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Drugs and Environmental Agents in Pregnancy and Lactation: Teratology, Epidemiology, and Patient Management

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OUTLINE

KEY ABBREVIATIONS

Angiotensin-converting enzyme	ACE	Neural tube defect	NTD
Antiepileptic drug	AED	Over the counter	OTC
Birth defect monitoring system	BDMS	Propylthiouracil	PTU
Dalton	Da	Saturated solution of potassium iodide	SSKI
Diethylstilbestrol	DES	Sudden infant death syndrome	SIDS
Electroencephalogram	EEG	Thyroid-stimulating hormone	TSH
Fetal alcohol syndrome	FAS	Tumor necrosis factor	TNF
Food and Drug Administration	FDA	Unfractionated heparin	UFH
Glucose-6-phosphate dehydrogenase	G6PD	Zidovudine	ZDV
Low-molecular-weight heparin	LMWH		
Maternal outcomes and neurodevelopmental effects of antiepileptic drugs	MONEAD		

OVERVIEW

Practicing obstetricians routinely address patient concerns and questions about the effects of using drugs during pregnancy and lactation or exposure to various environmental agents on their developing babies. This chapter provides some practical advice and direction for advising patients on the risks to the fetus from taking various prescription medicines and from being exposed to environmental toxins and illicit drugs. A basic understanding of drug pharmacology and the pharmacokinetics of drug passage across the placenta and into breast milk will help the practicing obstetrician provide the safest and soundest advice to patients.

The risks of drug exposure to the fetus must first be measured in terms of the overall rates of malformations. **The incidence of major malformations in the general population is 2% to 3%.**[1] These malformations include those incompatible with survival (e.g., anencephaly) as well as those requiring major surgery (e.g., cleft palate or congenital heart disease) or causing permanent disability or developmental delays. The malformation rate may be as high as 7% to 10% if minor defects are counted (ear tags, extra digits). The teratology data from animal studies may not be accurate, as animal studies estimate risk with a 24% malformation rate. For example, thalidomide was not found to be teratogenic in rats and mice but is a potent human teratogen.

The US Food and Drug Administration (FDA) no longer uses lettered risk factors for teratogenicity (Federal Register. Content and format of labeling for human prescription drug and biologic products; requirement for pregnancy and lactation labeling. December 4, 2014). In fact, the Teratology Society had suggested eliminating the FDA letter classification more than 20 years ago.[2] The FDA Pregnancy Risk Categorization by Trimester List names the risks from categories A to X. **These categories were designed for prescribing physicians and not to address inadvertent exposure. For example, isotretinoin (Accutane) and oral contraceptives are both category X, based on lack of benefit for oral contraceptives during pregnancy, yet oral contraceptives do not have any teratogenic risk with inadvertent exposure.** However, the drugs in different categories may pose similar risks but be in different categories based on risk/benefit considerations. Second, the categories create the impression that drugs within a category present similar risks, whereas the category definition permits inclusion in the same category of drugs that vary in type, degree, or extent of risk, depending on potential benefit. For these reasons, this chapter does not use category designations but simply lists the risks of a drug's use in pregnancy and refers to specific descriptions in teratogen information databases (Fig. 7.1). However, as a quick guide for clinicians, some selected medications on the FDA's Pregnancy Risk Categorization by Trimester List rated as Category X (contraindicated in pregnancy) are included (Box 7.1). This list, though

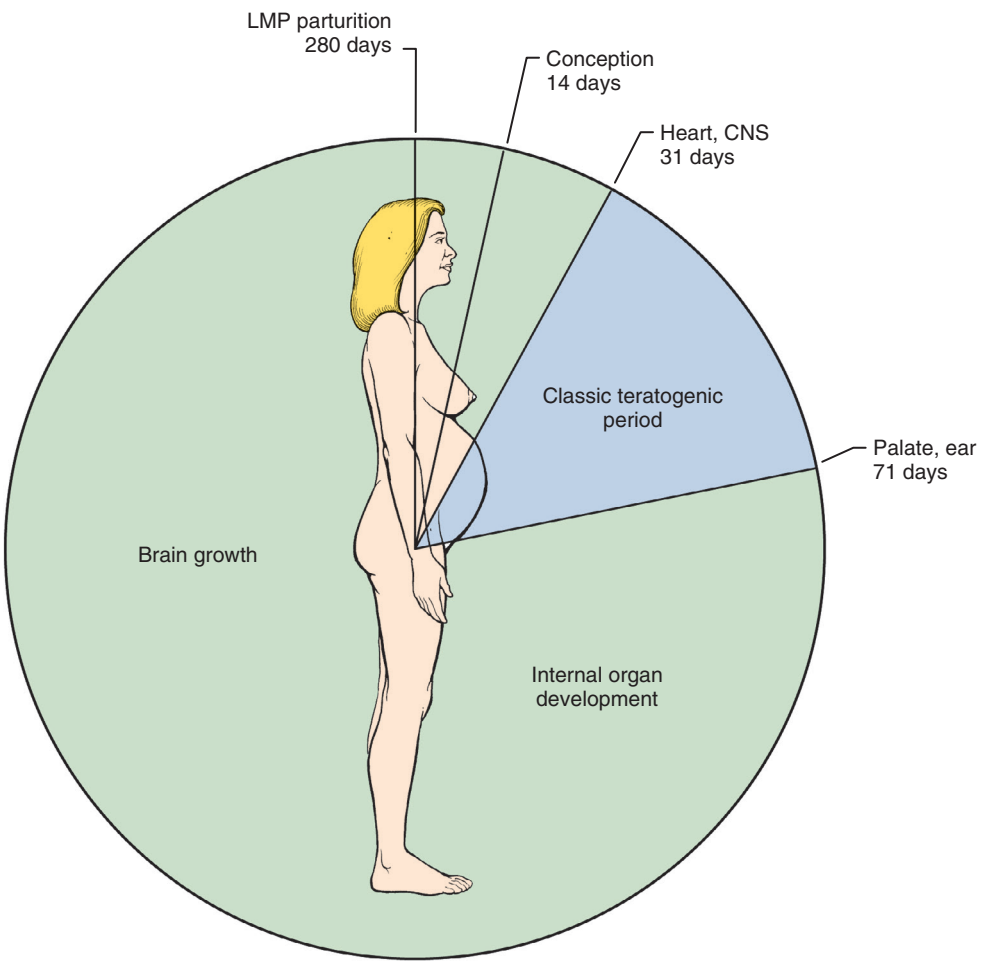

Fig. 7.1 Gestational Clock Showing the Classic Teratogenic Period. *CNS,* Central nervous system; *LMP,* last menstrual period. (From Blake DA, Niebyl JR. Requirements and limitations in reproductive and teratogenic risk assessment. In Niebyl JR, ed. *Drug Use in Pregnancy*. 2nd ed. Philadelphia: Lea & Febiger; 1988:2, with permission.)

BOX 7.1 Selected Drugs on the Food and Drug Administration Category X Pregnancy List

Hydroxyzine (early pregnancy)
Aspirin (third trimester)
Warfarin
"Statin" drugs (e.g., rosuvastatin, atorvastatin)
Flurazepam
Triazolam
Temazepam
Isotretinoin
Fluorouracil (topical)
Finasteride (avoid handling capsules in pregnancy)
Silver sulfadiazine (topical; late pregnancy)
Testosterone and derivatives
Leuprolide
Misoprostol
Ribavirin
NSAIDs (e.g., naproxen, piroxicam, meloxicam) (third trimester)
Celecoxib (third trimester)
Dantrolene
Methotrexate
Raloxifene
Dutasteride (avoid handling capsules in pregnancy)

NSAIDs, Nonsteroidal antiinflammatory drugs.
Modified from https://www.empr.com/clinical-charts/drugs-contraindicated-in-pregnancy/article/125914/.

not all-inclusive, adds or supports much of the information in this chapter.

The classic teratogenic period is from day 31 after the last menstrual period in a 28-day cycle to 71 days from the last period (see Fig. 7.1). During this critical period, organs are forming and teratogens may cause malformations that are usually overt at birth. Administration of drugs early in this period may affect the heart or neural tube; later exposure affects the formation of the ear and palate. **Before day 31, exposure to a teratogen produces an all-or-none effect, resulting in either death of the conceptus or survival with no anomalies.** Many parameters can influence the transfer of drugs from the maternal to the fetal circulation and then affect the impact of each individual drug on fetal development. The most of important of these factors are gestational age, the structure of the drug molecule, and the pattern of drug usage (sporadic or chronic). Additional or concomitant factors include interaction between drugs in multitherapy; individual maternal metabolism, which may be genetically driven; maternal disorders such as liver or kidney disease; and integrity of the placental structure, which may be altered by smoking and other substance abuse.

BASIC PRINCIPLES OF TERATOLOGY

To understand the etiology of birth defects, **Wilson's six general principles of teratogenesis[3] provide a framework for understanding how structural or functional teratogens may act.**

Genotype and Interaction With Environmental Factors

The first principle is that susceptibility to a teratogen depends on the *genotype of the conceptus* and the manner in which the genetic makeup of the conceptus interacts with environmental factors. For example, different genetic strains of mice vary greatly in their susceptibility to teratogens that lead to oral clefts. Some of the variability in responses to antiepileptic drugs (AEDs), like valproic acid and phenytoin, probably relates to the genotype of the embryo.

Timing of Exposure

Wilson's second principle is that susceptibility of the conceptus to teratogenic agents varies with the developmental stage at the time of exposure. This concept of *critical stages of development* directly affects alterations in structure. **It is during the second to eighth week of development after conception—the embryonic period—that most structural defects occur.** For example, neural tube defects (NTDs) may result from exposure between 22 and 28 days postconception. Thalidomide teratogenicity differs as a function of the developmental stage at exposure.

Mechanisms of Teratogenesis

The third principle is that teratogenic agents act in specific ways (*mechanisms*) on developing cells and tissues in initiating abnormal embryogenesis (pathogenesis). Teratogenic mechanisms are considered separately further on.

Manifestation

The fourth principle is that irrespective of the specific deleterious agent, the final manifestations of abnormal development are death, malformation, growth restriction, and/or functional disorder. The manifestation is thought to depend largely on the stage of development at which exposure occurs; a teratogen may have one effect if exposure occurs during embryogenesis (structural abnormalities or death) and another if the exposure is during the fetal period (functional deficits).

Agent

The fifth principle is that access of adverse environmental influences to developing tissues depends on the nature of the influence (*agent*). This principle relates to such pharmacologic factors as maternal metabolism and placental passage. For an adverse effect to occur, an agent must reach the conceptus, either transmitted indirectly through maternal tissues or directly by traversing the maternal body.

Dose Effect

Wilson's final principle is that manifestations of abnormal development increase in degree from the no-effect level to the lethal level as *dosage* increases. This means that the response (e.g., malformation, growth restriction) varies according to the dose, duration, or amount of exposure. For most human teratogens, this dose-response is not clearly understood, but along with the principle of critical stages of development, these concepts are important in supporting causal inferences about human reproductive hazards. In utero exposure to ionizing radiation clearly shows the importance of dose on teratogenic effect.

EPIDEMIOLOGIC STUDIES EVALUATING THE FETAL RISK OF DRUGS AND ENVIRONMENTAL AGENTS

Various studies can determine the risks of drugs and environmental agents on the fetus, from single case reports to larger clinical trials, all with varying degrees of strength of evidence.

Case Reports

Many known teratogens and reproductive toxicants were identified initially through single case reports. Published observations of abnormal

aggregations of cases or patterns of malformations are important; however, these observations are not reliable in identifying the true risk posed by various drugs and environmental agents.

Descriptive Studies

Descriptive epidemiologic studies provide information about the distribution and frequency of a given clinical outcome, resulting in comparable rates of occurrence. Descriptive studies first begin by describing a risk population and using that population as a denominator for calculating an outcome rate. Second, a numerator is defined as the outcome, validated by some specific method (case definition and ascertainment).

Surveillance programs are considered descriptive studies where an at-risk population is identified and then followed over time to detect outcomes of interest. **Birth defect monitoring systems (BDMSs) are designed to identify cases occurring in a defined population, usually by reviewing vital records or hospital record abstracts or charts.** BDMSs have grown in the last 20 years. However, despite increased surveillance and reporting, the true risk of exposure to drugs and environmental agents cannot be determined. One of the main issues in studying the impact of a specific drug on the fetus (e.g., in the case of commonly used drugs such as paracetamol or aspirin but also of maternal exposure to nicotine and caffeine) is that such exposures can never be excluded as confounding factors and are difficult to quantify. Descriptive studies should be employed initially, followed by case-control studies as listed further on. For example, after suspecting, on the basis of case observations, that thalidomide was teratogenic, Lenz[4] conducted a case-control study. **Also, the association between the use of valproic acid and the occurrence of spina bifida was verified by case-control studies.**[5,6]

Case-Control Studies

The most widely used approach in determining teratogenicity is the case-control study, where groups of individuals with some outcome or disease of interest (cases) (e.g., a congenital malformation) are compared with similar groups. After cases and controls have been identified, the hypothesis to be tested is whether these two groups differ in exposure as well as outcome. How accurately exposure and its timing are determined may vary greatly among studies, but in any study the same methods must be used to establish the exposure of both cases and controls. Case-control studies may have implicit bias in selecting controls and other variables.[7]

Cohort Studies

Cohort studies, often called *prospective studies,* require that groups differing in exposure be followed through time, with outcomes observed. Therefore these studies tend to be time-consuming and expensive. In addition, occurrence rates for many adverse reproductive outcomes, such as congenital malformations, are low; thus, large samples must be followed for a considerable period of time. **Cohort studies enable investigators to calculate incidence rates, which provide a measure of *relative risk* of an outcome after the exposure.** *Historical prospective studies* identify groups that have been exposed and follow their outcomes in a retrospective manner.

