically have outcome data on small numbers of pregnancies. These registries usually have insufficient sample sizes to detect an important increase in the frequency of specific birth defects.<sup>22</sup> Nevertheless, collaborative registry designs such as the Antiepileptic Drugs in Pregnancy Registry have demonstrated success in identifying signals or

establishing higher than expected rates for major birth defects after selected exposures.<sup>23</sup>

## OBSERVATIONAL COHORT STUDIES

Observational studies include prospectively designed exposure cohort studies in which women with or without the exposure of interest are enrolled during pregnancy (preferably before recognition of the outcome to eliminate bias) and followed to outcome. These studies can evaluate a spectrum of outcomes, including major and minor malformations. They also have the advantage of including a comparison group or groups, allowing for the control of key factors that may be confounders or effect modifiers such as maternal age, socioeconomic status, and ethanol or tobacco use. This type of study design was successful in identifying carbamazepine therapy as a human teratogenic exposure.<sup>24</sup> One disadvantage of this approach is that the sample sizes are typically too small to rule out anything but the most dramatically increased birth prevalence of specific major birth defects.

## DATABASE COHORTS

A variation of the observational cohort involves construction of a historical cohort using archived information in existing databases. For example, health maintenance organization claims data and records from government-supported health care agencies can be analyzed for information on pregnancies with or without specific medication exposures. The strengths of this approach include the potential cost savings for collecting data for a given number of pregnancies, but the limitations include sample sizes that are too small to detect increased risks for many or even most specific birth defects. Because database studies rely on information not collected primarily for research purposes, validation of exposure and outcome and data on some key potential confounders may be difficult or impossible to obtain. Nevertheless, database cohorts have been used, for example, to raise the question of a possible link between paroxetine and congenital heart defects.<sup>25</sup>

## CASE-CONTROL STUDIES

In case-control study designs, pregnancies are retrospectively selected for having a specific outcome, such as a particular birth defect. The frequency of exposure to an agent of interest among mothers of affected infants is compared with the frequency of exposure among mothers whose pregnancies did not result in that birth defect. A major strength of case-control studies is that with proper numbers of cases and controls, they can provide sufficient power to detect increased risks for rare outcomes. Because these studies include a comparison group, they can collect information on important potential confounding variables such as age, socioeconomic status, and ethanol and tobacco use. The case-control approach was used successfully to identify the association of misoprostol (used to induce abortion) with a very high risk of a rare congenital facial nerve paralysis, Möbius syndrome.<sup>26</sup> A limitation of case-control studies is the lag time inherent in collecting information on a new drug, especially if it is infrequently used by pregnant women. Another limitation is the inability to evaluate an agent for a spectrum of outcomes that have not been identified as part of the anomaly pattern. It is possible that women who are already aware of a negative outcome of their pregnancy may



recall exposures more carefully (or incorrectly) than those who had a normal outcome.

## SUMMARY OF DATA SOURCES

The strengths and weaknesses of the methodologies that are available to evaluate potential teratogenicity reveal that no single approach is sufficient. From the clinical perspective, this means that conclusions drawn from one type of study must be interpreted with caution until they are confirmed or refuted by other types of studies. From a public health perspective, a combination of complementary study designs is desirable, one that ideally is initiated in a coordinated, systematic fashion to provide clinicians and patients with the best and earliest possible information.<sup>27</sup>

## Risk Assessments and Resources

The FDA established a widely used pregnancy safety category system that is incorporated into the product label with the intent of informing clinicians and pregnant women of the teratogenic risks associated with prescription drugs. This category system is frequently misunderstood by health care providers and patients, and it is being replaced by a system that relies on plain text to give information about medications.

In practice, the current FDA category assigned to a medication often misrepresents or oversimplifies the evidence. For example, the category assignments usually do not take into consideration factors such as exposure timing in gestation or dose and route of administration. Although some drugs assigned to category X (i.e., contraindicated in pregnancy) are known to harm the embryo or fetus at therapeutic dose levels, others (e.g., ribavirin, statins) were assigned to that category based on theoretical concerns or animal data without human data to establish a teratogenic risk.<sup>28,29</sup> Incorporation of new data into the label and classification updates is often slow.

Communication of potential risk to a woman regarding an exposure that has already taken place varies substantially from that for an exposure that is anticipated. Such nuances are not reflected in the category statements.

Other information readily available to the clinician includes several print resources, each with different approaches to providing summary information.<sup>30,31</sup> Some of these references are available in hard copy, compact disk (CD), and smartphone versions. Online databases that provide summary statements prepared by experts in the field of teratology and updated on a regular basis include TERIS, REPROTOX, Briggs, and Shepard. The Organization of Teratology Information Specialists (OTIS) provides individualized information to clinicians and the public by toll-free telephone access and Internet (<http://otispregnancy.org>). Clinicians or patients who are interested in pregnancy registries that are open for enrollment can locate a current list provided by the FDA's Office of Women's Health (<http://www.fda.gov/ScienceResearch/SpecialTopics/WomensHealthResearch/ucm251314.htm>).

## Selected Human Teratogenic Exposures

For information about specific exposures, an updated information source such as those discussed previously should be consulted. Selected examples of teratogenic exposures are discussed in this section.

## VITAMIN K ANTAGONISTS

A specific pattern of congenital anomalies referred to as *warfarin syndrome* has been identified in some children of mothers who use medications such as phenprocoumon, coumatrol, fluindione, warfarin, and phenindione, vitamin K antagonists. The features include nasal hypoplasia, stippled epiphyses visible on radiographs, and growth retardation. CNS and eye abnormalities, including microphthalmia, hydrocephalus, Dandy-Walker malformation, agenesis of corpus callosum, optic atrophy, cataracts, and mental retardation, occur occasionally.<sup>32,33</sup> The critical period for the bony effects of warfarin embryopathy appears to be between 6 and 9 weeks' gestation. A systematic review of 17 studies including a total of 979 exposed pregnancies estimated a 6% risk of warfarin embryopathy. In addition, 22% of exposed pregnancies ended in spontaneous abortion, 4% in stillbirth, and 13% in preterm delivery.<sup>34</sup> A large, multicenter study of pregnancies with exposure to vitamin K antagonists reported a significant increase in the rate of major birth defects relative to unexposed healthy comparison women (OR = 3.86; 95% confidence interval [CI], 1.76 to 8.0). In this study, only 2 infants (0.6%) were thought to have warfarin embryopathy. The rate of preterm delivery was increased versus 7.6%; OR = 2.61; CI, 1.76 to 3.86; the mean weight of term infants was significantly lower (3113 g versus 3411 g); and the rate of spontaneous abortion was significantly higher (42% versus 14%; OR = 3.36; CI, 2.28 to 4.94) with exposure.<sup>14</sup>

In one study of 71 pregnancies occurring in 52 women with prosthetic heart valves who were being treated with warfarin, the risk for adverse outcome was significantly greater with exposure greater than 5 mg/day.<sup>35</sup> A review of 85 pregnancies with exposure to a coumarin drug only after the first trimester reported that 1 pregnancy ended in stillbirth, 3 in spontaneous abortion, and 19 in preterm births; 1 infant had a CNS defect and none had the warfarin embryopathy.<sup>34</sup> In a large study that evaluated the cognitive performance of 307 children exposed to warfarin compared with that of unexposed children, the mean IQ scores did not differ significantly, but low IQ (IQ < 80) occurred more frequently in children whose exposure was limited to the second and third trimester.<sup>36</sup>

## ANTIEPILEPTIC DRUGS

Most older drugs used to treat seizure disorders are associated with an increased risk of congenital malformations,<sup>37,38</sup> indicating that the underlying disease is the teratogen. Newer studies have challenged this concept.<sup>39-40</sup> The use of multiple anticonvulsant medications (i.e., polytherapy) in contrast to single drug (i.e., monotherapy) is associated with a greater risk of structural defects.<sup>39,41,42</sup> It is unclear whether the disease of polytherapy is a result of drug-drug interactions, the underlying disease in women requiring treatment with polytherapy, or a combination of the two.

### Phenytoin

Phenytoin as a treatment for seizure disorders has been associated with an increased risk for oral clefts and for other anomalies known as the *fetal hydantoin syndrome*. The pattern is estimated to occur in 10% of infants with exposure and includes prenatal or postnatal growth retardation.

microcephaly, hypoplasia of the digits and nails, and craniofacial abnormalities (i.e., short nose with low nasal bridge, ocular hypertelorism, abnormal ears, and a wide mouth with a prominent upper lip).<sup>43-45</sup> Initial reports suggested that mental deficiency was also a common feature of fetal hydantoin syndrome.<sup>46</sup> However, the limited data published subsequently suggest that neurobehavioral effects may be milder.<sup>47</sup> For example, Scolnik and colleagues<sup>48</sup> reported that average IQ scores were 10 points lower in children exposed to phenytoin monotherapy compared with unexposed children born to mothers who were matched by age and socioeconomic status.