Randomized and Controlled Clinical Trials

Ideally, analytical studies (case-control or cohort) are followed by a randomized clinical trial, in which the efficiency of a prevention or treatment regimen is evaluated. That is, subjects are randomly assigned to different treatment groups. Clinical trials of both NTD recurrence[6] and occurrence[8] showed the importance of folic acid supplementation in pregnancy.

PHARMACOKINETICS OF DRUGS ACROSS THE PLACENTA AND BREAST TISSUES

The permeability of the placenta is well known, dating back to around 1904; however, in the 1960s, the placenta was erroneously thought to be an effective barrier to harmful substances. That misconception resulted in serious birth defects from the prescription of thalidomide, benzodiazepines, and other toxic medications. Similarly, drug transfer to the newborn via maternal breast milk have been studied only recently and the corresponding data are limited. An understanding of the ways in which different drugs cross the placenta or into the breast milk is essential to the practicing obstetrician in assessing medication use in the pregnant and breastfeeding patient.

Placental Transfer

To reach the fetal tissues and organs, the molecules that have entered the placenta via the maternal circulation have to first cross the placental barrier. The placental villous barrier or membrane is made up of the trophoblast, which covers the villous tissue externally and is in direct contact with the maternal blood in the intervillous space, the villous mesenchymal tissue, and the endothelium of the fetal capillaries (see Chapter 1).

Important anatomic changes take place between the first and second trimesters of pregnancy. During most of the first trimester, the entire gestational sac is covered with villous tissue and the entry of maternal blood inside the placenta is limited by the presence of trophoblastic plugs blocking the mouths of the uteroplacental arteries in the area destined to become the definitive placenta. On the fetal side, the villous capillaries are small in numbers and size and located more centrally inside the villi at a much greater distance from the trophoblastic layer than later in pregnancy. During that period of gestation, the placental transfer route is described as histiotrophic via the uterine glands, extraembyonic coelom, and the secondary yolk sac. The placenta becomes truly hemochorial only from the end of the first trimester. The villous membrane becomes progressively thinner, facilitating maternal-fetal exchanges in both directions with advancing gestation.

For the most part, placental drug transfers have been studied using animal models, essentially rodents, or in vitro using third-trimester ex vivo isolated dual-side perfused human cotyledons. Both models have obvious limitations, in particular, regarding transfers during the first trimester of human pregnancy, which is the gestational period when the human fetus is at highest risk for teratogenic effects. Placental drug pharmacokinetics can be indirectly studied in vivo using coelocentesis (the aspiration of coelomic fluid) in the first trimester or cord blood samples at delivery.

Overall, it is assumed that all drugs will in some manner cross into the placenta, especially those that are lipid soluble; water-soluble drugs and metabolites of drugs pass less readily. Only free drug will pass into the placenta, so any portion of drug bound by protein will not cross the placenta. Substances cross mainly from the maternal to the fetal circulation by passive diffusion (Fig. 7.2).[9] Thus passive diffusion across the villous barrier is the predominant method of the fetus's exposure to drugs and environmental agents, with low-molecular-weight lipid-soluble substances and non-protein-bound drugs passing easily. Compounds greater than 600 Da—such as insulin, heparin, or drugs bound by proteins—do not pass easily into the placenta. Drug concentrations in the fetus may exceed maternal concentrations, with weakly basic drugs passing more easily. Passive drug transfer is flow dependent and membrane limited. As the flow volume in the placental circulations increases and the thickness of the villous barrier decreases, respectively, with advancing gestation, fetal exposure to drugs and

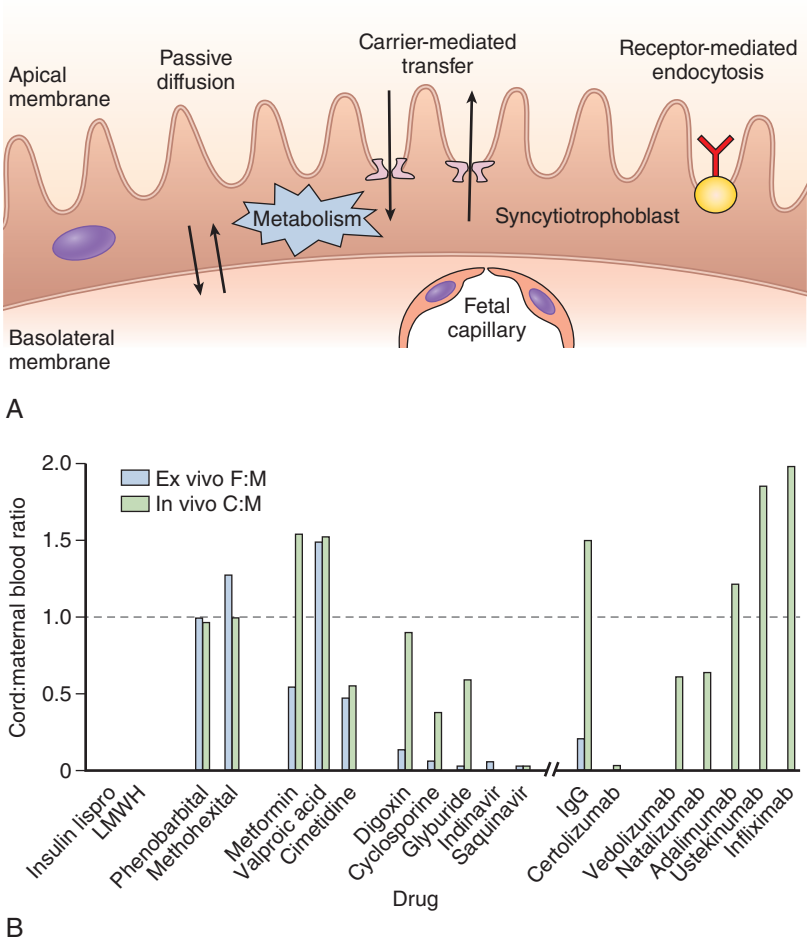

Fig. 7.2 Mechanisms of the Transplacental Transfer of Drugs. *C:M,* cord/maternal blood ratio; *F:M,* female/male ratio; *IgG,* Immunoglobulin G; *LMWH,* low-molecular-weight heparin. (From Tetro N, Moushaev S, Rubinchick-Stern M, et al. The placental barrier: the gate and fate of drug distribution. *Pharm Res.* 2018;35:73.)

environmental agents is greatest in the last trimester but the effect on fetal organs is the lowest.

Several drug transport systems have been found at the villous membrane level. The placenta expresses enzymes that facilitate the metabolism of various substances, including drugs. There are various cytochrome P450 enzymes that result in phase I and II reactions in the placental tissues. Phase I reactions include oxidation, reduction, and hydrolysis, whereas phase II reactions include conjugation. The metabolism of drugs in the placenta results in water-soluble substances, those that do not pass easily into the placenta; however, there may be a risk of toxic metabolites and exposure to the fetus. Drugs that have been shown to experience significant placental metabolism include zidovudine, dideoxynosine, and oxcarbazepine. **The metabolism of oxcarbazepine may explain the limited data showing it to be safe to use during pregnancy.**

Awareness of the pharmacokinetics may affect fetal exposure to drugs or environmental agents. The rate and extent of drug distribution across the placenta predict the fetal exposure to a drug. Drugs administered rapidly as a single dose may not accumulate in the fetus, since the drug concentration declines significantly before crossing the placenta. Drugs given on a continuous basis will accumulate more significantly in the placenta and cross into the fetus. For example, valproic acid crosses the placenta readily and equilibrates in the fetal plasma within 1.5 hours[10]; a prolonged-release formulation of valproic acid is recommended to prevent high fetal concentrations of this drug.[11] Other research to minimize (or enhance) the placental transfer of drugs includes developing nanoparticles of drugs. Currently there are two ongoing trials to evaluate this drug delivery system in pregnant women.

Breast Milk Transfer

Pharmacokinetic data on drug administration during lactation are limited and often inconsistent. **Many drugs can be detected in breast milk at low levels that are not usually of clinical significance to the infant.** The rate of transfer into milk depends on the drug's lipid solubility, molecular weight, and degree of protein binding, its degree of ionization, and the presence or absence of active secretion. Nonionized molecules of low molecular weight, such as ethanol/alcohol, cross easily. If the mother has unusually high blood concentrations as with increased dosage or decreased renal function, drugs may appear in higher concentrations in the milk.

The amount of drug in breast milk is a variable fraction of the maternal blood level, which itself is proportional to the maternal oral dose. Thus the dose to the infant is usually subtherapeutic, approximately 1% to 2% of the maternal dose on the average. This amount is usually so trivial that no adverse effects are noted. In the case of toxic drugs, however, any exposure may be inappropriate. Allergy may also exist or be initiated. Long-term effects of even small doses of drugs are yet be investigated. Also, drugs are eliminated more slowly in the infant with immature enzyme systems. Short-term effects of most maternal medications on breastfed infants are mild and pose little risk. As the benefits

of breastfeeding are well known, the risk of drug exposure must be weighed against these benefits.

With drug administration in the immediate few days postpartum, before lactation is fully established, the infant receives only a small volume of colostrum. Thus little drug is excreted into the milk. It is also helpful to allay the fears of undergoing cesarean deliveries regarding analgesics or other drugs administered at this time, assuring them that such drugs have no known adverse effects on the infant. For drugs requiring daily dosing during lactation, knowledge of pharmacokinetics in breast milk may minimize the dose to the infant. For example, dosing immediately after nursing decreases the neonatal exposure because the blood level will be at its nadir just before the next dose.

The metabolism of drugs affects the amount of medication in the breast milk. A classic case is the use of codeine during lactation; mothers who receive codeine and are "ultrarapid" metabolizers will convert codeine to high concentrations of morphine, which easily passes into the breast milk. Cases of respiratory depression and other serious consequences in the baby have been reported in rapid metabolizing breastfeeding mothers who have received codeine.[12] In addition, there is a risk of accumulation of the active metabolite of tramadol (O-desmethyltramadol, or M1) in ultrarapid metabolizers, causing serious effects in the baby.

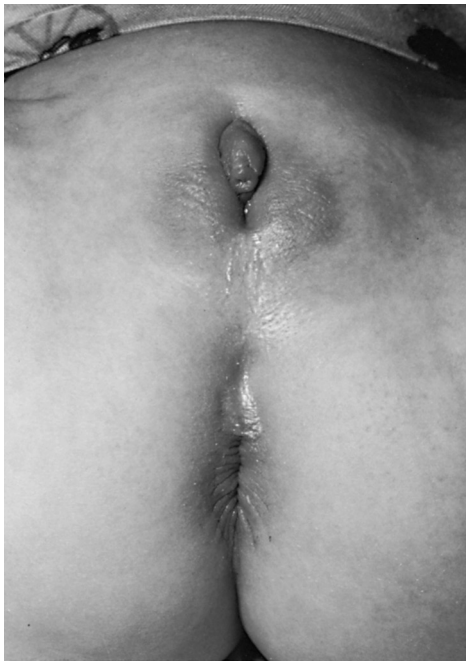

Fig. 7.3 Perineum of a Female Fetus Exposed to Danazol in Utero. (From Duck SC, Katayama KP. Danazol may cause female pseudohermaphroditism. *Fertil Steril.* 1981;35:230.)

PRESCRIPTION DRUGS, OVER-THE-COUNTER PRODUCTS, AND HERBAL SUPPLEMENTS

Patient assessment and education regarding drugs and pregnancy are covered briefly at the end of this chapter. **Generally the risks versus benefits of using drugs in pregnancy should be carefully weighed, with the goal of minimizing the use of over-the-counter (OTC) and prescription drugs.** Patients should be encouraged to use nonpharmacologic means of managing common pregnancy symptoms such as headaches, muscle pains, nausea and vomiting, and so on. Some drugs may also interact with the results of screening tests for conditions such as aneuploidy and NTDs. For example, methadone has been reported to cause false-positive tests for trisomy 18, and false-positive rates for NTDs were higher for those on corticosteroids, antibiotics, and antidepressants.[13]

Effects of Specific Drugs in Pregnancy

Estrogens and Progestin

Studies have not confirmed any teratogenic risk from the use of oral contraceptives or progestin. A meta-analysis of first-trimester sex hormone exposure revealed no association between exposure and fetal genital malformations.

Androgenic Steroids

Androgens may masculinize a developing female fetus. Danazol (Danocrine) has been reported in 23 of 57 female infants exposed to produce clitoral enlargement and labial fusion when given inadvertently for the first 9 to 12 weeks after conception (Fig. 7.3).

Spermicides

A meta-analysis of reports of spermicide exposure concludes that there is no increased risk of birth defects.[14]

Antiepileptic Drugs

Continuing AED therapy in pregnancy depends on seizure control prior to conception and understanding the ability to provide seizure control on a regimen adjusted for pregnancy. **Most experts agree that the benefits of AEDs in appropriates doses during pregnancy outweigh the risks of discontinuation.** Continuing AEDs also depends on the type of seizures, seizure control, adverse effects of the AED regimen, and patient adherence (determined by serum measurement of the AED). Poor adherence in the absence of seizures may not warrant AED therapy during pregnancy. Also, women who are seizure-free for at least 2 years as confirmed by electroencephalography (EEG) should consider stopping AED therapy during pregnancy.