### Valproic Acid

Studies during the past 2 decades have associated early-first-trimester exposure to valproic acid with an increased risk of neural tube defects, specifically spina bifida. The estimated risk is about 1% to 2%, with higher doses thought to be associated with higher risk.<sup>21,49</sup> It has been estimated that the overall risk for major birth defects is increased by fourfold to sevenfold after valproate monotherapy, with increased risks for specific cardiovascular, limb, and genital anomalies described in some reports.<sup>23</sup> As with other anticonvulsants, a pattern of minor malformations and growth deficiency has been identified for valproic acid; it includes midface hypoplasia, epicanthal folds, short nose, broad nasal bridge, thin upper lip, thick lower lip, micrognathia, and subtle limb defects (primarily hyperconvex fingernails).<sup>50</sup> Valproic acid monotherapy is associated with reduced cognitive ability and additional educational needs in children prenatally exposed.<sup>50-52</sup>

### Carbamazepine

Carbamazepine exposure in the early first trimester has been associated with an increased risk (approximately 1%) of spina bifida.<sup>12</sup> Carbamazepine has also been linked to a pattern of minor craniofacial abnormalities, including upslanting palpebral fissures, a long philtrum, and nail hypoplasia, as well as growth deficiency and microcephaly.<sup>24</sup> Although some small studies have suggested developmental delay after prenatal exposure to carbamazepine,<sup>53</sup> others have not.<sup>52,54,55</sup>

### Other Antiepileptic Drugs

Newer antiepileptic medications have been introduced into practice over the past several years. Increases in malformations, particularly cleft lip, and low birth weight have been associated with topiramate therapy by two registries, including the North American Antiepileptic Drugs in Pregnancy Registry conducted at Massachusetts General Hospital.<sup>56,57</sup>

The Massachusetts General Hospital registry monitors the outcome of pregnancies in which anticonvulsant medications have been used. More information is available and subjects can be enrolled by phone (1-888-233-2334) or online (<http://www.massgeneral.org/aed>). Outside North America, information can be obtained through the International Registry of Antiepileptic Drugs and Pregnancy (<http://www.eurapinternational.org>).

## CHEMOTHERAPEUTIC AND IMMUNOSUPPRESSIVE AGENTS

### Cyclophosphamide

Eight case reports documenting a unique pattern of malformation in infants prenatally exposed to cyclophosphamide have

been published.<sup>58</sup> Features include growth deficiency, craniofacial anomalies, and absent fingers and toes. In three of these cases, the infant survived, and developmental information was available; significant delays were seen in all three. The magnitude of the risk is unknown, and the lack of denominator-based information prevents conclusions about possible fetal harm from this agent.

### Methotrexate

Both aminopterin and its methyl derivative, methotrexate, have been associated with a specific pattern of malformation that includes prenatal-onset growth deficiency, severe lack of calvarial ossification, hypoplastic supraorbital ridges, small and low-set ears, micrognathia, limb abnormalities, and in some cases, developmental delay.<sup>59,60</sup> Most affected infants have been born to women treated with high-dose methotrexate for psoriasis or neoplastic disease or as an abortifacient. Although the magnitude of the risk is unknown, it has been suggested that the dose necessary to produce the aminopterin/methotrexate syndrome is greater than 10 mg/week.<sup>61,62</sup>

## ADRENAL CORTICOSTEROIDS

Among four case-control studies, three concluded that systemic corticosteroid use in the first trimester was associated with a threefold to sixfold increased risk for cleft lip with or without cleft palate and possibly cleft palate alone.<sup>63-66</sup> It is unclear to what extent this association was related to the various underlying maternal diseases involved in these studies. If only the positive studies are considered, this relative risk translates to a risk of approximately 3 to 6 cases per 1000 pregnancies exposed around the time of lip and palate closure toward the end of the first trimester. An association has long been recognized between prenatal exposure to corticosteroids and intrauterine growth restriction in humans. The risk appears to be dose related, suggesting that this concern can be minimized with lower doses.<sup>67,68</sup>

## MYCOPHENOLATE

Mycophenolate is available as mycophenolate mofetil or sodium, and it is used as an immunosuppressant in transplantation regimens and for lupus nephritis. The U.S. National Transplant Pregnancy Registry reported in 2006 that among 15 liveborn mycophenolate-exposed children, 4 had malformations.<sup>69</sup> Three of the children had microtia, and 2 of these children also had cleft lip and palate. There followed several case reports of infants exposed to mycophenolate with a variety of birth defects, the most characteristic of which were microtia or anotia, oral clefts, and conotruncal heart disease.<sup>70</sup>

Denominator-based reports do not give a clear picture of the prevalence of a mycophenolate embryopathy. Adverse event reports summarized in the product labeling indicates that of 77 pregnancies exposed to mycophenolate, 25 spontaneously aborted, and 14 resulted in a malformed infant or fetus. Six of the 14 malformed offspring had ear abnormalities. As the labeling points out, spontaneous adverse event reporting does not give reliable prevalence rates, because adverse outcomes may be more likely to be reported compared with normal outcomes. However, the European Network of Teratology Information Services reported that malformations occurred in 8 of 57 prospectively ascertained pregnancies after mycophenolate

exposure (4 of whom had a clinical phenotype consistent with the case reports) and that the miscarriage rate (excluding voluntary abortions) was 28%.<sup>71</sup>

### ACE INHIBITORS AND ANGIOTENSIN II RECEPTOR ANTAGONISTS

Based on case reports and case series, prenatal exposures to an ACEI (e.g., benazepril, captopril, enalapril, enalaprilat, fosinopril, lisinopril, moexipril, quinapril, ramipril) or to an angiotensin II receptor antagonist (e.g., losartan, candesartan, valsartan, tasosartan, telmisartan) during the second or third trimester of pregnancy have been associated with an increased risk of fetal hypotension, renal failure, and oligohydramnios leading to fetal growth restriction, joint contractures, pulmonary hypoplasia, and stillbirth or neonatal death. Calvarial hypoplasia has also been reported as part of the fetopathy. In children who survive the neonatal period, renal insufficiency may occur. The magnitude of the risk after second- or third-trimester exposure is not known.<sup>16,72</sup>

First-trimester exposure to ACEIs or angiotensin receptor blockers (ARBs) was suggested by one database linkage study to be associated with an increased risk of cardiovascular defects (risk ratio [RR] = 3.72; CI, 1.89 to 7.30) and CNS defects (RR = 4.39; CI, 1.37 to 14.02) in infants born to mothers who had received a prescription for an ACEI in the first trimester of pregnancy compared with infants born to women with no exposure to antihypertensive medications during pregnancy. However, these findings have not been replicated, and it is possible that they were confounded by an inability to completely control for maternal diabetes.<sup>73</sup> The Swedish Medical Birth Registry described an association between antihypertensive medication use during early pregnancy and cardiovascular defects in the offspring; however, there was no difference in the risk estimates for ACEIs and  $\beta$ -blockers, and the association for ACEIs was not statistically significant.<sup>74</sup> A teratology information service study from Israel and Italy found no increase in malformations in the offspring of 252 women exposed to ACEIs or ARBs in the first trimester.<sup>75</sup>

### LITHIUM

Early reports from a lithium exposure registry<sup>76</sup> included information on 143 infants exposed to lithium in utero; 13 of them were reported to have malformations, 4 of which were Ebstein anomaly (i.e., downward displacement of the tricuspid valve within the right ventricle with atrialization of the right ventricle above the valve). This finding represented an excess over expected numbers, because the baseline incidence of Ebstein anomaly is approximately 1 in 20,000 births. The registry data are questionable because some women were reported to the registry after the pregnancy outcome was known, likely representing biased ascertainment. A subsequent prospective cohort study involving follow-up of 148 women with first-trimester exposure to lithium identified one case of Ebstein anomaly and no other cardiac malformations identified in the sample.<sup>77</sup> In contrast, a case-control study published by Zalstein and associates<sup>78</sup> found no prenatal exposure to lithium among 59 patients with Ebstein anomaly. The available data suggest that the use of lithium in the first trimester of pregnancy is associated with only a very small increased risk for Ebstein anomaly if there is any increased risk at all.

## RETINOIDS

### Vitamin A

The teratogenic potential of excessive doses of vitamin A (retinol) is well described in animal models; however, the threshold dose at which naturally occurring vitamin A may be teratogenic in humans remains unclear. Two studies suggested that preformed vitamin A supplementation at amounts greater than 10,000 IU per day in the first trimester of pregnancy is associated with a small increase in selected defects that are consistent with those known to be induced by synthetic retinoids.<sup>81,82</sup> However, other studies have not confirmed these findings or suggested that the effect occurs only at doses greater than 40,000 IU per day, well above the current recommended daily allowance (RDA) for pregnant women carrying a single fetus is 2560 IU of vitamin A. In light of these potential concerns, many prenatal vitamin formulations have replaced retinol with  $\beta$ -carotene, which has no known teratogenic potential.  $\beta$ -Carotene is cleaved in the body to vitamin A, but the extent of conversion is controlled by the body and does not exceed the body's needs.

### Isotretinoin and Other Oral Synthetic Retinoids

Consistent with experimental animal data, an increased risk of pregnancy loss and a characteristic pattern of major physical and mental deficiency have been identified after exposure to isotretinoin. This pattern includes CNS defects, microtia or anotia, micrognathia, cleft palate, cardiac and great vessel defects, thymic abnormalities, and some limb reduction defects.<sup>18,86</sup> These risks are at least as high as 22% for spontaneous abortion for structural defects, and 47% for mild to moderate deficiency, even if no structural abnormalities are present. Affected children have been reported with exposure to therapeutic doses and with treatment for durations of 1 week in the first trimester. There does not appear to be an increase in malformations when the drug is discontinued before conception, which is consistent with the half-life of isotretinoin.

Pregnancy prevention among women who are taking isotretinoin continues to be a challenge. A third-trimester restricted distribution program, iPledge, was implemented in March 2006; it mandates close monitoring of blood levels and negative pregnancy testing before dispensing prescriptions for isotretinoin.<sup>90</sup>

Retinoid embryopathy is a risk with the use of synthetic retinoids, including etretinate and its active metabolite, acitretin, which have been used for the treatment of severe psoriasis. The extremely long half-life of etretinate led to its removal from the U.S. market in 1998. The half-life of acitretin is considerably longer than that of isotretinoin (50 to 60 hours), and it can be converted to etretinate with maternal intake of ethanol. The drug should be discontinued before conception and ethanol avoided during the entire period of treatment for at least 2 months after discontinuation of therapy.