The MONEAD monitored the prescribing of AEDs over a 4-year period and shows a changing pattern of AED prescribing. From 2012 to 2016, the most common medications used in pregnancy and epilepsy were lamotrigine, leviteracetam, carbamazepine, and zonisamide, respectively; this compares with the most common therapies prescribed from 1999 to 2004, which were carbamazepine, lamotrigine, phenytoin, and valproate.[15] Given the fetal risks associated with valproate and phenytoin, one could assume that possible fetal risk may be reduced by the changing patterns of AED prescribing to less teratogenic AEDs.

Women with epilepsy taking AEDs during pregnancy have nearly double the risk of malformations (5%) compared with pregnant women without epilepsy (2% to 3%). The major malformations include cleft lip (with or without cleft palate) and congenital heart disease. **Importantly, valproic acid (Depakene and its various generic formulations) and carbamazepine (Tegretol and its various generic formulations) each carry approximately a 1% risk of NTDs and other anomalies.** Valproic acid monotherapy significantly increases the risk for spina bifida (odds ratio [OR], 12.7), atrial septal defect (OR, 2.5), cleft palate (OR, 5.2), hypospadias (OR, 4.8), polydactyly (OR, 2.2), and craniosynostosis (OR, 6.8).[16] A high daily dose or a combination of two or three of these drugs increases the chance of malformations. **Most pregnancy and AED data registries note that the highest risk of malformations is associated with valproate. In addition, exposure to more than one AED increases the risk of a malformation.**[17]

Phenytoin (Dilantin) decreases folic acid levels, thus increasing the risk of birth defects. Therefore folic acid supplementation should be given to these mothers, but this may require adjustment of the AED. Although women with epilepsy were not included in the Medical Research Council study, most authorities would recommend 4 mg/d of folic acid

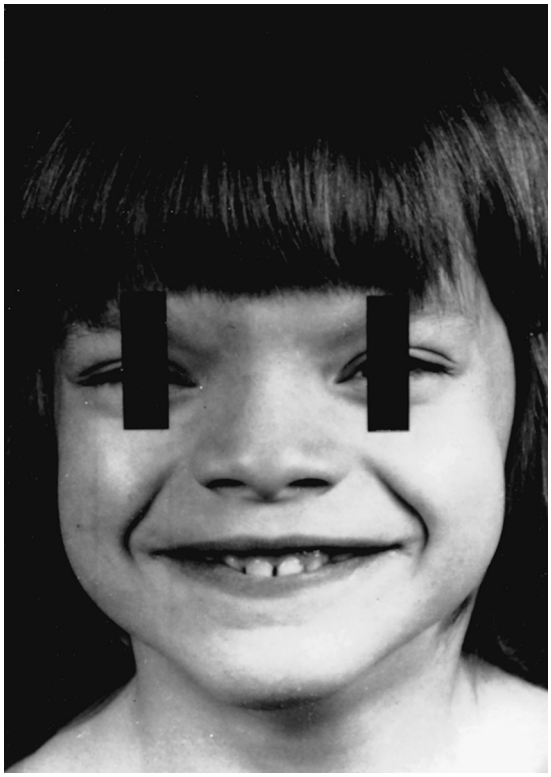

Fig. 7.4 Facial Features of an Infant With Fetal Hydantoin Syndrome. Note broad, flat nasal ridge, epicanthic folds, mild hypertelorism, and wide mouth with prominent upper lip. (Courtesy Dr. Thaddeus Kelly, Charlottesville, VA.)

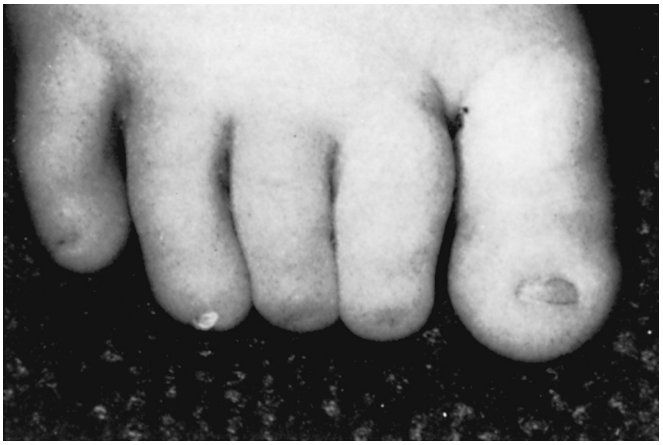

Fig. 7.5 Hypoplasia of the Toenails and Distal Phalanges. (From Hanson JWM. Fetal hydantoin syndrome. *Teratology*. 1976;13:186.)

for high-risk women. One study suggested that folic acid at doses of 2.5 to 5 mg daily could reduce birth defects in women on AEDs.[18]

Fewer than 10% of offspring show the fetal hydantoin syndrome, which consists of microcephaly, growth deficiency, developmental delays, mental retardation, and dysmorphic craniofacial features (Fig. 7.4). In fact, the risk may be as low as 1% to 2%. Although several of these features are also found in other syndromes, such as fetal alcohol syndrome (FAS), more common in the fetal hydantoin syndrome are hypoplasia of the nails and distal phalanges (Fig. 7.5) and hypertelorism. Carbamazepine (Tegretol and its various generic formulations) is also associated with an increased risk of a dysmorphic syndrome.[19] A genetically determined metabolic defect in arene oxide detoxification in the infant may increase the risk of a major birth defect. Epoxide hydrolase deficiency may indicate susceptibility to fetal hydantoin syndrome.[20] Lamotrigine exposures have been compiled in a voluntary registry established by the manufacturer, GlaxoSmithKline. After 1558 exposures in the first trimester, no increased risk of birth defects overall has been observed.[21] Of 1532 infant exposures to newer-generation AEDs, 1019 were to lamotrigine, and 3.7% involved major birth defects. **In 393 infants exposed to oxcarbazepine, the rate was 2.8%, and in 108 exposed to topiramate, the rate was 4.6%. None of these were statistically different from the rates found controls.** Valproic acid carries significantly higher risks than lamotrigine or carbamazepine.[22] One study suggested a fivefold increased risk of cleft lip and/or cleft palate with the use of topiramate.[23]

Isotretinoin

Isotretinoin (Accutane and its various generic formulations) is a significant human teratogen. This drug is marketed for the treatment of cystic acne and unfortunately has been taken inadvertently by women who were not planning pregnancy.[24] Long-acting reversible contraceptives such as an intrauterine device (IUD) or Nexplanon, another birth control implant, are recommended. **Isotretinoin is contraindicated in pregnancy** (FDA category X); pregnancy testing prior to the initiation of therapy is recommended. Of 154 exposed human pregnancies, the following have been reported: 21 cases of birth defects, 12 spontaneous abortions, 95 elective abortions, and the birth of 26 normal infants in women who took isotretinoin during early pregnancy. **The risk of structural anomalies in patients studied prospectively is estimated at 25%. An additional 25% have developmental delays.** The malformed infants have a characteristic pattern of craniofacial, cardiac, thymic, and central nervous system anomalies. They include microtia/anotia (small/absent ears) (Fig. 7.6), micrognathia, cleft palate, heart defects, thymic defects, retinal or optic nerve anomalies, and central nervous system malformations including hydrocephalus.[24] Microtia is rare as an isolated anomaly yet appears commonly as part of the retinoic acid embryopathy. Cardiovascular defects include transposition of the great vessels and ventricular septal defects. A pregnancy after discontinuing isotretinoin is not at risk, as the drug is no longer present in the serum after 5 days of discontinuation. Topical tretinoin (Retin-A) has not been associated with any teratogenic risk.

Vitamin A

There is no evidence that vitamin A in the diet in in normal doses or beta carotene is teratogenic. Prenatal vitamins containing 5000 IU have not been associated with any documented risk. **Eighteen cases of birth defects have been reported after exposure to levels of 25,000 IU of vitamin A or greater during pregnancy.**

Psychoactive Drugs

There is no clear documented risk for most psychoactive drugs with respect to overt birth defects. However, effects of chronic use of these agents on the developing brain in humans are difficult to study; therefore a conservative approach to prescribing these drugs is recommended, primarily weighing the benefits of treatment against the risks of untreated depression or other mental illnesses.

Tranquilizers. Fetal benzodiazepine syndrome has been reported in seven infants of 36 mothers who regularly took benzodiazepines during pregnancy; this number is complicated by cases where alcohol and substance abuse were also present. Generally the chronic use of benzodiazepines is not recommended in pregnancy.

Lithium (Eskalith, Lithobid, and Various Generic Formulations). In the International Register of Lithium Babies, 217 infants were listed as

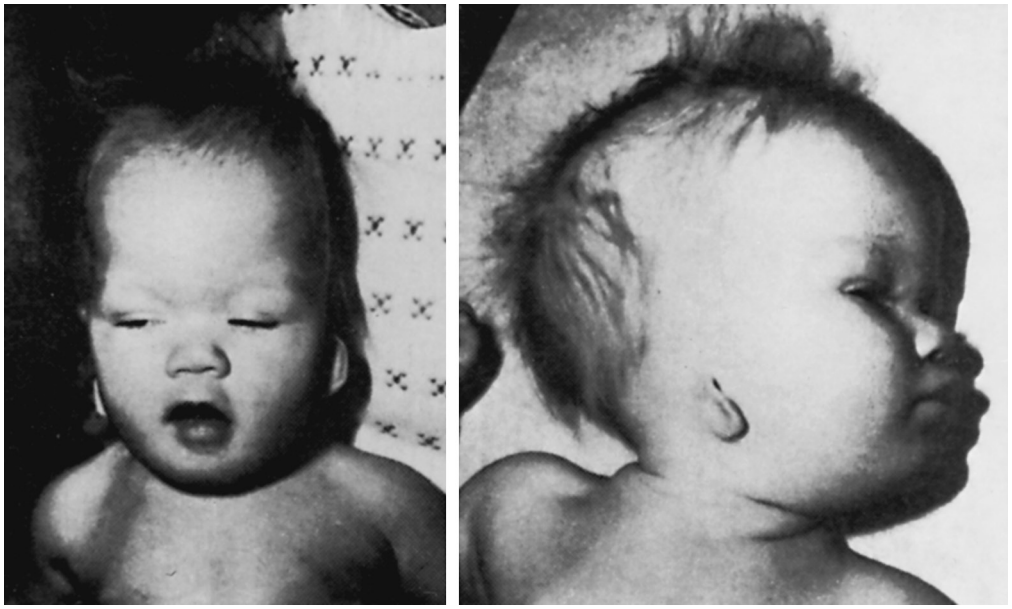

Fig. 7.6 Infant Exposed to Accutane in Utero. Note the high forehead, hypoplastic nasal bridge, and abnormal ears. (From Lot IT, Bocian M, Pribam HW, Leitner M. Fetal hydrocephalus and ear anomalies associated with use of isotretinoin. *J Pediatr.* 1984;105:598.)

exposed at least during the first trimester of pregnancy, and 25 (11.5%) were malformed. Eighteen had cardiovascular anomalies, including six cases of the rare Ebstein anomaly, which occurs in only 1 in 20,000 in the nonexposed population. Of 60 unaffected infants who were followed to age 5 years, no increased mental or physical abnormalities were noted compared with unexposed siblings.

However, two other reports suggest bias of ascertainment in the registry and a risk of anomalies much lower than previously thought. A case-control study of 59 patients with the Ebstein anomaly showed no difference in the rate of lithium exposure in pregnancy from a control group of 168 children with neuroblastoma.[25] **A prospective study of 148 women exposed to lithium in the first trimester showed no difference in the incidence of major anomalies compared with controls.**[26] We recommend that women exposed to lithium be offered ultrasound and fetal echocardiography.

Lithium is excreted more rapidly during pregnancy; thus serum lithium levels should be monitored. Perinatal effects of lithium on the infant have been noted, including hypotonia, lethargy, and poor feeding. Also, complications similar to those seen in adults on lithium have been noted in newborns, including goiter and hypothyroidism. Two cases of polyhydramnios from lithium toxicity caused by fetal diabetes insipidus have been reported with maternal lithium treatment. **Lithium therapy should be discontinued during pregnancy; however, close monitoring for relapsing manic and depressive symptoms and their complications (harm to self, others, substance abuse, etc.) may be required. These women should be offered appropriate prenatal diagnosis with ultrasound, including fetal echocardiography.** Tapering over 10 days delays the risk of relapse. Lithium may be withheld for 24 to 48 hours before delivery to reduce both neonatal complications and infant hospital stays.[27]

Antidepressants. **When the use of antidepressant drugs during pregnancy is being considered, it should be noted that among women who maintained their medication throughout pregnancy, 26% relapsed compared with 68% who discontinued their medication.**[38] **Also, fetal alcohol spectrum disorders were 10 times more common in offspring who had been exposed to selective serotonin reuptake inhibitors (SSRIs) than those who had not been exposed.** Counseling such as cognitive behavioral therapy may be as effective as drug therapy in the treatment of such women.[39]

No increased risk of major malformations has been found after first-trimester exposure to fluoxetine (Prozac) in several studies.[28] **However, one recent study showed a twofold increased risk of ventricular septal defects.**[29] Chambers et al. found more minor malformations and perinatal complications among infants exposed to fluoxetine throughout pregnancy, but this study is difficult to interpret because the authors did not control for depression. One study suggested an increased risk of low-birthweight infants with higher doses of fluoxetine (40 to 80 mg) throughout pregnancy.