## IONIZING RADIATION

Prenatal exposure to high-dose radiation is associated with an increased risk of microcephaly, mental deficiency, and growth retardation based on data derived from a small number of survivors of the atomic bombs in Nagasaki and Hiroshima.<sup>94</sup> It is estimated that doses of 50 rad (50 cGy) or more during the first trimester of pregnancy are associated with an increased risk of these effects.



to the uterus are required to produce these effects. The highest risk appears to be associated with exposures between 8 and 15 weeks' gestation, with a higher threshold dose at more advanced gestational ages.<sup>95</sup> The available data do not support an increase in the risk of mental retardation associated with high-dose radiation exposure beyond 25 weeks' or before 8 weeks' gestation.<sup>93</sup> Based on dose-response calculations, diagnostic procedures involving radiation do not pose a risk to the fetus unless the cumulative dose to the uterus is greater than 10 cGy; conservative guidelines suggest that doses should be kept below 5 cGy to the uterus during pregnancy.<sup>96</sup>

## ENVIRONMENTAL AGENTS

### Methylmercury

Prenatal exposure to methylmercury was recognized as a cause of neurodevelopmental disability after instances of contamination in Japan (Minamata Bay) and Iraq in the mid-20th century.<sup>97,98</sup> The reported effects, called *Minamata disease*, include a cerebral palsy-like disorder and mental deficiency.<sup>99</sup> Although the lower limit of exposure that may pose a risk in prenatal development remains unclear, an independent U.S. National Research Council expert committee concluded that limiting maternal intake to no more than 0.1 mg/kg body weight/day was sufficient to protect the fetus.<sup>100</sup> Currently, consumption of contaminated fish or marine mammals is the major source of methylmercury exposure in most populations. In 2004, the U.S. Environmental Protection Agency and FDA advised pregnant women and women of childbearing age who may become pregnant to avoid eating predator fish (i.e., shark, swordfish, king mackerel, and tilefish) in which organic mercury may be bioconcentrated and to limit their average consumption of other cooked fish to 12 ounces (340 g) per week to prevent fetal exposure to excessive amounts of methylmercury.<sup>101</sup> There are, however, substantial benefits from fish in the diet during pregnancy.<sup>102</sup> In a large, longitudinal study conducted in the United Kingdom, maternal seafood consumption during pregnancy correlated with developmental outcomes on a variety of measures up to 8 years of age. Beneficial effects on child development in this study were shown only in children born to women with maternal seafood intakes of more than 340 g per week, suggesting that advice to limit seafood consumption may be detrimental.<sup>103</sup>

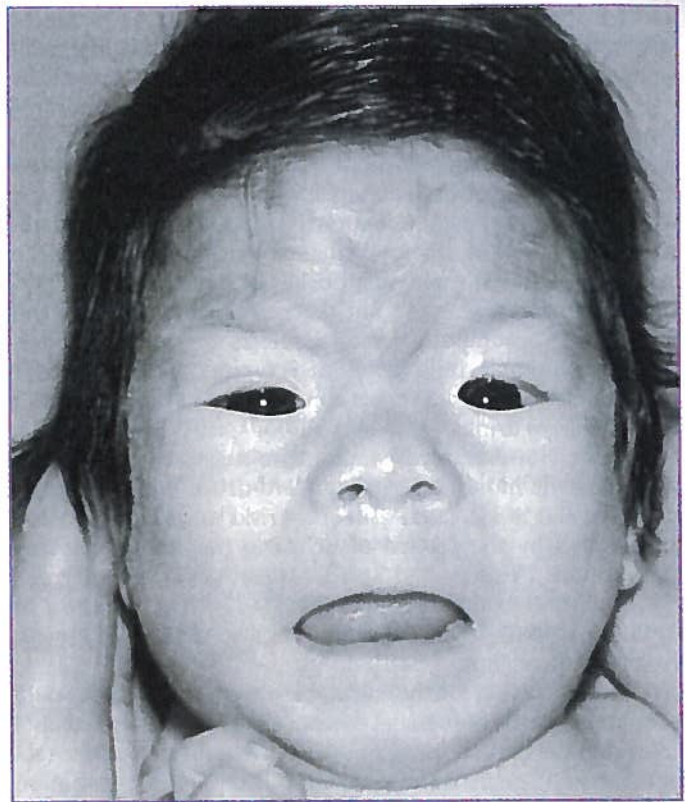
### Lead

In utero exposure to high levels of lead (maternal blood concentrations >30 mg/dL) has been associated with an increase in spontaneous abortion, preterm birth, and mental deficiency in the offspring.<sup>104-106</sup> Prenatal exposure to lower levels (>10 mg/dL) may be associated with subtle neurobehavioral effects, but these effects may not persist into older childhood.<sup>106-108</sup> Adverse effects of lower levels of lead exposure during pregnancy have been suggested but not confirmed. Occupational and environmental exposures to lead that precede pregnancy may result in fetal exposure due to mobilization of lead stored in maternal bone. These effects may be modified by maternal intake of calcium.<sup>109</sup>

## SOCIAL AND ILLICIT DRUGS

### Ethanol

A pattern of anomalies, known as the *fetal alcohol syndrome* (FAS), was first described more than 35 years ago in a case series



**Figure 31-1** Nine-month-old infant with fetal alcohol syndrome. (From Streissguth AP, Aase JM, Clarren SK, et al: *Fetal alcohol syndrome in adolescents and adults*, JAMA 265:1961, 1991. Copyright 1991, American Medical Association.)

of infants born to alcoholic women.<sup>110</sup> The characteristic features of this disorder are prenatal and postnatal growth retardation; microcephaly or other CNS dysfunction including neurobehavioral deficits, neurologic impairment; and characteristic facial anomalies consisting of short palpebral fissures and a smooth philtrum with a smooth, thin vermilion border of the upper lip (Fig. 31-1).<sup>111,112</sup> Although FAS is difficult to diagnose, particularly in the newborn period, estimates of its incidence in selected U.S. and Western European populations are approximately 1 to 4 cases per 1000 live births.<sup>113</sup>

Many more children are thought to have alcohol-related neurobehavioral or neurologic impairment with or without some structural features of FAS. Congenital heart defects, oral clefts, and abnormalities of the eyes, brain, and kidneys are more common than expected among the children of women who drink moderately to heavily during pregnancy.<sup>114-117</sup> These children, described as having partial FAS, alcohol-related neurodevelopmental abnormalities (ARNDs), or alcohol-related birth defects (ARBDs), are now considered to represent a continuum of fetal alcohol spectrum disorders (FASDs). Accurate estimates of the prevalence of FASDs are lacking; however, one population-based study in the Seattle, Washington, area suggested that the rates may be as high as 1 case per 100 children.<sup>113</sup> Increased risks for spontaneous abortion, stillbirth, and sudden infant death syndrome have been linked to prenatal ethanol exposure, particularly exposure from ethanol consumed in a heavy episodic or binge pattern.<sup>118-121</sup>

Experimental animal and human data support a dose-response relationship in terms of risk for FAS/FASD. However,

because of variability in diagnosis and difficulties in obtaining and validating exposure information reported by pregnant women, estimates vary widely regarding the magnitude of the risk. For example, estimates for the fully expressed syndrome range from about 4% to 44% of children born to women who drink heavily during pregnancy.<sup>122,123</sup> The women at highest risk appear to be those who have already had an affected child and who continue to consume ethanol during subsequent pregnancies. Lower levels of maternal ethanol consumption have been associated with less severe neurobehavioral outcomes and persistent growth effects,<sup>124-126</sup> but the exact threshold doses and patterns of consumption for these effects are not well understood. For example, full-blown FAS is typically seen among the children of women who report consuming an average of six or more standard drinks (i.e., beer, wine, or spirits) per day during pregnancy. However, some studies have suggested that women who consume more than two standard drinks per day during pregnancy are at increased risk. These risks may be mediated or ameliorated by the pattern of drinking (i.e., binge drinking versus more frequent and smaller quantities), maternal age, nutrition, and genetic susceptibility.<sup>117,126-129</sup> The duration of exposure is likely to be important because CNS development continues throughout gestation.<sup>130</sup>

Current data are insufficient to assign a risk to certain common patterns of prenatal ethanol exposure, such as ethanol consumption limited to occasional binge episodes before recognition of pregnancy. However, the data do support the notion that reduction or discontinuation of ethanol consumption at any point in pregnancy may be beneficial. A lower threshold of exposure, below which no effects will be seen, has not been defined. For women who are planning pregnancy or who have the potential to become pregnant, the U.S. Surgeon General has recommended that the safest course is to avoid ethanol entirely during pregnancy.<sup>131</sup>

### Tobacco

Maternal cigarette smoking is associated with a variety of harmful effects on the embryo and fetus, including increased risks for specific congenital malformations, spontaneous abortion, placental complications, preterm delivery, reduced birth weight, and sudden infant death syndrome. The structural malformations that have been significantly associated with first-trimester smoking include oral clefts and gastroschisis. A meta-analysis of 24 studies estimated the risk of oral clefts to be low; the relative risk for cleft lip with or without cleft palate was 1.34 (CI, 1.25 to 1.44), and that for cleft palate alone was 1.22 (CI, 1.10 to 1.35).<sup>132</sup> Some studies have suggested gene-environment interactions in susceptibility for oral clefts when mothers smoke during early pregnancy. Infants who have a null deletion of the detoxifying gene *GSTT1* or certain polymorphisms at the *Taq1*-identified site for transforming growth factor- $\alpha$  (a gene known to be involved in facial development) and whose mothers smoke are at higher risk for certain oral

clefts than infants with either risk factor alone.<sup>133,134</sup> Elevated risks for gastroschisis after maternal smoking are estimated to be low.<sup>135</sup> However, as with oral clefts, there is some evidence for gene-environment interactions between maternal smoking and polymorphisms of fetal genes involved in vascular responses.<sup>136</sup> Other defects that occur with increased frequency after pregnancy exposure to tobacco smoke include craniofacial dysostosis and clubfoot.<sup>137-139</sup> Most studies with dose information available have suggested a dose-response relationship for each of these defects, with the heaviest smokers being at highest risk.

The deleterious effects of cigarette smoking on other pregnancy outcomes are well documented. Intrauterine growth restriction is the most consistently reported adverse outcome. On average, babies born to women who smoke during pregnancy are 200 g lighter than those born to comparable women who do not smoke, with a clear dose-response gradient, in part because of the reduction in uterine blood flow associated with plasma nicotine in women who smoke.<sup>141</sup> Smaller reductions in birth weight have occurred when exposure is limited to environmental or passive smoke.<sup>142</sup> Strong gene-environment and gene-gene-environment interactions have been demonstrated between the cytochrome P450 isozyme *CYP1A1* and *GSTT1* maternal metabolic genes and infant birth weight in mothers who smoke.<sup>143</sup>

Perinatal mortality is increased with maternal smoking, in part because of the increased risks of placental complications and preterm delivery. In one large study, the combined risk for fetal or infant death for primiparous women who smoked less than one pack per day was estimated to be 25% higher than that for nonsmoking women, and the risk was 56% higher for those who smoked one pack per day or more.<sup>144</sup> However, if smoking is discontinued in the first half of gestation, evidence indicates that the effects on birth weight can be eliminated.<sup>145-147</sup> Based on dose-response data, any reduction in the number of cigarettes smoked may reduce the risks of low birth weight, preterm birth, and placental complications.<sup>147-151</sup>

### Cocaine

The most consistently reported effects of prenatal cocaine exposure are a small but statistically significant increase in intrauterine growth restriction<sup>152</sup> and abnormalities in neonatal state regulation and motor performance.<sup>153</sup> However, based on a synthesis of 36 published studies of children 6 years of age or younger, Frank and colleagues<sup>154</sup> concluded that no consistent negative association existed between prenatal cocaine exposure and postnatal physical growth, developmental test scores, receptive language, or standardized parent and teacher reports of child behavior. An association between prenatal cocaine exposure and decreased emotional expressiveness has been suggested.<sup>155</sup>

The complete reference list is available online at [www.expertconsult.com](http://www.expertconsult.com).



# Creasy and Resnik's Maternal-Fetal Medicine

## PRINCIPLES AND PRACTICE

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## 31 – Teratogenesis and Environmental Exposure

**Christina Chambers, PhD, MPH,  
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A *teratogenic exposure* is defined as one that has the potential to interfere with the normal functional or structural development of an embryo or fetus. An exposure includes an agent (e.g., chemical) and an exposure level (e.g., dose). Although teratogenic exposures typically increase the risk of major congenital anomalies, they also increase the risk of a spectrum of adverse pregnancy outcomes, including spontaneous abortion, stillbirth, minor structural anomalies, shortened gestational age, growth restriction, and behavioral or cognitive deficits. Excess risks for the latter events may be much more difficult to recognize.

Known teratogenic exposures comprise a wide range of doses and agents, including some prescription and over-the-counter medications, recreational drugs and alcohol, chemicals, physical agents, and maternal diseases. Although studies specifically evaluating human teratogenicity are lacking for most environmental agents, including prescription medications, it is estimated that about 10% of major birth defects are attributable to environmental exposures and are therefore preventable to some extent.

### Historical Perspective

Before the 1940s, it was somewhat naively thought by clinicians that the placenta provided a protective barrier for the developing embryo and fetus and that agents to which the mother was exposed could not interfere with normal prenatal development. The revolutionary concept that a maternal exposure could pose a risk to the developing embryo or fetus was first raised in the clinical literature by an Australian ophthalmologist, Norman Gregg, who observed in his clinical practice an unusual number of children diagnosed with congenital cataracts shortly after a rubella epidemic. Gregg's work led to investigations that identified additional features of a variable but characteristic pattern of developmental abnormalities associated with fetal rubella infection, including congenital heart defects, hearing deficits, poor growth, and thrombocytopenia, which came to be known as the congenital rubella syndrome. [1]

In the early 1960s, an Australian obstetrician and a German geneticist independently recognized that first-trimester maternal use of thalidomide, a sedative-hypnotic drug, was associated with the appearance of a characteristic pattern of limb reduction anomalies and other defects. [2,3] Although the drug had undergone premarket testing in rodents, it had not shown the characteristic limb defects in these species. In the United States, subsequent recognition that therapeutic agents could induce malformations was a major stimulus for the implementation of the Kefauver-Harris Amendment to the Food, Drug, and Cosmetic Act, which expanded the role of the U.S. Food and Drug Administration (FDA) as a regulatory agency charged with ensuring the efficacy and safety of products. [4]

Although the thalidomide experience raised public awareness of the potential risks of prenatal exposures, the thalidomide episode was accompanied by misunderstandings about how to differentiate exposures that cause birth defects from coincidental exposures occurring in women whose pregnancy outcome is abnormal for other, unrelated reasons. A classic example is doxylamine succinate and pyridoxine hydrochloride with or without dicyclomine hydrochloride (Bendectin), a once-popular antiemetic medication used by as many as 30% of American women for the treatment of nausea and vomiting of pregnancy. In 1983, this agent was voluntarily withdrawn from the market after an onslaught of litigation claiming teratogenicity despite voluminous scientific evidence to the contrary. [5]

Within the past 40 years, research in the field of teratology has advanced, and several new human teratogenic exposures have been identified, including several anticonvulsants, selected antineoplastic agents, inhibitors of enzymes in the renin-angiotensin system, methylmercury, ethanol, hyperthermia, tetracycline, warfarin, and isotretinoin. Work continues to better define the range of adverse outcomes associated with these exposures, the

magnitude of the risk for a given dose at a specific gestational age, and the subpopulations of mothers and infants who may be at particularly increased risk because of their genotype. However, major knowledge gaps exist for most agents, few of which have been adequately evaluated in human pregnancy.

Drug exposure during pregnancy is extremely common. In one U.S. health care system sample of 98,182 deliveries, 64% of women were prescribed at least one medication during their pregnancy other than a vitamin or mineral supplement.<sup>[6]</sup> In another U.S. population-based sample of women, more than 65% reported the use of one or more over-the-counter medications during pregnancy.<sup>[7]</sup> In many cases, these medications are necessary for the health of the mother or fetus, but in other cases, the exposures could have been avoided. A theoretical and practical framework is necessary to aid clinicians in advising patients, who are likely to have experienced several exposures by the time their pregnancy is recognized, and to support clinical decision making in the common situations in which treatment during pregnancy is recommended.

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## Principles of Teratology

James G. Wilson<sup>[8]</sup> outlined the basic principles of teratology in the early 1970s. These six principles, given in Wilson's own words, were based on experience with experimental animal studies, but they can be applied equally well to human pregnancy.

*1. Susceptibility to teratogenesis depends on the genotype of the conceptus and the manner in which this interacts with environmental factors.*

Exposures do not occur in a vacuum; women and their fetuses bring different genetic makeups to the exposure scenario. Different genetic characteristics may alter the way a drug or chemical is metabolized or may alter the susceptibility of a developmental process to disturbance by an exposure. For example, women with infants who have cleft lip with or without cleft palate or isolated cleft palate are approximately twice as likely to report heavy first-trimester tobacco use than are mothers of normal newborns. However, women who have a certain transforming growth factor- $\alpha$  (TGF- $\alpha$ ) polymorphism and who smoke heavily have a 3 to 11 times higher risk of having a child with an oral cleft, suggesting an interaction of the genetic characteristics of the mother with the tobacco smoke exposure. This risk appears to be lessened by maternal multivitamin use.<sup>[9,10]</sup> Similarly, a low level of epoxide hydrolase enzyme activity influenced by epoxide hydrolase polymorphisms has been implicated as a risk factor for fetal hydantoin syndrome in children whose mothers have taken phenytoin for the treatment of a seizure disorder during pregnancy.<sup>[11]</sup>

*2. Susceptibility to teratogenic agents varies with the developmental stage at the time of exposure.*

The principle of *gestational timing*, or critical developmental windows of exposure, requires that the exposure occur during the stage in development when the targeted developmental process is most susceptible. For example, the critical window for an agent that interferes with closure of the neural tube in the human embryo is approximately 21 to 28 days after conception. Carbamazepine, an anticonvulsant linked to a 10-fold increased risk of neural tube defects, does not produce the defect if maternal exposure occurs after the second month of pregnancy.<sup>[12,13]</sup>

Depending on the gestational timing of exposure, different outcomes may be induced. For example, warfarin therapy is associated with a pattern of nasal hypoplasia and skeletal abnormalities when prenatal exposure occurs during the latter portion of the first trimester, whereas later gestational exposure is associated with central nervous system (CNS) abnormalities.<sup>[14]</sup> The first-trimester effects likely reflect vitamin K deficiency, and later effects are a complication of fetal bleeding.