Nulman et al. have evaluated the neurobehavioral effects of long-term fluoxetine exposure during pregnancy and found no abnormalities among 228 children aged 16 to 86 months (average age, 3 years). Theoretically some psychiatric or neurobehavioral abnormality might occur as a result of exposure, but it would be very difficult to ascertain because of all of the confounding variables.

Current data on other SSRI exposures show no consistent teratogenic risk.[30] Citalopram is transferred across the placenta the most, followed by fluoxetine. No major malformations have occurred in 133 infants exposed to bupropion (Zyban, Wellbutrin, and their various generic formulations).[37] The lowest transfer is found with sertraline, followed by paroxetine.[31] **However, two studies found an increased risk of cardiac defects after exposure to paroxetine (Paxil).**[29] On the other hand, a recent large population-based cohort study suggested no substantial increased risk of cardiac defects attributable to antidepressant use in the first trimester.[32] **One study showed a twofold increased risk of NTDs after citalopram** (Celexa).[29] Finally, a large Nordic cohort showed no increased risk of stillbirth, neonatal mortality, or postnatal mortality from SSRI use in pregnancy.[33]

Studies have described neonatal withdrawal in the first 2 days after in utero exposure to these drugs.[34] Infants exposed during pregnancy exhibited more tremulousness and sleep changes at 1 to 2 days of age. However, no abnormalities were found when children were examined at age 16 to 86 months after prolonged exposure during pregnancy.

A sixfold increased risk of persistent pulmonary hypertension in the newborn has been reported in infants exposed to SSRIs after 20

weeks of pregnancy,[35] raising the absolute risk from 1 to 2 per 1000 in unexposed infants to 6 to 12 per 1000 in exposed infants. Another study did not confirm this finding but confirmed a fivefold increased risk of persistent pulmonary hypertension with cesarean section before labor.[36] Exposure to SSRIs in the first trimester did not increase the risk of miscarriage.[34]

Anticoagulants

Anticoagulation for various thrombotic diseases is important to prevent new or recurrent embolization. Warfarin (Coumadin and various generic formulations) has been associated with *chondrodysplasia punctata*, which is similar to the genetically determined Conradi-Hünermann syndrome. **Warfarin embryopathy occurs in about 5% of exposed pregnancies; it includes nasal hypoplasia, bone stippling seen on radiologic examination, ophthalmologic abnormalities including bilateral optic atrophy, and mental retardation (Fig. 7.7).** Ophthalmologic abnormalities and mental retardation may occur even with use only beyond the first trimester. **The risk for pregnancy complications is higher when the mean daily dose of warfarin is more than 5 mg. If warfarin is prescribed, maintaining the consistency of drug formulation (e.g., not switching generic formulations or brands) minimizes the risks of adverse events.**

The alternative drugs, heparin or enoxaparin, do not cross the placenta because their molecules are too large. **Heparin is the drug of choice in anticoagulation therapy for pregnant women without heart valves who require anticoagulation.** Patients receiving more than 20,000 U/day of heparin for long periods (>20 weeks) should be monitored for bone density reduction; high-dose heparin increases the risk of spinal fractures fourfold. **Low-molecular-weight heparins (LMWHs) may have substantial benefits over standard unfractionated heparin (UFH).** The molecules are still relatively large and do not cross the placenta. The half-life is longer, allowing for once-daily administration. **However, enoxaparin (Lovenox) is cleared more rapidly during pregnancy; therefore twice-daily dosing is advised.** LMWHs have a much more predictable dose-response relationship, thus obviating the need for monitoring partial thromboplastin time. There is less risk of heparin-induced thrombocytopenia and clinical bleeding at delivery, but studies suggesting less risk of osteoporosis are preliminary.

Women with mechanical heart valves, especially the first-generation valves, require warfarin anticoagulation or LMWH because heparin is not safe or effective. Heparin treatment is also associated with more thromboembolic complications and more bleeding complications than warfarin therapy. Evaluation of pooled incidences (95% confidence intervals) in a large meta-analysis comparing warfarin treatment, LMWH, and heparin, maternal mortality occurred in 0.9% (95% CI, 0.4–1.4), 2.0% (95% CI, 0.8–3.1), and 2.9% (95% CI, 0.2–5.7): thromboembolic complications in 2.7% (95% CI, 1.4–4.0), 5.8% (95% CI, 3.8–7.7), and 8.7% (95% CI, 3.9–13.4); live births in 64.5% (95% CI, 48.8–80.2), 79.9% (95% CI, 74.3–85.6), and 92.0% (95% CI, 86.1–98.0); anticoagulant-related fetal adverse events (embryopathy) occurred in 2.0% (95% CI, 0.3–3.7), 1.4% (95% CI, 0.3–2.5), and 0%, respectively. When UFH was used throughout pregnancy, 11.2% (95% CI, 2.8–19.6) of the women suffered thromboembolic complications. Stillbirth occurred with first-trimester warfarin doses equal to or greater than 5 mg/day, although there were more live births (83.6% [95% CI, 75.8–91.4] vs. 43.9% [95% CI, 32.8–55.0]) and fewer malformations (2.3% [95% CI, 0.7–4.0] vs. 12.4% [95% CI, 3.3–21.6]) with lower doses than with warfarin in doses greater than 5 mg/day.[38]

Thyroid and Thyroid-Blocking Drugs

Propylthiouracil (PTU) and methimazole (Tapazole) both cross the placenta and may cause some degree of fetal goiter. In contrast, the thyroid hormones triiodothyronine and thyroxine cross the placenta

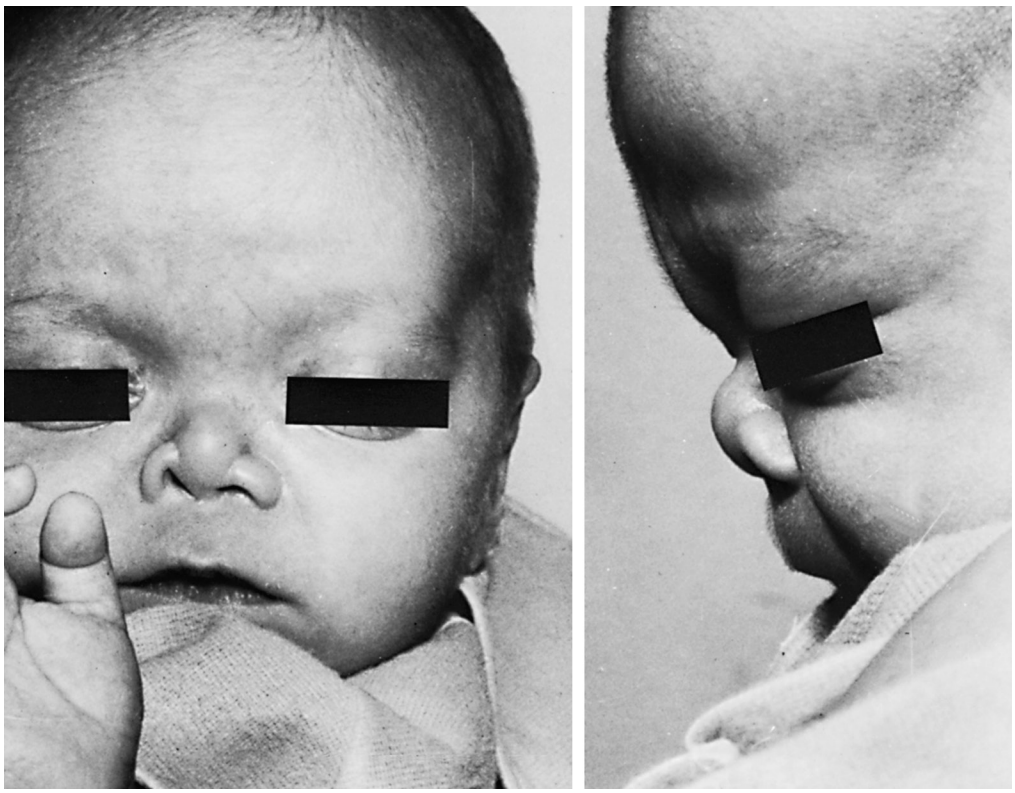

Fig. 7.7 Warfarin Embryopathy. Note the small nose with hypoplastic bridge. (From Shaul W, Hall JG. Multiple congenital anomalies associated with oral anticoagulants. *Am J Obstet Gynecol.* 1977;127:191.)

poorly, so that fetal hypothyroidism produced by antithyroid drugs cannot be corrected satisfactorily by administering thyroid hormone to the mother. Thus the goal of such therapy during pregnancy is to keep the mother slightly hyperthyroid to minimize fetal drug exposure. By the third trimester, 30% of women no longer need antithyroid medication.[40]

Methimazole has been associated with scalp defects in infants and choanal or esophageal atresia[40] as well as a higher incidence of maternal side effects. However, PTU and methimazole are equally effective and safe for the treatment of hyperthyroidism. **In 2009 the FDA released a black box warning highlighting serious liver injury with PTU treatment, to a greater extent than methimazole. The Endocrine Society is now advocating treatment with PTU only during the first trimester and switching to methimazole for the remainder of the pregnancy.**[41, 42]

Radioactive iodine (^{131}I or ^{125}I) administered for thyroid ablation or for diagnostic studies is not concentrated by the fetal thyroid until after 12 weeks of gestation. Thus, with inadvertent exposure before 12 weeks, there is no specific risk to the fetal thyroid from ^{131}I or ^{125}I administration.

The need for thyroxine increases in many women with primary hypothyroidism when they are pregnant, as reflected by an increase in serum thyroid-stimulating hormone (TSH) concentrations.[43] Because hypothyroidism in pregnancy may adversely affect the fetus, possibly by increasing prematurity, it is prudent to monitor thyroid function throughout pregnancy and to adjust the thyroid dose to maintain a normal TSH level. **It is recommended that women with hypothyroidism increase their levothyroxine dose by approximately 30% as soon as pregnancy is confirmed (two extra doses each week) and then have dosing adjustments based on TSH levels.**[43]

Antihypertensive Drugs (See Also Chapter 31)

α methyldopa (Aldomet and various generic formulations) has been widely used for the treatment of chronic hypertension in pregnancy. Although postural hypotension may occur, no unusual fetal effects have been noted. Hydralazine (Apresoline) is used frequently in pregnancy and no teratogenic effect has been observed.

Sympathetic Blocking Agents. Propranolol (Inderal) is a β-adrenergic blocking agent in widespread use for various indications. No evidence of teratogenicity has been found. Bradycardia has been reported in the newborn as a direct effect of a dose of the drug given to the mother within 2 hours of delivery.

Calcium channel blockers—for example, nifedipine (Procardia) and amlodipine—have been widely used to treat chronic hypertension in pregnancy without evidence of teratogenicity. Magnesium sulfate should be used with caution in women on these agents.

Angiotensin-Converting Enzyme Inhibitors and Angiotensin Receptor Blockers. Fetal exposure in the first trimester is not associated with an increased risk of birth defects. **Angiotensin-converting enzyme (ACE) inhibitors (e.g., enalapril [Vasotec and various generic formulations], captopril [Capoten and various generic formulations]), and angiotensin II receptor blockers (e.g., valsartan [Diovan]) can cause fetal renal tubular dysplasia in the second and third trimesters, leading to oligohydramnios, fetal limb contractures, craniofacial deformities, and hypoplastic lung development.** Fetal skull ossification defects have also been described. **For these reasons, women on these medications who plan pregnancy should be switched to other agents.**

Antineoplastic and Immunosuppressant Drugs

When cancer chemotherapy must be used during embryogenesis, there is an increased rate of spontaneous abortion and major birth defects. Later in pregnancy, there is a greater risk of stillbirth and intrauterine growth restriction, and myelosuppression is often present in the infant. **Mycophenolate mofetil (CellCept) carries a moderate teratogenic risk.**[44] Frequent features include microtia or anotia, cleft lip and/or palate, heart defects, and dysmorphic facial features. The numbers are too small to determine the actual rate of malformations.

Methotrexate, a folic acid antagonist, appears to be a human teratogen, although experience is limited. Methotrexate is known to inhibit the proliferation of the trophoblast; thus, when used in early pregnancy, it is associated with a high rate of miscarriage. Infants of three women known to have received methotrexate in the first trimester of pregnancy who continued with the pregnancy had babies with multiple congenital anomalies, including cranial defects and malformed extremities. Of eight women inadvertently treated with methotrexate due to misdiagnoses of ectopic pregnancy, two bore severely malformed infants, three miscarried, and three chose to terminate their pregnancies.[45]

Azathioprine (Imuran and various generic formulations) has been used by patients with renal transplants or systemic lupus erythematosus. The frequency of anomalies in 375 women treated in the first trimester was not increased. Some infants had leukopenia, some were small for gestational age, and the others were normal.

No increased risk of anomalies in fetuses exposed to cyclosporine (Sandimmune) in utero has been reported. An increased rate of prematurity and growth restriction has been noted, but it is difficult to separate the contributions of the underlying disease and the drugs given to these transplant patients. The B-cell line may be depleted more than the T-cell line, and one author recommends that infants exposed to immunosuppressive agents be followed for possible immunodeficiency.

Eight malformed infants were born after first-trimester exposure to cyclophosphamide (Cytoxan), but these infants were also exposed to other drugs or radiation. Low birthweight may be associated with the use of this drug after the first trimester, but this may also reflect the underlying medical problem.

Chloroquine (Aralen) is safe in doses used for malarial prophylaxis, and there was no increased incidence of birth defects among 169 infants exposed to 300 mg once weekly. However, after exposure to larger antiinflammatory doses (250 to 500 mg/day), two cases of cochleovestibular paresis were reported.[46] No abnormalities were noted in 114 other infants.

No association was found between the administration of the tumor necrosis factor (TNF) inhibitors infliximab (Remicade) or adalimumab (Humira) and congenital anomalies.[47]

Bronchodilators

Terbutaline (Brethine and Various Generic Formulations). Terbutaline has been widely used in the treatment of preterm labor. It is more rapid in onset and has a longer duration of action than epinephrine; it is preferred for the treatment of asthma in the pregnant patient. No risk of birth defects has been reported. Long-term use has been associated with an increased risk of glucose intolerance.

Cromolyn Sodium (Intal). Cromolyn sodium may be administered in pregnancy; the systemic absorption is minimal. Teratogenicity in humans has not been reported.

Isoproterenol (Isuprel) and Metaproterenol (Alupent). When isoproterenol and metaproterenol are given as topical aerosols for the treatment of asthma, the total dose absorbed is usually not significant. With oral or intravenous doses, however, the cardiovascular effects of these agents may decrease uterine blood flow. For this reason they should be used with caution. No teratogenicity has been reported.

Corticosteroids. All steroids cross the placenta to some degree, but prednisone (Deltasone and various generic formulations) and prednisolone are inactivated by the placenta. When prednisone or prednisolone

(Depo Medrol and various generic formulations) is maternally administered, the concentration of active compound in the fetus is less than 10% of that in the mother. Therefore these agents are the drugs of choice for treating medical diseases such as asthma. Inhaled and intranasal corticosteroids are also effective therapy and very little drug is absorbed. When steroid effects are desired in the fetus to accelerate lung maturity, betamethasone (Celestone) and dexamethasone (Decadron) are preferred because they are minimally inactivated by the placenta. **A meta-analysis of exposure to corticosteroids in the first trimester showed an odds ratio of 3.0 for cleft lip and/or cleft palate.**

Iodide. Iodide, such as found in a saturated solution of potassium iodide (SSKI) expectorant, crosses the placenta and may produce a fetal goiter large enough to produce respiratory obstruction in the newborn (Fig. 7.8). Before a pregnant patient is advised to take a cough medicine, it is important to ascertain that it does not contain iodide.

Antinausea and Motion Sickness Drugs

Remedies suggested to help nausea and vomiting in pregnancy without pharmacologic intervention include eating crackers at the bedside on first awakening in the morning (before getting out of bed), getting up very slowly, omitting iron tablets, consuming frequent small meals, and eating protein snacks at night. **None of the medications used to treat nausea and vomiting have been found to be teratogenic.**

Doxylamine. Delayed release doxylamine 10 mg plus pyridoxine 10 mg (Diclegis) is effective and well tolerated.[48] **Doxylamine (Unisom Sleeptabs) is an effective antihistamine for nausea in pregnancy and can be combined with vitamin B_6 to produce a therapy similar to Diclegis.** Vitamin B_6 (25 mg) and doxylamine (25 mg) at bedtime and 12.5 mg doxylamine (a half tablet) with vitamin B_6 (25 mg) in the morning and afternoon is an effective combination.

Meclizine (Bonine and Various Generic Formulations). In one randomized placebo-controlled study, meclizine gave significantly better results than placebo. Prospective clinical studies have provided no evidence that meclizine is teratogenic in humans. In 1014 patients in the Collaborative Perinatal Project and an additional 613 patients from the Kaiser Health Plan, no teratogenic risk was found.

Dimenhydrinate (Dramamine). No teratogenicity has been noted with dimenhydrinate, but a 29% failure rate and a significant incidence of side effects, especially drowsiness, has been reported.

Diphenhydramine (Benadryl). In 595 patients treated in the Collaborative Perinatal Project, no teratogenicity was noted with diphenhydramine. Drowsiness can be a problem.

Phenothiazines. Evaluated as a group, the phenothiazines do not appear to pose a problem of teratogenicity. In the Kaiser Health Plan Study, 976 patients were treated, and in the Collaborative Perinatal Project, 1309 patients were treated; in both studies no evidence of an association between these drugs and malformations was noted. In 114 women treated with promethazine (Phenergan) and 877 given prochlorperazine (Compazine), no increased risk of malformations was found.

Metoclopramide. **Of 3458 infants exposed to metoclopramide (Reglan and various generic formulations) during the first trimester, no increased risk of malformations, low birthweight, or preterm delivery was found.**[49]

Ondansetron (Zofran and Various Generic Formulations). Ondansetron is no more effective than promethazine (Phenergan and various generic formulations), but it is less sedating.[48] It has not been associated

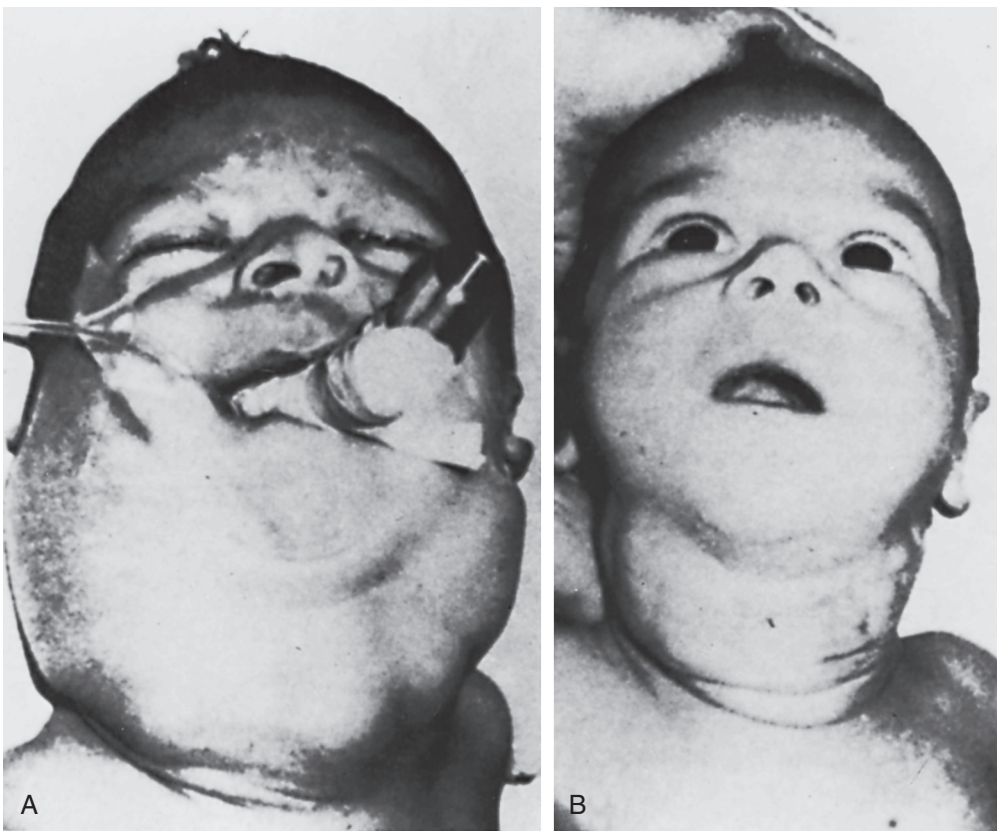

Fig. 7.8 Iodide-Induced Neonatal Goiter. (A) Appearance on the first day of life. (B) Appearance at 2 months of age. (From Senior B, Chernoff HL. Iodide goiter in the newborn. *Pediatrics*. 1971;47:510.)

with a significant risk for adverse fetal outcomes.[49] One study showed no increased risk of birth defects after ondansetron exposure.[50] However, a larger study[51] found a doubling in the prevalence of heart defects in newborns who had been exposed.

Methylprednisolone. Forty patients with hyperemesis who were admitted to the hospital were randomized to oral methylprednisolone or oral promethazine, and methylprednisolone was found to be more effective.[5] In a larger study in which all patients received both promethazine and metoclopramide, methylprednisolone did not reduce the need for readmission. **The drug should be used only after 10 weeks of pregnancy owing to the potential risk of cleft lip and/or cleft palate.**

Ginger. **Ginger has been used with success for treating both hyperemesis and nausea/vomiting in the outpatient setting.** Significantly greater relief of symptoms was found after ginger treatment than with placebo. Patients took 250-mg capsules containing ginger as powdered root four times a day.

Acid-Suppressing Drugs

After 2261 exposures, the use of omeprazole and ranitidine was not found to be associated with any teratogenic risk.[54] Of an additional 3651 infants who were exposed to proton-pump inhibitors in the first trimester, no increased risk of birth defects was found.[55] Drugs taken were mostly omeprazole but also included lansoprazole, esomeprazole, and pantoprazole.

Antihistamines and Decongestants

No increased risk of anomalies has been associated with most of the commonly used antihistamines, such as chlorpheniramine (Chlor-Trimeton). **However, in one study terfenadine (Seldane) has been associated with an increased risk of polydactyly.** Astemizole (Hismanal) did not increase the risk of birth defects in 114 infants exposed in the first trimester.

An increased risk of birth defects was noted with phenylpropanolamine (Entex LA and various generic formulations) exposure in the first trimester, specifically ear defects and pyloric stenosis.[56] In one retrospective study, an increased risk of gastroschisis was associated with first-trimester pseudoephedrine (Sudafed) use. Phenylephrine has been associated with endocardial cushion defects.[56] Use of these drugs for trivial indications should be discouraged because their long-term effects are unknown. If decongestion is necessary, topical nasal sprays will result in a lower dose to the fetus than systemic medications.

Antibiotics and Antiinfective Agents

Because pregnant patients are particularly susceptible to vaginal yeast infections, antibiotics should be used only when clearly indicated. However, it may be important to treat sexually transmitted diseases (STDs); if left untreated, STDs may contribute to low birthweight, preterm birth, and spontaneous abortion. Physiologic changes in pregnancy lead to an increase in glomerular filtration and enhanced elimination of antibiotics; dosage adjustments (increases) may be necessary to ensure an appropriate serum level of drug.

Penicillins. Penicillin, ampicillin, and amoxicillin (Amoxil) are safe to use in pregnancy. In the Collaborative Perinatal Project, 3546 mothers took penicillin derivatives in the first trimester of pregnancy with no increased risk of anomalies. Among 86 infants exposed to dicloxacillin in the first trimester, there was no increase in birth defects.

Clavulanate is added to penicillin derivatives to broaden their antibacterial spectrum. Of 556 infants exposed in the first trimester, no increased risk of birth defects was observed. Amoxicillin/clavulanate (Augmentin) was studied in randomized controlled trials as potential therapy for chorioamnionitis in women with preterm premature rupture of membranes. During this trial, amoxicillin/clavulanate was compared with both placebo and erythromycin. An increased incidence of necrotizing enterocolitis was found in the amoxicillin/clavulanate group when compared with both the placebo and erythromycin groups. It has been suggested that amoxicillin/clavulanate selects for specific pathogens, which leads to abnormal microbial colonization of the gastrointestinal tract and ultimately the initiation of necrotizing enterocolitis. **Therefore amoxicillin/clavulanate should be avoided in women at risk for preterm delivery.**

Cephalosporins. In a study of 5000 Michigan Medicaid recipients, there was a suggestion of possible teratogenicity (25% increased birth defects) with cefaclor, cephalexin, and cephradine but not with other cephalosporins. However, another study of 308 women exposed in the first trimester showed no increase in malformations. **The consensus is that these drugs are safe.**

Sulfonamides. Among 1455 infants exposed to sulfonamides during the first trimester, no teratogenic effects were noted. However, the administration of sulfonamides should be avoided in women deficient in glucose-6-phosphate dehydrogenase (G6PD) because dose-related hemolysis may occur.

Sulfonamides cause no known damage to the fetus in utero because the fetus can clear free bilirubin through the placenta. These drugs might theoretically have deleterious effects if they are present in the blood of the neonate after birth, however. Sulfonamides compete with bilirubin for binding sites on albumin, thus raising the levels of free bilirubin in the serum and increasing the risk of hyperbilirubinemia in the neonate. Although this toxicity occurs with direct administration to the neonate, kernicterus in the newborn following in utero exposure has not been reported.

Sulfamethoxazole With Trimethoprim (Bactrim, Septra, and Various Generic Formulations). Trimethoprim is often given with sulfa to treat urinary tract infections. However, one unpublished study of 2296 Michigan Medicaid recipients suggested an increased risk of cardiovascular defects after exposure in the first trimester. **In one retrospective study of trimethoprim/sulfamethoxazole, the odds ratio for birth defects was 2.3, whereas in another study it was 2.5 to 3.4.**

Nitrofurantoin (Macrodantin and Various Generic Formulations). Nitrofurantoin is used in the treatment of acute uncomplicated lower urinary tract infections as well as for long-term suppression in patients with chronic bacteriuria. Nitrofurantoin is capable of inducing hemolytic anemia in patients deficient in G6PD. However, hemolytic anemia in the newborn as a result of in utero exposure to nitrofurantoin has not been reported.

No reports have associated nitrofurantoins with congenital defects. In the Collaborative Perinatal Project, 590 infants were exposed, 83 in the first trimester, with no increased risk of adverse effects. In another study[57] including 1334 women exposed in the first trimester, there was no increase in malformations. Use in the last 30 days before delivery was associated with an increased risk of neonatal jaundice.