Consistent with this concept, very early gestational exposure, usually limited to the first 2 weeks after conception, poses little potential for teratogenicity, because pluripotent cells of the early embryo are able to replace one another if there is exposure-induced damage, or if the magnitude of cell loss is too great, the conceptus is lost, resulting in spontaneous abortion.<sup>[8]</sup>

*3. Teratogenic agents act in specific ways (mechanisms) on developing cells and tissues to initiate abnormal embryogenesis (pathogenesis).*

There is no teratogenic exposure that increases the risk of all adverse outcomes; rather, teratogenic exposures act on specific developmental processes to produce a characteristic pattern of effects. This principle underlies the methods by which many human teratogens have been suspected. The pattern of abnormalities associated with a particular teratogenic exposure helps to identify the exposure as the cause of an outcome. For example, the characteristic pattern of abnormalities comprising the fetal alcohol syndrome includes minor craniofacial features (i.e., short palpebral fissures, smooth philtrum, and thin vermilion of the upper lip) accompanied by microcephaly, growth deficiency, and cognitive and behavioral deficits. The prenatal effects of ethanol, although pervasive, nevertheless represent a constellation of features that is unlikely to randomly occur without exposure to alcohol in substantial doses and during certain gestational weeks.

There are a few general mechanisms that lead to abnormal development. For example, a teratogenic agent can interact with a receptor, bind to DNA or protein, degrade cell membranes or proteins, inhibit an enzyme, or modify proteins. These mechanisms manifest as excessive or reduced cell death, failed cell interactions, reduced biosynthesis, impeded morphogenetic movement, or mechanical disruption of tissues. For this reason, some teratogenic exposures have the same end result because they act through a common pathway. For example, some anticonvulsants may increase the risk for neural tube defects through folate antagonism.<sup>[15]</sup> Angiotensin I–converting enzyme inhibitors (ACEIs) such as enalapril and lisinopril may induce ACEI fetopathy, which consists of renal tubular dysplasia and hypocalvarium, possibly through drug-induced fetal hypotension that leads to hypoperfusion and oligohydramnios.<sup>[16]</sup>

*4. The final manifestations of abnormal development are death, malformation, growth retardation, and functional disorder.*

Depending on the nature of the exposure and timing during gestation, adverse outcomes may encompass effects ranging from spontaneous abortion or stillbirth to major and minor structural defects, prenatal or postnatal growth deficiency, preterm delivery, and functional deficits or learning disabilities. For example, moderate to heavy maternal ethanol intake, particularly if consumed in a binge pattern, increases the risks for spontaneous abortion; stillbirth; a characteristic pattern of minor craniofacial abnormalities; selected major structural defects, including atrial and ventricular septal defects and oral clefts; prenatal and postnatal growth deficiency; deficits in global IQ; and specific behavioral and learning abnormalities.<sup>[17]</sup> Experimental animal and human studies support the notion that the entire spectrum of outcomes associated with ethanol may not manifest in any single affected pregnancy; rather, the results vary by dose and pattern of drinking, may correlate with gestational timing of exposure, and may be influenced by genetic susceptibility and other modifying factors such as maternal nutrition.

*5. The access of adverse environmental influences to developing tissues depends on the nature of the influences (agents).*

The effective dose of an agent is that dose biologically available to the embryo or fetus. This principle can be applied to human exposures by oral dosing compared with topical application. For example, therapy with oral retinoids increases the risk of malformations in human pregnancy. Isotretinoin (13-*cis*-retinoic acid) taken as an oral medication for only a few days in early pregnancy is associated with an approximately 20% risk of a pattern of brain, conotruncal heart, ear, and thymus abnormalities and mental deficiency in liveborn children.<sup>[18]</sup> In contrast, topical tretinoin (all-*trans*-retinoic acid) used for acne or to reduce signs of skin aging has not been associated with an increased risk of the same pattern of adverse effects.<sup>[19,20]</sup> These findings are attributed to the much lower blood concentration of retinoic acids from topical than from oral therapy.

*6. Manifestations of deviant development increase in degree as dosage increases from the no-effect level to the totally lethal level.*

The principle of *dose response* suggests that for all exposures, there is a threshold dose below which no effect is detected, higher doses produce stronger effects compared with lower doses, and the highest dose often is lethal. When the anticonvulsant and mood stabilizer valproic acid is taken by a pregnant woman during the critical window for neural tube closure, the risk for that defect increases by approximately 10- to 20-fold, from a baseline risk of 0.1% to a risk of 1% to 2%. However, there is evidence that the risk is dose related, because valproate-treated mothers who deliver infants with spina bifida on average have taken significantly higher doses than valproate-treated mothers of normal newborns.<sup>[21]</sup>



## Sources of Safety Data on Exposures in Pregnancy

For most medications, information on pregnancy effects comes exclusively from experimental animal studies. These studies are useful in indicating the exposure level at which adverse effects are seen, the nature of those effects, and associated effects on the mother. Interpretation of this information for counseling women requires an understanding of similarities and differences in the pharmacokinetics of the drug in the experimental model and in humans, information that may not be readily available. Although precautions may appear in the product labeling solely on the basis of experimental animal data, it is desirable that experimental animal data be supplemented by data obtained in humans.

### Case Reports of Adverse Events

Reports of pregnancy exposures with adverse outcomes may appear as case reports in the literature, through safety data provided to the FDA by manufacturers, or in voluntary reports by clinicians or patients. Individual adverse outcome reports have the potential to generate hypotheses regarding teratogenicity, but case reports lack critical information about the number of exposed pregnancies with normal outcomes and cannot be used to determine whether the adverse event reports represent an excess risk over the baseline for that event or simply coincidence.

### Pregnancy Registries

Pregnancy registries retrospectively and prospectively collect data regarding exposures to a specific drug or group of drugs. The outcome of primary interest in traditional pregnancy registries is major birth defects. Registry data are periodically summarized and reviewed for signals that may lead to recommendations for initiation of a hypothesis-testing study. Strengths of registries include their potential for gathering early information about a new drug and the possibility of identifying a unique pattern of malformation that is associated with exposure to the drug of interest. However, traditional registries lack formal comparison groups and typically have outcome data on small numbers of pregnancies. These registries usually have insufficient sample sizes to detect an important increase in the frequency of specific birth defects.<sup>[22]</sup> Nevertheless, collaborative registry designs such as the Antiepileptic Drugs in Pregnancy Registry have demonstrated success in identifying signals or establishing higher than expected rates for major birth defects after selected exposures.<sup>[23]</sup>

### Observational Cohort Studies

Observational studies include prospectively designed exposure cohort studies in which women with or without the exposure of interest are enrolled during pregnancy (preferably before recognition of the outcome to eliminate bias) and followed to outcome. These studies can evaluate a spectrum of outcomes, including major and minor malformations. They also have the advantage of including a comparison group or groups, allowing for the control of key factors that may be confounders or effect modifiers such as maternal age, socioeconomic status, and ethanol or tobacco use. This type of study design was successful in identifying carbamazepine therapy as a human teratogenic exposure.<sup>[24]</sup> One disadvantage of this approach is that the sample sizes are typically too small to rule out anything but the most dramatically increased birth prevalence of specific major birth defects.

### Database Cohorts

A variation of the observational cohort involves construction of a historical cohort using archived information in existing databases. For example, health maintenance organization claims data and records from government-supported health care agencies can be analyzed for information on pregnancies with or without specific medication exposures. The strengths of this approach include the potential cost savings for collecting data for a given number of pregnancies, but the limitations include sample sizes that are too small to detect increased risks for many or even most specific birth defects. Because database studies rely on information not collected primarily for research

purposes, validation of exposure and outcome and data on some key potential confounders may be difficult or impossible to obtain. Nevertheless, database cohorts have been used, for example, to raise the question of a possible link between paroxetine and congenital heart defects.[25]

## **Case-Control Studies**

In case-control study designs, pregnancies are retrospectively selected for having a specific outcome, such as a particular birth defect. The frequency of exposure to an agent of interest among mothers of affected infants is compared with the frequency of exposure among mothers whose pregnancies did not result in that birth defect. A major strength of case-control studies is that with proper numbers of cases and controls, they can provide sufficient power to detect increased risks for rare outcomes. Because these studies include a comparison group, they can collect information on important potential confounding variables such as age, socioeconomic status, and ethanol and tobacco use. The case-control approach was used successfully to identify the association of misoprostol (used to induce abortion) with a very high risk of a rare congenital facial nerve paralysis, Möbius syndrome.[26] A limitation of case-control studies is the lag time inherent in collecting information on a new drug, especially if it is infrequently used by pregnant women. Another limitation is the inability to evaluate an agent for a spectrum of outcomes that have not been identified as part of the anomaly pattern. It is possible that women who are already aware of a negative outcome of their pregnancy may recall exposures more carefully (or incorrectly) than those who had a normal outcome.

## **Summary of Data Sources**

The strengths and weaknesses of the methodologies that are available to evaluate potential teratogenicity reveal that no single approach is sufficient. From the clinical perspective, this means that conclusions drawn from one type of study must be interpreted with caution until they are confirmed or refuted by other types of studies. From a public health perspective, a combination of complementary study designs is desirable, one that ideally is initiated in a coordinated, systematic fashion to provide clinicians and patients with the best and earliest possible information.[27]

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## Risk Assessments and Resources

The FDA established a widely used pregnancy safety category system that is incorporated into the product label with the intent of informing clinicians and pregnant women of the teratogenic risks associated with prescription drugs. This category system is frequently misunderstood by health care providers and patients, and it is being replaced by a system that relies on plain text to give information about medications.