Tetracyclines. **Tetracyclines readily cross the placenta and are firmly bound by chelation to calcium in developing bone and tooth structures. This produces brown discoloration of the deciduous teeth, hypoplasia of the enamel, and inhibition of bone growth. The staining of the teeth takes place in the second or third trimesters of pregnancy, whereas bone incorporation can occur earlier.** Depression of skeletal growth was particularly common among premature infants treated with tetracycline. **First-trimester exposure to doxycycline is not known to carry any risk. First-trimester exposure to tetracyclines was not found to have any teratogenic risk in 341 women in the Collaborative Perinatal Project or in 174 women in another study. Alternate antibiotics are currently recommended during pregnancy.**

Aminoglycosides. Streptomycin and kanamycin have been associated with congenital deafness in the offspring of mothers who took these drugs during pregnancy. Ototoxicity was reported with doses as low as 1 g of streptomycin twice a week for 8 weeks during the first trimester. Among 391 mothers who had received 50 mg/kg of kanamycin for prolonged periods during pregnancy, 9 of their children (2.3%) were later found to have hearing loss.

Nephrotoxicity may be greater when aminoglycosides are combined with cephalosporins. Neuromuscular blockade may be potentiated by the combined use of aminoglycosides and curariform drugs. Potentiation of magnesium sulfate–induced neuromuscular weakness has also been reported in a neonate exposed to magnesium sulfate and gentamicin.

No known teratogenic effect other than ototoxicity has been associated with aminoglycosides in the first trimester. In 135 infants exposed to streptomycin in the Collaborative Perinatal Project, no teratogenic effects were observed. Among 1619 newborns whose mothers were treated for tuberculosis with multiple drugs including streptomycin, the incidence of congenital defects was the same as in a healthy control group.

Antituberculosis Drugs. There is no evidence of any teratogenic effect of isoniazid, para-aminosalicylic acid, rifampin (Rifadin), or ethambutol (Myambutol).

Erythromycin. No teratogenic risk associated with erythromycin has been reported. In 79 patients in the Collaborative Perinatal Project and 260 in another study, no increase in birth defects was noted.

Clarithromycin. After 122 first-trimester exposures, no significant risk of birth defects was found.

Fluoroquinolones. The quinolones (e.g., ciprofloxacin [Cipro] and norfloxacin [Noraxin]) have a high affinity for bone tissue and cartilage; therefore they may cause arthralgia in children. However, no malformations or musculoskeletal problems were noted in 38 infants exposed in utero in the first trimester, in 132 newborns exposed in the first trimester in the Michigan Medicaid data, or in 200 other first-trimester exposures.

Metronidazole (Flagyl). **Studies have failed to show any increase in the incidence of congenital defects among the newborns of mothers treated with metronidazole during early or late gestation.** Among 1387 prescriptions filled, no increase in birth defects could be determined. A meta-analysis confirmed lack of teratogenic risk.

Newer Antibiotics. There are limited data to support the safety of newer antibiotics such as linezolid and quinopristin/dalfopristin. A case report, however, says that daptomycin was used safely in a pregnant patient with a urinary tract infection resistant to vancomycin.

Antiviral Agents

The Acyclovir Registry has recorded 756 first-trimester exposures with no increased risk of abnormalities in the infants.[58] Among 1561 pregnancies exposed to acyclovir, 229 exposed to valacyclovir, and 26 exposed to famciclovir, all in the first trimester, there was no increased risk of birth defects.[59] The Centers for Disease Control and Prevention (CDC) recommends that pregnant women with disseminated infection (e.g., herpetic encephalitis, hepatitis, or varicella pneumonia) be treated with acyclovir.

Lindane (Kwell). After application of lindane to the skin, about 10% of the dose used can be recovered in the urine. Toxicity in humans after use of topical 1% lindane has been observed almost exclusively after misuse and overexposure to the agent. Although no evidence of specific fetal damage is attributable to lindane, the agent is a potent neurotoxin, and its use during pregnancy should be limited. Pregnant women should be cautioned about shampooing their children's hair, because absorption could easily occur across the skin of the hands. An alternate drug for lice is usually recommended, such as pyrethrins with piperonyl butoxide (RID).

Antiretroviral Agents

Zidovudine (ZDV) should be included as a component in the antiretroviral regimen whenever possible because of its record of safety and efficacy. In a prospective cohort study, children exposed to ZDV in the perinatal period through the Pediatric AIDS Clinical Trials Group Protocol 076 were studied up to a median age of 4.2 years. No adverse effects were observed in these children. The International Antiretroviral Registry was established in 1989 to detect any major teratogenic effect of the antiretroviral drugs. Through January 2004, more than 1000 pregnancies had first-trimester exposures to ZDV and lamivudine and no increase in teratogenicity was reported.

Concerns have been raised regarding use of other antiretroviral therapies. Efavirenz is not recommended during pregnancy owing to reports of significant malformations in monkeys receiving efavirenz during the first trimester and also three case reports of fetal NTDs in the babies of women who had received the drug.[60] In 2001, Bristol-Myers Squibb issued a warning advising against the use of didanosine and stavudine in pregnant women because of case reports of lactic acidosis, some of which were fatal. These two drugs should be used only if no other alternatives are available.

Antifungal Agents

Nystatin (Mycostatin) is poorly absorbed from intact skin and mucous membranes, and its topical use has not been associated with teratogenesis. Clotrimazole (Lotrimin) or miconazole (Monistat) in pregnancy is not known to be associated with congenital malformations. However, in one study, a statistically significantly increased risk of first-trimester abortion was noted after use of these drugs, but these findings were considered not to be definitive evidence of risk. Of 2092 newborns who had been exposed in the first trimester in the Michigan Medicaid data, there was no increased risk of anomalies.

Limb deformities were reported in three infants exposed to 400 to 800 mg/day of fluconazole in the first trimester. However, in systematic studies of 460 patients who received a single 150-mg dose of fluconazole, no increased risk of defects was observed.[61] In one registry study,[62] fluconazole was associated with an increased risk of tetralogy of Fallot.

Drugs for Induction of Ovulation

In more than 2000 exposures, no evidence of teratogenic risk of clomiphene (Clomid, various generic formulations) has been noted, and the percentage of spontaneous abortions is close to the expected rate. Although infants are often exposed to bromocriptine (Parlodel) in early pregnancy, no teratogenic effects have been observed in more than 1400 pregnancies.

Analgesic Drugs

Aspirin. There is no evidence of any teratogenic effect of aspirin taken in the first trimester. **Aspirin does have antiplatelet effects and reduces uterine contractility through prostaglandin inhibition, and there is a risk of bleeding.**

Acetaminophen (Tylenol, Datril, and Various Generic Formulations). Acetaminophen has also shown no evidence of teratogenicity.[63] **Bleeding time is not prolonged with acetaminophen, in contrast to aspirin;** acetaminophen is therefore preferred in pregnancy.

Patients should be counseled on the risks associated with taking excessive amounts of acetaminophen. Chronic doses of greater than 4 g/day (eight extra-strength or 12 regular-strength acetaminophen) are associated with acute liver injury, leading to liver fibrosis, cirrhosis, and liver failure. Patients should understand the doses of acetaminophen in all the products taken for pain to avoid exceeding the 4-g daily limit.

Other Nonsteroidal Antiinflammatory Agents. No evidence of teratogenicity has been reported for other nonsteroidal antiinflammatory

drugs (e.g., ibuprofen [Motrin, Advil], naproxen [Naprosyn], diclofenac [Zorvolex], and piroxicam [Feldene]).[64, 65] Chronic use may lead to oligohydramnios, and constriction of the fetal ductus arteriosus or neonatal pulmonary hypertension—as has been reported with indomethacin—might occur.

Codeine. In the Collaborative Perinatal Project, no increased relative risk of malformations was observed in 563 codeine users. In one recent study, maternal treatment with opioid analgesics was associated with an increased risk of heart defects, spina bifida, and gastroschisis. **Codeine can cause addiction and newborn withdrawal symptoms if used to excess perinatally.**

Sumatriptan. Of 479 exposures to sumatriptan (Imitrex) in the first trimester,[66] 4.6% of infants had birth defects, not significantly different from the nonexposed population. **For women whose severe headaches do not respond to other therapy, sumatriptan may be used during pregnancy.**[67]

Bisphosphonates. The bisphosphonate drug class represents a group of medications used to treat a variety of bone disorders including osteoporosis and Paget disease and for controlling excess blood calcium in the setting of cancer or after chemotherapy. A published review of case reports for the bisphosphonate drug class (alendronate, ibandronate, risedronate, etidronate, pamidronate, tiludronate, and zoledronic acid) in both short- and long-term use showed no serious fetal or neonatal adverse effects. Marginal decreases in gestational age, birthweight, and neonatal abnormalities are possibly attributed to the use of bisphosphonate. The decision to continue bisphosphonate use in pregnancy is based on the patient's duration and amount of osteopenia or osteoporosis. Patients should also be counseled on appropriate calcium and vitamin D supplementation, which mitigates the risk of bone-related issues.[67a]

DRUGS OF ABUSE

Smoking and Nicotine Replacement Therapies

Smoking is associated with a fourfold increase in newborns who are small for gestational age as well as an increased prematurity rate. **The higher perinatal mortality rate associated with smoking is related to the number of cigarettes smoked, also increasing the risk of abruptio placentae, placenta previa, premature and prolonged rupture of membranes, and intrauterine growth restriction.** Maternal passive smoking was also associated with spontaneous abortion, a twofold risk of low birthweight at term, increased respiratory illness in children, and possibly sudden infant death syndrome (SIDS). Electronic cigarettes and other forms of smoking, such as a hookah, may be perceived as safe alternatives to cigarettes during pregnancy. A survey of pregnant women agreed that electronic cigarettes were harmful to the fetus; however, they were considered acceptable when used as a smoking cessation intervention.[68]

As the pregnant patient makes the decision to quit smoking, nicotine withdrawal may be simply managed by switching to brands of cigarettes with progressively less nicotine over a 3-week period. **Nicotine-containing medications are indicated for patients with nicotine dependence,** defined as smoking greater than one pack a day, smoking within 30 minutes of getting up in the morning, or prior withdrawal symptoms. **Although one might question the logic of prescribing nicotine during pregnancy, cessation of smoking eliminates many other toxins, including carbon monoxide; nicotine-containing medications do not increase blood levels of nicotine over those of smokers.** In a randomized trial,[69] adding a nicotine patch to behavioral cessation support did not increase the rate of abstinence from smoking until delivery.

Congenital anomalies occurred in 5 of 188 infants of women treated with bupropion (Zyban) during the first trimester of pregnancy—not a significant difference from the number expected. There is no knowledge regarding the safety of varenicline (Chantix) use in pregnancy.[70] However, both of these medications have recently had product warnings mandated by the FDA about the risk of psychiatric symptoms and suicide associated with their use.

Alcohol

The FAS includes the features of gross physical retardation, with an onset prenatally and continuing after birth (Fig. 7.9). **FAS occurs in 6% of infants of heavy drinkers, and less severe birth defects and neurocognitive deficits occur in a larger proportion of children whose mothers drink heavily during pregnancy.** FAS is diagnosed by finding at least one of the following characteristics:

1. Growth retardation before and/or after birth
2. Facial anomalies, including small palpebral fissures, indistinct or absent philtrum, epicanthic folds, flattened nasal bridge, short length of nose, thin upper lip, low-set uneven ears, and retarded midfacial development
3. Central nervous system dysfunction including microcephaly, varying degrees of developmental disabilities, or other evidence of abnormal neurobehavioral development

Sokol et al. have addressed history taking for the prenatal detection of risk drinking. Four questions help in differentiating those patients who drink enough to potentially damage the fetus (Box 7.2). The patient is considered at risk if more than two drinks are required to make her feel "high." The probability of "risk drinking" increases to 63% for those responding positively to all four questions in Box 7.2.

Although Ouellette and colleagues addressed the risks of smaller amounts of alcohol, we stress that *any* consumption of alcohol is not safe in pregnancy. Nine percent of infants of abstinent or rare drinkers and 14% of infants of moderate drinkers were abnormal—not a significant difference. **In heavy drinkers (average daily intake of 3 oz of 100-proof liquor or more), 32% of the infants had anomalies. The reduction of alcohol intake in midpregnancy alone can reduce fetal risk.**[71] The aggregate pool of anomalies, growth restriction, and an abnormal neurologic examination was found in 71% of the children of heavy drinkers, twice the frequency in the moderate and rarely drinking groups. In this study, an increased frequency of abnormality was not found until 45 mL of ethanol (equivalent to three drinks) daily were exceeded.

Marijuana

No significant teratogenic effects of marijuana have been documented, but the data are insufficient to say that there is no risk. As more US states legalize the use of marijuana, obstetricians will be asked more

BOX 7.2 T-ACE Questions Found to Identify Women Drinking Sufficiently to Potentially Damage the Fetus

T How many drinks does it take to make you feel high (can you hold) (*tolerance*)?
A Have people *annoyed* you by criticizing your drinking?
C Have you felt you ought to *cut down* on your drinking?
E Have you ever had to drink first thing in the morning to steady your nerves or to get rid of a hangover (*eye-opener*)?

Two points are scored as a positive answer to the tolerance question and one each for the other three. A score of ≥2 correctly identified 69% of risk drinkers.

From Sokol RJ, Martier SS, Ager JW. The T-ACE questions: practical prenatal detection of risk-drinking. *Am J Obstet Gynecol.* 1989;160:863.

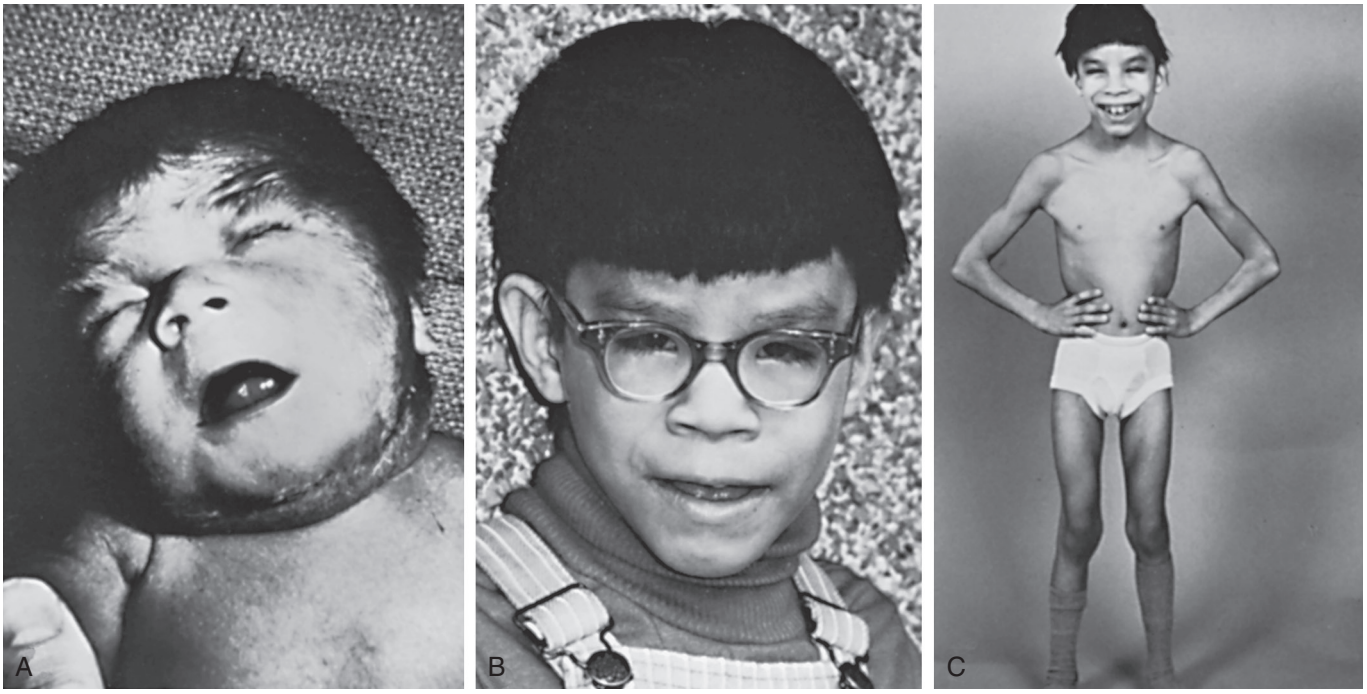

Fig. 7.9 Fetal Alcohol Syndrome. Patient photographed at (A) birth, (B) 5 years, and (C) 8 years. Note the short palpebral fissures, short nose, hypoplastic philtrum, thinned upper lip vermilion, and flattened midface. (From Streissguth AP. *CIBA Foundation Monograph 105*. London: Pitman; 1984.)

questions regarding its safety. One study, which found a mean 73-g decrease in birthweight associated with marijuana use, validated exposure with urine assays rather than relying on self-reporting. Other studies have not shown an effect on birthweight or length. Behavioral and developmental alterations have been observed in some studies but not others.

Cocaine

Mothers using cocaine often abuse other drugs, smoke, have poor nutrition, fail to seek prenatal care, and live in poor socioeconomic conditions. All of these factors make it difficult to discern the fetal effects of cocaine. Also, the neural systems likely to be affected by cocaine are involved in neurologic and behavioral functions that are not easily quantitated by standard infant development tests.

Studies have suggested an increased risk of congenital anomalies after first-trimester cocaine use, most frequently affecting the cardiac and central nervous systems. In the study of Bingol et al., the malformation rate was 10% in cocaine users, 4.5% in "polydrug users," and 2% in controls. MacGregor et al. reported a 6% anomaly rate compared with 1% for controls.

Cocaine is a central nervous system stimulant and has local anesthetic and marked vasoconstrictive effects. Not surprisingly, **abruptio placentae has been reported to occur immediately after nasal or intravenous administration.**[72] Several studies have also noted increased stillbirths, preterm labor, premature birth, and small-for-gestational-age infants with cocaine use.

The most common brain abnormality in infants exposed to cocaine in utero is impairment of intrauterine brain growth as manifested by microcephaly.[73] In one study, 16% of newborns had microcephaly, compared with 6% of controls. Somatic growth is also impaired, so the growth restriction may be symmetric or characterized by a relatively low ratio of head circumference to abdominal circumference. Aside from causing congenital anomalies in the first trimester, cocaine has been reported to cause fetal disruption, presumably due to interruption of blood flow to various organs. Bowel infarction has been noted with unusual ileal atresia and bowel perforation. Limb infarction has resulted in missing fingers in a distribution different from the usual congenital limb anomalies. Central nervous system bleeding in utero may result in porencephalic cysts.

Opioids

The pregnant patient with narcotic addiction is at increased risk for abortion, prematurity, and growth restriction. Withdrawal should be treated aggressively in the neonatal period.[74] Medical intervention is more likely to involve methadone maintenance, with the goal being an individualized dose of approximately 20 to 40 mg/day to prevent the use of supplemental illicit drugs. Dose changes during the last trimester are avoided because of increased fetal complications and deaths due to in utero withdrawal. Buprenorphine (Subutex) is also an acceptable treatment for women addicted to opioids and their derivatives, and infants exposed have shorter durations of treatment for neonatal abstinence syndrome than infants exposed to methadone.

Methamphetamine

Methamphetamine use has not resulted in teratogenesis but does cause low birthweight and is not recommended to be used in pregnancy. Methamphetamine, often in the form of "crystal meth" is considered one of the greatest drug threats to society; however, it has lost much of its focus as a threat owing to the emerging problems with opioid analgesics. Methamphetamine is a preferred drug of abuse, since it causes an extreme euphoria, loss of appetite, and increased attention span. It is considered to be more addicting than cocaine, with the effects lasting for a longer time and a larger percentage of the drug remaining in the body.

In a large meta-analysis, 626 women taking amphetamines were compared with a control population showing that routine methamphetamine

users had smaller babies than did controls, as indicated by smaller head circumference and birthweight, younger gestational age at birth, and shorter body length. Methamphetamine as a stimulant may also increase blood pressure; there were no differences in pregnancy complications related to blood pressure control.[75]

Caffeine

There is no evidence of teratogenic effects of caffeine in humans. The Collaborative Perinatal Project showed no increased incidence of congenital defects in 5773 women taking caffeine in pregnancy, usually in a fixed-dose analgesic medication. The average cup of coffee contains about 100 mg of caffeine and a 12 oz can of caffeinated soda contains about 50 mg. Early studies suggested that the intake of greater than seven to eight cups of coffee per day was associated with low-birthweight infants, spontaneous abortions, prematurity, and stillbirths. However, these studies were not controlled for the concomitant use of tobacco and alcohol. **In one report that controlled for smoking, other habits, demographic characteristics, and medical history, no relationship was found between malformations, low birthweight, or shorter gestation and heavy coffee consumption.** When pregnant women consumed more than 300 mg of caffeine per day, one study suggested an increase in low-birthweight infants at term, or a weight below 2500 g at greater than 36 weeks.

Two other studies have shown conflicting results. One retrospective investigation reporting a higher risk of fetal loss was biased by ascertainment of the patients at the time of fetal loss, because these patients typically have less nausea and would be expected to drink more coffee. A prospective cohort study found no evidence that moderate caffeine use increased the risk of spontaneous abortion or growth restriction. **The American College of Obstetricians and Gynecologists concluded that moderate caffeine consumption (less than 200 mg/day) does not appear to be a major contributing factor to miscarriage or preterm birth, but the relationship to growth restriction remains undetermined.**[76]

DRUGS IN BREAST MILK

Short-term effects, if any, of most maternal medications on breastfed infants are mild and pose little risk to the infants.[77] Overall, only a small proportion of medications are contraindicated in breastfeeding mothers or associated with adverse effects on their babies. Of 838 breastfeeding women, 11.2% reported minor adverse reactions in the infants, but these reactions did not require medical attention. In 19%, antibiotics caused diarrhea; in 11%, narcotics caused drowsiness; in 9%, antihistamines caused irritability; and in 10%, sedatives, antidepressants, or antiepileptics caused drowsiness.[77] In discussions with patients, the benefits of breastfeeding must be weighed against the risks of not continuing certain medications that might interfere with the infant during breastfeeding (e.g., antidepressants).

The American Academy of Pediatrics has reviewed drugs in lactation[78, 79] and now refers providers to LactMed (http://toxnet.nlm.nih.gov) for information about the effects of specific drugs.

Drugs Commonly Listed as Contraindicated During Breastfeeding

Cytotoxic Drugs That May Interfere With the Cellular Metabolism of the Nursing Infant

Cyclosporine (Sandimmune), doxorubicin (Adriamycin), and cyclophosphamide (Cytoxan) may cause immune suppression in the infant, although data are limited with respect to these drugs. In general the potential risks posed by these drugs would outweigh the benefits of continuing nursing.[77]

Drugs of Abuse for Which Adverse Effects on the Infant During Breastfeeding Have Been Reported

Drugs of abuse such as amphetamines, methamphetamine, cocaine, heroin, lysergic acid diethylamide (LSD), marijuana, and phencyclidine are all contraindicated during breastfeeding because they are hazardous to the nursing infant and to the health of the mother.[79]

Radioactive Compounds That Require Temporary Cessation of Breastfeeding

Radiopharmaceuticals require variable intervals of interruption of nursing. The American Academy of Pediatrics[79] suggests consultation with a nuclear medicine physician to use the radionuclide with the shortest excretion time in breast milk. The mother may store breast milk and continue to pump to maintain milk production but discard the milk during therapy. The physician may reassure the patient by counting the radioactivity of the milk before nursing is resumed.

Drugs for Which the Effect on Nursing Infants Is Unknown but May Be of Concern

This category includes several classes of psychotropic drugs, amiodarone (associated with hypothyroidism), lamotrigine (potential for therapeutic serum concentration in the infant), metoclopramide (potential dopaminergic blocking but no reported detrimental effects), and metronidazole.[79]

Antianxiety, antidepressant, and antipsychotic agents are sometimes given to nursing mothers. Although there are no data about adverse effects in infants exposed to these drugs through breast milk, they could theoretically alter central nervous system function.[79] Some psychoactive drugs have been reported to appear in breast milk at levels approaching clinical significance (10% or more). These include bupropion, fluoxetine, citalopram, sertraline, and venlafaxine.[79] Fluoxetine (Prozac) is excreted in breast milk at low levels, so the infant receives approximately 6.7% of the maternal dose.[80] The level in the breastfed newborn is certainly lower than that during pregnancy.

Sertraline causes a decline in the levels of 5-hydroxytryptamine in mothers but not in their breastfed infants.[81] **This implies that the small amount of drug the infant ingests in breast milk is not enough to cause a pharmacologic effect (Fig. 7.10). Infants of mothers on psychotropic drugs should be monitored for sedation during use and for withdrawal after cessation of the drug.**

Temporary cessation of breastfeeding after a single dose of metronidazole (Flagyl) may be considered. Its half-life is such that interruption of lactation for 12 to 24 hours after single-dose therapy usually results in negligible exposure to the infant. However, no adverse effects in infants have been reported.

Drugs That Have Been Associated With Significant Effects in Some Nursing Infants and That Should Be Given to Nursing Mothers With Caution

Bromocriptine is an ergot alkaloid derivative. Because it has an inhibitory effect on lactation, it should be avoided unless the mother has taken it during the pregnancy.

Ergotamine, as used by those with migraine headaches, has been associated with vomiting, diarrhea, and convulsions in the infant. Administration of an ergot alkaloid for the treatment of uterine atony does not contraindicate lactation.

Breast milk levels of lithium are one-third to one-half maternal serum levels, and the infant's serum levels while nursing are much lower than the fetal levels that occur when the mother takes lithium during pregnancy. The benefits of breastfeeding must be weighed against the theoretical effects of small amounts of the drug on the developing brain.[79]

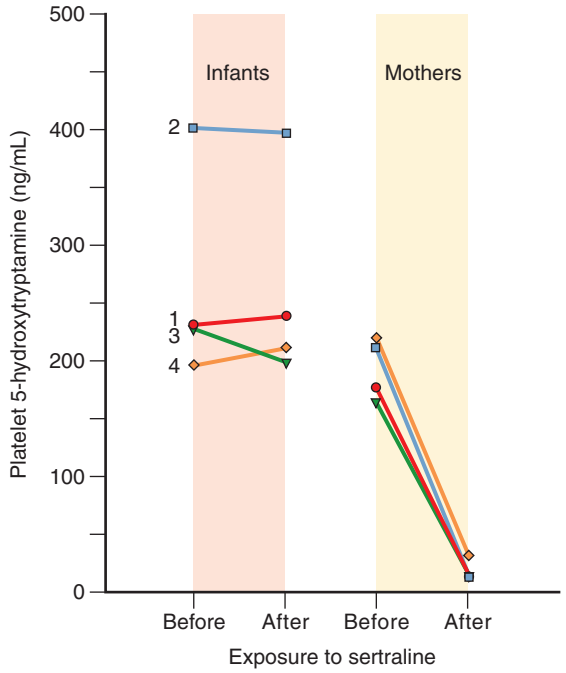

Fig. 7.10 Effect of Sertraline on Platelet 5-Hydroxytryptamine Levels in Four Breast-Fed Infants and Their Mothers. (From Epperson CN, Anderson GM, McDougle CJ. Sertraline and breast-feeding. *N Engl J Med.* 1997;336:1189. Copyright 1997, Massachusetts Medical Society.)