In practice, the current FDA category assigned to a medication often misrepresents or oversimplifies the evidence. For example, the category assignments usually do not take into consideration factors such as exposure timing in gestation or dose and route of administration. Although some drugs assigned to category X (i.e., contraindicated in pregnancy) are known to harm the embryo or fetus at therapeutic dose levels, others (e.g., ribavirin, statins) were assigned to that category based on theoretical concerns or animal data without human data to establish a teratogenic risk.<sup>[28,29]</sup> Incorporation of new data into the label and classification updates is often slow.

Communication of potential risk to a woman regarding an exposure that has already taken place varies substantially from that for an exposure that is anticipated. Such nuances are not reflected in the category statements.

Other information readily available to the clinician includes several print resources, each with different approaches to providing summary information.<sup>[30,31]</sup> Some of these references are available in hard copy, compact disk (CD), and smartphone versions. Online databases that provide summary statements prepared by experts in the field of teratology and updated on a regular basis include TERIS, REPROTOX, Briggs, and Shepard. The Organization of Teratology Information Specialists (OTIS) provides individualized information to clinicians and the public by toll-free telephone access and Internet (<http://otispregnancy.org>). Clinicians or patients who are interested in pregnancy registries that are open for enrollment can locate a current list provided by the FDA's Office of Women's Health (<http://www.fda.gov/ScienceResearch/SpecialTopics/WomensHealthResearch/ucm251314.htm>).

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## Selected Human Teratogenic Exposures

For information about specific exposures, an updated information source such as those discussed previously should be consulted. Selected examples of teratogenic exposures are discussed in this section.

### Vitamin K Antagonists

A specific pattern of congenital anomalies referred to as the *fetal warfarin syndrome* has been identified in some children born to mothers who use medications such as phenprocoumon, acenocoumarol, fluindione, warfarin, and phenindione, which are vitamin K antagonists. The features include nasal hypoplasia, stippled epiphyses visible on radiographs, and growth restriction. CNS and eye abnormalities, including microcephaly, hydrocephalus, Dandy-Walker malformation, agenesis of the corpus callosum, optic atrophy, cataracts, and mental retardation, occur occasionally.<sup>[32,33]</sup> The critical period for the nasal and bony effects of warfarin embryopathy appears to be between 6 and 9 weeks' gestation. A systematic review of 17 studies involving a total of 979 exposed pregnancies estimated a 6% incidence of warfarin embryopathy. In addition, 22% of exposed pregnancies ended in spontaneous abortion, 4% in stillbirth, and 13% in preterm delivery.<sup>[34]</sup> A large, multicenter study of 666 pregnancies with exposure to vitamin K antagonists reported a significant increase in the rate of major birth defects overall, relative to unexposed healthy comparison women (odds ratio [OR] = 3.86; 95% confidence interval [CI], 1.76 to 8.00). In that study, only 2 infants (0.6%) were thought to have warfarin embryopathy. The rate of preterm delivery was increased (16.0% versus 7.6%; OR = 2.61; CI, 1.76 to 3.86); the mean birth weight of term infants was significantly lower (3166 versus 3411 g); and the rate of spontaneous abortion was significantly higher (42% versus 14%; OR = 3.36; CI, 2.28 to 4.93) with exposure.<sup>[14]</sup>

In one study of 71 pregnancies occurring in 52 women with prosthetic heart valves who were being treated with warfarin, the risk for adverse outcome was significantly greater with doses greater than 5 mg/day.<sup>[35]</sup> A review of 85 pregnancies involving exposure to a coumarin drug only after the first trimester reported that 1 pregnancy ended in stillbirth, 3 in spontaneous abortion, and 19 in preterm births; 1 infant had a CNS anomaly, and none had the warfarin embryopathy.<sup>[34]</sup> In a large study that evaluated the cognitive performance of 307 children prenatally exposed to warfarin compared with that of unexposed children, the mean IQ scores did not differ significantly, but low scores (IQ < 80) occurred more frequently in children whose exposure was limited to the second and third trimester.<sup>[36]</sup>

### Antiepileptic Drugs

Most older drugs used to treat seizure disorders are associated with an increased risk of congenital malformations,<sup>[37,38]</sup> perhaps indicating that the underlying disease is the teratogenic cause. Newer studies have challenged this concept.<sup>[38-40]</sup> The use of multiple anticonvulsant medications (i.e., polytherapy) instead of a single drug (i.e., monotherapy) is associated with a greater risk of structural defects.<sup>[39,41,42]</sup> It is unclear whether the disadvantage of polytherapy is a result of drug-drug interactions, more severe disease in women requiring treatment with polytherapy, or a combination of the two.

### Phenytoin

Phenytoin as a treatment for seizure disorders has been associated with an increased risk for oral clefts and for a pattern of anomalies known as the *fetal hydantoin syndrome*. This pattern is estimated to occur in 10% of infants with prenatal exposure and includes prenatal or postnatal growth restriction, microcephaly, hypoplasia of the digits and nails, and craniofacial abnormalities (i.e., short nose with low nasal bridge, ocular hypertelorism, abnormal ears, and a wide mouth with a prominent upper lip).<sup>[43-45]</sup> Initial reports suggested that mental deficiency was also a common feature of fetal hydantoin syndrome.<sup>[46]</sup> However, the limited data published subsequently suggest that neurobehavioral effects may be milder.<sup>[47]</sup> For example, Scolnik and colleagues<sup>[48]</sup> reported that average IQ scores were 10 points lower in children exposed to phenytoin monotherapy compared with unexposed children born to

mothers who were matched by age and socioeconomic status.

## Valproic Acid



Studies during the past 2 decades have associated early-first-trimester exposure to valproic acid with an increased risk of neural tube defects, specifically spina bifida. The estimated risk is about 1% to 2%, with higher doses thought to be associated with higher risk.<sup>[21,49]</sup> It has been estimated that the overall risk for major birth defects is increased by fourfold to sevenfold after valproate monotherapy, with increased risks for specific cardiovascular, limb, and genital anomalies described in some reports.<sup>[23]</sup> As with other anticonvulsants, a pattern of minor malformations and growth deficiency has been identified for valproic acid; it includes midface hypoplasia, epicanthal folds, short nose, broad nasal bridge, thin upper lip, thick lower lip, micrognathia, and subtle limb defects (primarily hyperconvex fingernails).<sup>[50]</sup> Valproic acid monotherapy is associated with reduced cognitive ability and additional educational needs in children prenatally exposed.<sup>[50-52]</sup>

## Carbamazepine

Carbamazepine exposure in the early first trimester has been associated with an increased risk (approximately 1%) of spina bifida.<sup>[12]</sup> Carbamazepine has also been linked to a pattern of minor craniofacial abnormalities, including upslanting palpebral fissures, a long philtrum, and nail hypoplasia, as well as growth deficiency and microcephaly.<sup>[24]</sup> Although some small studies have suggested developmental delay after prenatal exposure to carbamazepine,<sup>[53]</sup> others have not.<sup>[52,54,55]</sup>

## Other Antiepileptic Drugs

Newer antiepileptic medications have been introduced into practice over the past several years. Increases in malformations, particularly cleft lip, and low birth weight have been associated with topiramate therapy by two registries, including the North American Antiepileptic Drugs in Pregnancy Registry conducted at Massachusetts General Hospital.<sup>[56,57]</sup>

The Massachusetts General Hospital registry monitors the outcome of pregnancies in which anticonvulsant medications have been used. More information is available and subjects can be enrolled by phone (1-888-233-2334) or online (<http://www.massgeneral.org/aed> ). Outside North America, information can be obtained through the International Registry of Antiepileptic Drugs and Pregnancy (<http://www.eurapinternational.org> .

## Chemotherapeutic and Immunosuppressive Agents

### Cyclophosphamide

Eight case reports documenting a unique pattern of malformation in infants prenatally exposed to cyclophosphamide have been published.<sup>[58]</sup> Features include growth deficiency, craniofacial anomalies, and absent fingers and toes. In three of these cases, the infant survived, and developmental information was available; significant delays were seen in all three. The magnitude of the risk is unknown, and the lack of denominator-based information prevents conclusions about possible fetal harm from this agent.

### Methotrexate

Both aminopterin and its methyl derivative, methotrexate, have been associated with a specific pattern of malformation that includes prenatal-onset growth deficiency, severe lack of calvarial ossification, hypoplastic supraorbital ridges, small and low-set ears, micrognathia, limb abnormalities, and in some cases, developmental delay.<sup>[59,60]</sup> Most affected infants have been born to women treated with high-dose methotrexate for psoriasis or neoplastic disease or as an abortifacient. Although the magnitude of the risk is unknown, it has been suggested that the dose necessary to produce the aminopterin/methotrexate syndrome is greater than 10 mg/week.<sup>[61,62]</sup>

## Adrenal Corticosteroids

Among four case-control studies, three concluded that systemic corticosteroid use in the first trimester was associated with a threefold to sixfold increased risk for cleft lip with or without cleft palate and possibly cleft palate alone.<sup>[63-66]</sup> It is unclear to what extent this association was related to the various underlying maternal diseases

involved in these studies. If only the positive studies are considered, this relative risk translates to a risk of approximately 3 to 6 cases per 1000 pregnancies exposed around the time of lip and palate closure toward the end of the first trimester. An association has long been recognized between prenatal exposure to corticosteroids and intrauterine growth restriction in humans. The risk appears to be dose related, suggesting that this concern can be minimized with lower doses.[67,68]

## ***Mycophenolate***

Mycophenolate is available as mycophenolate mofetil or sodium, and it is used as an immunosuppressant in transplantation regimens and for lupus nephritis. The U.S. National Transplant Pregnancy Registry reported in 2006 that among 15 liveborn mycophenolate-exposed children, 4 had malformations.[69] Three of the children had microtia, and 2 of these children also had cleft lip and palate. There followed several case reports of infants exposed to mycophenolate with a variety of birth defects, the most characteristic of which were microtia or anotia, oral clefts, and conotruncal heart disease.[70]

Denominator-based reports do not give a clear picture of the prevalence of a mycophenolate embryopathy. Adverse event reports summarized in the product labeling indicates that of 77 pregnancies exposed to mycophenolate, 25 spontaneously aborted, and 14 resulted in a malformed infant or fetus. Six of the 14 malformed offspring had ear abnormalities. As the labeling points out, spontaneous adverse event reporting does not give reliable prevalence rates, because adverse outcomes may be more likely to be reported compared with normal outcomes. However, the European Network of Teratology Information Services reported that malformations occurred in 8 of 57 prospectively ascertained pregnancies after mycophenolate exposure (4 of whom had a clinical phenotype consistent with the case reports) and that the miscarriage rate (excluding voluntary abortions) was 28%.[71]

## ***Ace Inhibitors and Angiotensin II Receptor Antagonists***

Based on case reports and case series, prenatal exposures to an ACEI (e.g., benazepril, captopril, enalapril, enalaprilat, fosinopril, lisinopril, moexipril, quinapril, ramipril) or to an angiotensin II receptor antagonist (e.g., losartan, candesartan, valsartan, tasosartan, telmisartan) during the second or third trimester of pregnancy have been associated with an increased risk of fetal hypotension, renal failure, and oligohydramnios leading to fetal growth restriction, joint contractures, pulmonary hypoplasia, and stillbirth or neonatal death. Calvarial hypoplasia has also been reported as part of the fetopathy. In children who survive the neonatal period, renal insufficiency may occur. The magnitude of the risk after second- or third-trimester exposure is not known.[16,72]

First-trimester exposure to ACEIs or angiotensin receptor blockers (ARBs) was suggested by one database linkage study to be associated with an increased risk of cardiovascular defects (risk ratio [RR] = 3.72; CI, 1.89 to 7.30) and CNS defects (RR = 4.39; CI, 1.37 to 14.02) in infants born to mothers who had received a prescription for an ACEI in the first trimester of pregnancy compared with infants born to women with no exposure to antihypertensive medications during pregnancy. However, these findings have not been replicated, and it is possible that they were confounded by an inability to completely control for maternal diabetes.[73] The Swedish Medical Birth Registry described an association between antihypertensive medication use during early pregnancy and cardiovascular defects in the offspring; however, there was no difference in the risk estimates for ACEIs and  $\beta$ -blockers, and the association for ACEIs was not statistically significant.[74] A teratology information service study from Israel and Italy found no increase in malformations in the offspring of 252 women exposed to ACEIs or ARBs in the first trimester.[75]

## ***Lithium***

Early reports from a lithium exposure registry[76] included information on 143 infants exposed to lithium in utero; 13 of them were reported to have malformations, 4 of which were Ebstein anomaly (i.e., downward displacement of the tricuspid valve within the right ventricle with atrialization of the right ventricle above the valve). This finding represented an excess over expected numbers, because the baseline incidence of Ebstein anomaly is approximately 1 in 20,000 births. The registry data are questionable because some women were reported to the registry after the pregnancy outcome was known, likely representing biased ascertainment. A subsequent prospective cohort study involving follow-up of 148 women with first-trimester exposure to lithium identified one case of Ebstein anomaly and no other cardiac malformations identified in the sample.[77] In contrast, a case-control study published by Zalstein and associates[78] found no prenatal exposure to lithium among 59 patients with Ebstein anomaly. The available data suggest that the use of lithium in the first trimester of pregnancy is associated



with only a very small increased risk for Ebstein anomaly if there is any increased risk at all.

## **Retinoids**

### **Vitamin A**

The teratogenic potential of excessive doses of preformed vitamin A (retinol) is well described in animal models<sup>[79,80]</sup>; however, the threshold dose at which naturally occurring vitamin A may be teratogenic in humans remains controversial. Two studies suggested that preformed vitamin A supplementation at amounts greater than 10,000 IU per day in the first trimester of pregnancy is associated with a small increased risk of selected defects that are consistent with those known to be induced by synthetic retinoids.<sup>[81,82]</sup> However, other studies did not confirm these findings or suggested that the elevated risk occurs only at doses greater than 40,000 IU per day.<sup>[83-85]</sup> The current recommended daily allowance (RDA) for pregnant women carrying a single fetus is 2560 IU of vitamin A. To avoid any of these potential concerns, many prenatal vitamin formulations have replaced retinol with  $\beta$ -carotene, which has no teratogenic potential.  $\beta$ -Carotene is cleaved in the liver to vitamin A, but the extent of conversion is controlled to meet and not exceed the body's needs.

### **Isotretinoin and Other Oral Synthetic Retinoids**

Consistent with experimental animal data, an increased risk of pregnancy loss and a characteristic pattern of malformations and mental deficiency have been identified after prenatal exposure to isotretinoin. This pattern includes CNS malformations, microtia or anotia, micrognathia, cleft palate, conotruncal cardiac and great vessel defects, thymic abnormalities, eye anomalies, and some limb reduction defects.<sup>[18,86]</sup> The estimated risks are at least as high as 22% for spontaneous abortion, 28% for structural defects, and 47% for mild to moderate mental deficiency, even if no structural abnormalities are present.<sup>[18,87,88]</sup> Affected children have been reported with exposures to usual therapeutic doses and with treatment for durations shorter than 1 week in the first trimester. There does not appear to be a risk of malformations when the drug is discontinued before conception, which is consistent with the half-life of isotretinoin.<sup>[88,89]</sup>

Pregnancy prevention among women who are prescribed isotretinoin continues to be a challenge. A third-generation restricted distribution program, iPledge, was implemented in March 2006; it mandates close monitoring of birth control practices and negative pregnancy testing before dispensing of prescriptions for isotretinoin.<sup>[90]</sup>

Retinoid embryopathy is a risk with the use of other oral synthetic retinoids, including etretinate and its metabolite acitretin, which have been used for the treatment of psoriasis.<sup>[91]</sup> The extremely long half-life of etretinate led to its removal from the U.S. market in 1998. The half-life of acitretin is considerably longer than that of isotretinoin (50 to 60 hours), and acitretin can be converted to etretinate with maternal ingestion of ethanol. The drug should be discontinued before pregnancy and ethanol avoided during the entire period of treatment and for at least 2 months after discontinuation of therapy.<sup>[92,93]</sup>

## **Ionizing Radiation**

Prenatal exposure to high-dose radiation is associated with an increased risk of microcephaly, mental deficiency, and growth deficiency based on data derived from a small number of pregnant survivors of the atomic bombs in Nagasaki and Hiroshima.<sup>[94]</sup> It is estimated that doses of 50 rad (50 cGy) or greater to the uterus are required to produce these effects. The highest risk appears to be associated with exposures between 8 and 15 weeks' gestation, with a higher threshold dose at more advanced gestational ages.<sup>[95]</sup> The available data do not support an increase in the risk of mental retardation associated with high-dose radiation exposure beyond 25 weeks' or before 8 weeks' gestation.<sup>[93]</sup> Based on dose-response calculations, diagnostic procedures involving radiation do not pose a risk to the fetus unless the cumulative dose to the uterus is greater than 10 cGy; conservative guidelines suggest that doses should be kept below 5 cGy to the uterus during pregnancy.<sup>[96]</sup>

## **Environmental Agents**

### **Methylmercury**

Prenatal exposure to methylmercury was recognized as a cause of neurodevelopmental disability after instances of contamination in Japan (Minamata Bay) and Iraq in the mid-20th century.<sup>[97,98]</sup> The reported effects, called

*Minamata disease*, include a cerebral palsy-like disorder and mental deficiency.<sup>[99]</sup> Although the lower limit of exposure that may pose a risk in prenatal development remains unclear, an independent U.S. National Research Council expert committee concluded that limiting maternal intake to no more than 0.1 mg/kg body weight/day was sufficient to protect the fetus.<sup>[100]</sup> Currently, consumption of contaminated fish or marine mammals is the major source of methylmercury exposure in most populations. In 2004, the U.S. Environmental Protection Agency and FDA advised pregnant women and women of childbearing age who may become pregnant to avoid eating predator fish (i.e., shark, swordfish, king mackerel, and tilefish) in which organic mercury may be bioconcentrated and to limit their average consumption of other cooked fish to 12 ounces (340 g) per week to prevent fetal exposure to excessive amounts of methylmercury.<sup>[101]</sup> There are, however, substantial benefits from fish in the diet during pregnancy.<sup>[102]</sup> In a large, longitudinal study conducted in the United Kingdom, maternal seafood consumption during pregnancy correlated with developmental outcomes on a variety of measures up to 8 years of age. Beneficial effects on child development in this study were shown only in children born to women with maternal seafood intakes of more than 340 g per week, suggesting that advice to limit seafood consumption may be detrimental.<sup>[103]</sup>

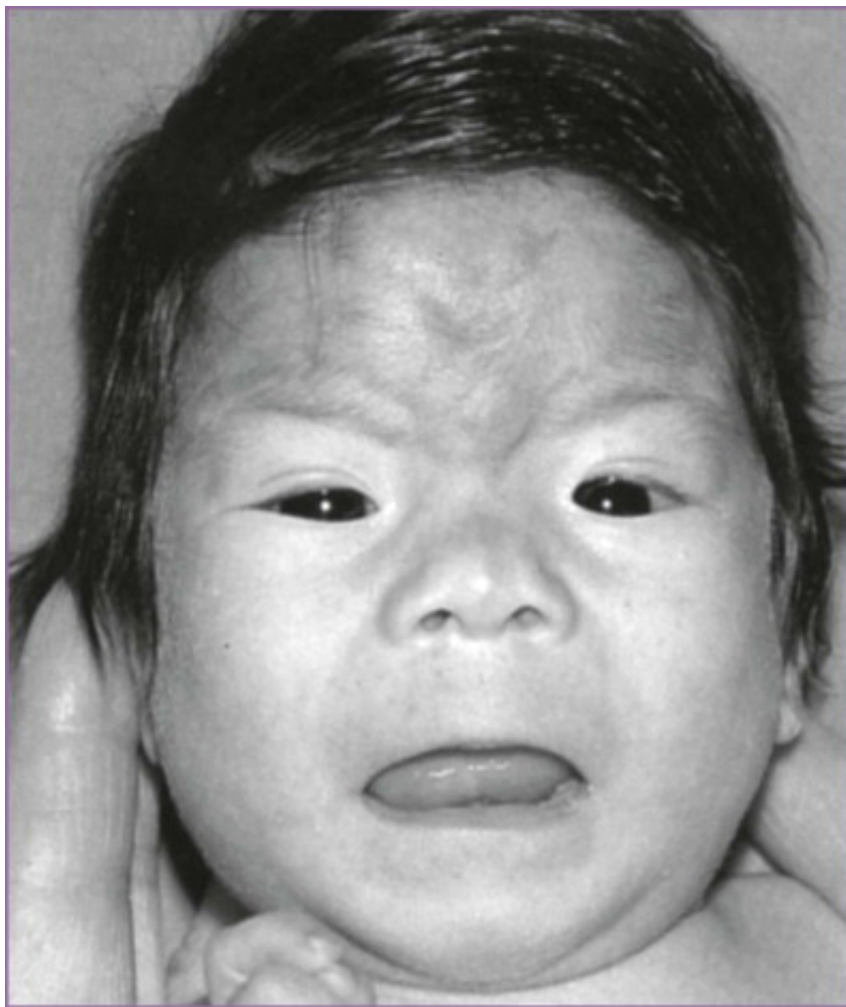
## Lead

In utero exposure to high levels of lead (maternal blood concentrations >30 mg/dL) has been associated with an increase in spontaneous abortion, preterm birth, and mental deficiency in the offspring.<sup>[104-106]</sup> Prenatal exposure to lower levels (>10 mg/dL) may be associated with subtle neurobehavioral effects, but these effects may not persist into older childhood.<sup>[106-108]</sup> Adverse effects of lower levels of lead exposure during pregnancy have been suggested but not confirmed. Occupational and environmental exposures to lead that precede pregnancy may result in fetal exposure due to mobilization of lead stored in maternal bone. These effects may be modified by maternal intake of calcium.<sup>[109]</sup>

## Social and Illicit Drugs

### Ethanol

A pattern of anomalies, known as the *fetal alcohol syndrome* (FAS), was first described more than 35 years ago in a case series of infants born to alcoholic women.<sup>[110]</sup> The characteristic features of this disorder are prenatal and postnatal growth retardation; microcephaly or other CNS dysfunction including neurobehavioral deficits, neurologic impairment; and characteristic facial anomalies consisting of short palpebral fissures and a smooth philtrum with a smooth, thin vermilion border of the upper lip (Fig. 31-1).<sup>[111,112]</sup> Although FAS is difficult to diagnose, particularly in the newborn period, estimates of its incidence in selected U.S. and Western European populations are approximately 1 to 4 cases per 1000 live births.<sup>[113]</sup>



**Figure 31-1** Nine-month-old infant with fetal alcohol syndrome.

(From Streissguth AP, Aase JM, Clarren SK, et al: *Fetal alcohol syndrome in adolescents and adults*, JAMA 265:1961, 1991. Copyright 1991, American Medical Association.)

Many more children are thought to have alcohol-related neurobehavioral or neurologic impairment with or without some structural features of FAS. Congenital heart defects, oral clefts, and abnormalities of the eyes, brain, and kidneys are more common than expected among the children of women who drink moderately to heavily during pregnancy.<sup>[114-117]</sup> These children, described as having partial FAS, alcohol-related neurodevelopmental abnormalities (ARNDs), or alcohol-related birth defects (ARBDs), are now considered to represent a continuum of fetal alcohol spectrum disorders (FASDs). Accurate estimates of the prevalence of FASDs are lacking; however, one population-based study in the Seattle, Washington, area suggested that the rates may be as high as 1 case per 100 children.<sup>[113]</sup> Increased risks for spontaneous abortion, stillbirth, and sudden infant death syndrome have been linked to prenatal ethanol exposure, particularly exposure from ethanol consumed in a heavy episodic or binge pattern.<sup>[118-121]</sup>

Experimental animal and human data support a dose-response relationship in terms of risk for FAS/FASD. However, because of variability in diagnosis and difficulties in obtaining and validating exposure information reported by pregnant women, estimates vary widely regarding the magnitude of the risk. For example, estimates for the fully expressed syndrome range from about 4% to 44% of children born to women who drink heavily during pregnancy.<sup>[122,123]</sup> The women at highest risk appear to be those who have already had an affected child and who continue to consume ethanol during subsequent pregnancies. Lower levels of maternal ethanol consumption have been associated with less severe neurobehavioral outcomes and persistent growth effects,<sup>[124-126]</sup> but the exact threshold doses and patterns of consumption for these effects are not well understood. For example, full-blown FAS is typically seen among the children of women who report consuming an average of six or more standard drinks (i.e., beer, wine, or spirits) per day during pregnancy. However, some studies have suggested that women who



consume more than two standard drinks per day during pregnancy are at increased risk. These risks may be mediated or ameliorated by the pattern of drinking (i.e., binge drinking versus more frequent and smaller quantities), maternal age, nutrition, and genetic susceptibility.[117,126-129] The duration of exposure is likely to be important because CNS development continues throughout gestation.[130]

Current data are insufficient to assign a risk to certain common patterns of prenatal ethanol exposure, such as ethanol consumption limited to occasional binge episodes before recognition of pregnancy. However, the data do support the notion that reduction or discontinuation of ethanol consumption at any point in pregnancy may be beneficial. A lower threshold of exposure, below which no effects will be seen, has not been defined. For women who are planning pregnancy or who have the potential to become pregnant, the U.S. Surgeon General has recommended that the safest course is to avoid ethanol entirely during pregnancy.[131]

## Tobacco

Maternal cigarette smoking is associated with a variety of harmful effects on the embryo and fetus, including increased risks for specific congenital malformations, spontaneous abortion, placental complications, preterm delivery, reduced birth weight, and sudden infant death syndrome. The structural malformations that have been significantly associated with first-trimester smoking include oral clefts and gastroschisis. A meta-analysis of 24 studies estimated the risk of oral clefts to be low; the relative risk for cleft lip with or without cleft palate was 1.34 (CI, 1.25 to 1.44), and that for cleft palate alone was 1.22 (CI, 1.10 to 1.35).[132] Some studies have suggested gene-environment interactions in susceptibility for oral clefts when mothers smoke during early pregnancy. Infants who have a null deletion of the detoxifying gene *GSTT1* or certain polymorphisms at the *Taq1*-identified site for transforming growth factor- $\alpha$  (a gene known to be involved in facial development) and whose mothers smoke are at higher risk for certain oral clefts than infants with either risk factor alone.[133,134] Elevated risks for gastroschisis after maternal smoking are estimated to be low.[135] However, as with oral clefts, there is some evidence for gene-environment interactions between maternal smoking and polymorphisms of fetal genes involved in vascular responses.[136] Other defects that occur with increased frequency after pregnancy exposure to tobacco smoke include craniosynostosis and clubfoot.[137-139] Most studies with dose information available have suggested a dose-response relationship for each of these defects, with the heaviest smokers being at highest risk.

The deleterious effects of cigarette smoking on other pregnancy outcomes are well documented. Intrauterine growth restriction is the most consistently reported adverse outcome. On average, babies born to women who smoke during pregnancy are 200 g lighter than those born to comparable women who do not smoke, with a clear dose-response gradient,[140] in part because of the reduction in uterine blood flow associated with plasma nicotine in women who smoke.[141] Smaller reductions in birth weight have occurred when exposure is limited to environmental or passive smoke.[142] Strong gene-environment and gene-gene-environment interactions have been demonstrated between the cytochrome P450 isozyme *CYP1A1* and *GSTT1* maternal metabolic genes and infant birth weight in mothers who smoke.[143]


Perinatal mortality is increased with maternal smoking, in part because of the increased risks of placental complications and preterm delivery. In one large study, the combined risk for fetal or infant death for primiparous women who smoked less than one pack per day was estimated to be 25% higher than that for nonsmoking women, and the risk was 56% higher for those who smoked one pack per day or more.[144] However, if smoking is discontinued in the first half of gestation, evidence indicates that the effects on birth weight can be eliminated.[145-147] Based on dose-response data, any reduction in the number of cigarettes smoked may reduce the risks of low birth weight, preterm birth, and placental complications.[147-151]

## Cocaine

The most consistently reported effects of prenatal cocaine exposure are a small but statistically significant increase in intrauterine growth restriction[152] and abnormalities in neonatal state regulation and motor performance.[153] However, based on a synthesis of 36 published studies of children 6 years of age or younger, Frank and colleagues[154] concluded that no consistent negative association existed between prenatal cocaine exposure and postnatal physical growth, developmental test scores, receptive language, or standardized parent and teacher reports of child behavior. An association between prenatal cocaine exposure and decreased emotional expressiveness has been suggested.[155]

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