Maternal Medications Usually Compatible With Breastfeeding

Narcotics, Sedatives, and Anticonvulsants

In general no evidence of adverse effect is noted with most of the sedatives, narcotic analgesics, and anticonvulsants. Patients may be reassured that in normal doses, carbamazepine, phenytoin, magnesium sulfate, codeine, morphine, and meperidine do not cause any obvious adverse effects in the infants because the dose detectable in the breast milk is approximately 1% to 2% of the mother's dose, which is sufficiently low to have no significant pharmacologic activity.

Although short-term use of codeine by a breastfeeding mother appears to be harmless, there is one case where the mother was taking codeine and acetaminophen for episiotomy pain and breastfeeding. On day 7, the infant was lethargic and had difficulty feeding. The infant died on day 13. The mother was an ultra-rapid metabolizer who converted codeine to morphine at a rapid rate. The milk level of morphine was 87 ng/mL, whereas the infant's level was 70 ng/mL.[80a] **Because a mother's metabolizer status is rarely known, the use of any codeine product should be restricted to less than 2 days.**

In two patients who took carbamazepine (Tegretol) while nursing, the concentration of the drug in breast milk at 4 and 5 weeks postpartum was similar, about 60% of the maternal serum level. Accumulation does not seem to occur, and no adverse effects were noted in either infant.

Cold Preparations

No harmful effects of acetaminophen (Tylenol, Datril) have been noted. Although studies are not extensive, no harmful effects have been noted from antihistamines or decongestants. Less than 1% of a pseudoephedrine or triprolidine dose ingested by the mother is excreted in the breast milk.

Antihypertensives

After a single 500-mg oral dose of chlorothiazide (Diuril), no drug was detected in the patient's breast milk. In one mother taking 50 mg of hydrochlorothiazide (HydroDiuril) daily, the drug was not detectable in the nursing infant's serum, and the infant's electrolytes were normal. Thiazide diuretics may decrease milk production in the first month of lactation.

Propranolol (Inderal) is excreted in breast milk, with milk concentrations after a single 40-mg dose less than 40% of peak plasma concentrations. Thus an infant consuming 500 mL/day of milk would ingest an amount representing approximately 1% of a therapeutic dose, which is unlikely to cause any adverse effect.

Atenolol (Tenormin) is concentrated in breast milk to about three times the plasma level. One case has been reported in which a 5-day-old term infant had signs of beta-adrenergic blockade with bradycardia (at 80 beats/min) with the breast milk dose calculated to be 9% of the maternal dose. Adverse effects in other infants have not been reported. Because milk accumulation occurs with atenolol, infants must be monitored closely for bradycardia. Propranolol is a safer alternative.

Clonidine (Catapres) concentrations in milk are almost twice maternal serum levels. Neurologic and laboratory parameters in the infants of treated mothers are similar to those of controls.

Captopril (Capoten) is excreted into breast milk at low levels, and no effects on nursing infants have been observed.

Nifedipine is excreted into breast milk at a concentration of less than 5% of the maternal dose, and verapamil at an even lower level. Neither drug has caused adverse effects in the infant.

Anticoagulants

Most mothers requiring anticoagulation may continue to nurse their infants with no problems. Heparin does not cross into milk and is not active orally. At a maternal dose of warfarin (Coumadin and various generic formulations) of 5 to 12 mg/day in seven patients, no warfarin was detected in breast milk or infant plasma. This low concentration probably occurs because warfarin is 98% protein bound, and the milk would contain an insignificant amount of drug with no anticoagulant effect.[82] Another report confirmed that warfarin appears in only insignificant amounts in breast milk.[83] **Thus, with careful monitoring of maternal prothrombin time so that the dosage is minimized and of neonatal prothrombin times to ensure lack of drug accumulation, warfarin may be administered safely to nursing mothers.**

Corticosteroids

Prednisone enters breast milk in an amount not likely to have any deleterious effect. In a study of seven patients, 0.14% of a sample was secreted in the milk in the subsequent 60 hours, a negligible quantity. Even at 80 mg/day, the nursing infant would ingest less than 0.1% of the dose, or less than 10% of its endogenous cortisol.

Antibiotic and Other Antiinfective Drugs

Penicillin derivatives are safe in nursing mothers. With the usual therapeutic doses of penicillin or ampicillin, no adverse effects are noted in the infants. In susceptible individuals or with prolonged therapy, diarrhea and candidiasis are concerns.

Cephalosporins appear only in trace amounts in milk. In one study after cefazolin (Ancef, Kefzol) 500 mg was administered intramuscularly three times a day, no drug was detected in breast milk. After 2 g of cefazolin was administered intravenously, the infant was exposed less than 1% of the maternal dose.

Tooth staining or delayed bone growth from tetracyclines has not been reported after the drug was taken by a breastfeeding mother. This occurred probably because of the high binding capacity of the drug to calcium and protein, thus limiting its absorption from the milk. The amount of free tetracycline that would be available is too small to be significant.

Sulfonamides appear in only small amounts in breast milk and are ordinarily not contraindicated during nursing. However, these drugs are best avoided in premature, ill, or stressed infants in whom hyperbilirubinemia may be a problem, because the drug may displace bilirubin from binding sites on albumin. On the other hand, sulfasalazine was not detected in the breast milk of a mother taking this drug.[84]

Gentamicin (Garamycin) is transferred into breast milk, and half of nursing newborn infants have the drug detectable in their serum. The low levels detected would not be expected to cause clinical effects.

Nitrofurantoin (Macrodantin) is excreted into breast milk in very low concentrations. In one study, the drug could not be detected in 20 samples from mothers receiving 100 mg four times a day.

Erythromycin is excreted into breast milk in small amounts. There have been no reports of adverse effects on infants exposed to erythromycin in breast milk. Azithromycin (Zithromax) also appears in breast milk in low concentrations. Clindamycin (Cleocin) is excreted into breast milk at low levels, and nursing is usually continued during administration of this drug.

There are no reported adverse effects on the infant of isoniazid administered to nursing mothers, and its use is considered compatible with breastfeeding.[79]

Acyclovir is compatible with breastfeeding. If a mother takes 1 g/day, the infant receives less than 1 mg/day, a very low dose.

Antifungal Agents

No data are available with nystatin, miconazole, or clotrimazole in breast milk. However, with only small amounts absorbed vaginally, and poor oral bioavailability, this would not be expected to be a clinical problem. Infant exposure to ketoconazole in human milk was 0.4% of the therapeutic dose, again unlikely to cause adverse effects.

Oral Contraceptives

Estrogen and progestin combination oral contraceptives cause a dose-related suppression of milk production. Oral contraceptives containing 50 µg and more of estrogen during lactation have been associated with a shortened duration of lactation, decreased milk production, decreased infant weight gain, and decreased protein content of the milk. Lactation is inhibited to a lesser degree if the pill is started about 3 weeks postpartum and with lower doses of estrogen than 50 µg. Although the magnitude of the changes is low, they may be of nutritional importance, particularly in malnourished mothers.

An infant consuming 600 mL of breast milk daily from a mother using an oral contraceptive containing 50 µg of ethinyl estradiol receives a daily dose in the range of 10 ng of the estrogen. The amount of natural estradiol received by infants who consume a similar volume of milk from mothers not using oral contraceptives is estimated at 3 to 6 ng during anovulatory cycles and 6 to 12 ng during ovulatory cycles. No consistent long-term adverse effects on growth and development have been described.

Evidence indicates that norgestrel (Ovrette) is metabolized rather than accumulated by the infant, and to date no adverse effects from progestational agents taken by the mother have been identified. The American College of Obstetricians and Gynecologists recommends placement of the etonogestrel contraceptive implant 4 weeks or more after childbirth. Progestin-only contraceptives do not cause alterations in breast milk composition or volume, making them ideal for the breastfeeding mother. **Once the infant has been weaned, the mother should be switched to a combined oral contraceptive for maximum contraceptive efficacy.**

Alcohol

Alcohol levels in breast milk are similar to those in maternal blood. If a moderate social drinker had two cocktails and had a blood alcohol concentration of 50 mg/dL, the nursing infant would receive about 82 mg of alcohol, which would produce insignificant blood concentrations. There is no evidence that the occasional ingestion of alcohol by a nursing mother is harmful to the infant. However, one study showed that ethanol ingested chronically through breast milk might have a detrimental effect on an infant's motor development but not mental development.[85] Also, alcohol in breast milk has an immediate effect on the odor of the milk, which may decrease the amount of milk the infant consumes.[86]

Propylthiouracil

PTU is found in breast milk in small amounts. If the mother takes 200 mg of PTU three times a day, the child would receive 149 µg daily, or the equivalent of a 70-kg adult receiving 3 mg/day. Several infants studied up to 5 months of age show no changes in thyroid parameters. **Lactating mothers on PTU can thus continue nursing with close supervision of the infant.** PTU has been preferred over methimazole (Tapazole) because of its high level of protein binding (80%) and lower breast milk concentrations. However, it has recently been observed that liver injury is higher with PTU than with methimazole, but no cases of liver damage in infants of nursing mothers on PTU have been reported.

H_2-Receptor Blockers

In theory, H_2-receptor antagonists (e.g., ranitidine, cimetidine) might suppress gastric acidity and cause central nervous system stimulation in the infant, but these effects have not been confirmed. The American Academy of Pediatrics now considers H_2-receptor antagonists to be compatible with breastfeeding. Famotidine, nizatidine, and roxatidine are less concentrated in breast milk and may be preferable in nursing mothers.

Caffeine

Caffeine has been reported to have no adverse effects on the nursing infant, even after the mother consumes five cups of coffee per day. In one study, the milk level contained 1% of the total dose 6 hours after coffee ingestion, which is not enough to affect the infant. In another report, no significant difference in 24-hour heart rate or sleep time was observed in nursing infants when their mothers drank coffee for 5 days or abstained for 5 days.[87]

Smoking and Nicotine

Nicotine and its metabolite cotinine enter breast milk. Infants of smoking mothers achieve significant serum concentrations of nicotine even if they are not exposed to passive smoking; exposure to passive smoking further raises the levels of nicotine. Women who smoke should be encouraged to stop during lactation as well as during pregnancy.

OCCUPATIONAL AND ENVIRONMENTAL HAZARDS

Ionizing Radiation

The general hazards of radiation exposure are well known. To provide counseling in specific clinical situations, key variables are dose, timing, and temporal sequence.

Acute Exposure

Systematic studies of atomic bomb survivors in Japan showed conclusively that in utero exposure to high-dose radiation increased the risk of microcephaly and mental and growth restriction in the offspring. Distance from the hypocenter—the area directly beneath the detonated

bomb—and gestational age at the time of exposure were directly related to microcephaly and mental and growth restriction in the infant. **The greatest number of children with microcephaly, mental retardation, and growth restriction were in the group exposed at 15 weeks' gestation or earlier.** Exposures were calculated by the distance of the victims from the epicenter. Microcephaly and mental retardation were associated with ionizing radiation at doses of 50 rad or greater, with 20 rad being the lowest dose at which microcephaly was observed. Although teratogenic effects have been found in several organ systems of animals exposed to acute high-dose radiation, the only structural malformations reported among humans exposed prenatally are those mentioned earlier. Using data from animals and from outcomes of reported human exposures at various times during pregnancy, DeKaban[88] constructed a timetable for extrapolating acute high-dose radiation (>250 rad) to various reproductive outcomes in humans. Similarities between animal and known human effects support DeKaban's proposal.

Effects of chronic low-dose radiation on reproduction have not been identified in animals or humans. Increased risk of adverse outcomes was not detected among animals with continuous low-dose exposure (<5 rad) throughout pregnancy. The National Council for Radiation Protection[89] concluded that exposures of less than 5 rad were not associated with an increased risk of malformations.

Exposures are expressed as Gray (Gy): 1 Gy equals 1000 mGy equals 100 rad (Table 7.1). Thus, 10 mGy equals 1 rad. **Fortunately almost no single diagnostic test produces a substantive risk.** Table 7.1 shows mean and maximum fetal exposure. Only multiple CT scans and fluoroscopies would lead to cumulative exposures of 100 mGy or 10 rad. Internal exposures are 50% less than maternal surface doses.

Female frequent flyers or crew members may be exposed to radiation during frequent long high-altitude flights. The Federal Aeronautics Administration (FAA) recommends limiting exposure to 1 mSv (0.1 rad) during a pregnancy.[90]

TABLE 7.1 Approximate Fetal Doses From Common Diagnostic Procedures

Examination	Mean (mGY[a])	Maximum (mGY)
Conventional X-Ray Examinations		
Abdomen	1.4	4.2
Chest	<0.01	<0.01
Intravenous urogram	1.7	10
Lumbar spine	1.7	10
Pelvis	1.1	4
Skull	<0.01	<0.01
Thoracic spine	<0.01	<0.01
Fluoroscopic Examinations		
Barium meal (upper GI)	1.1	5.8
Barium enema	6.8	24
Computed Tomography		
Abdomen	8.0	49
Chest	0.06	0.96
Head	<0.005	<0.005
Lumbar spine	2.4	8.6
Pelvis	25	79

[a]10 mGY = 1 rad.
GI, Gastrointestinal.
From Lowe SA. Diagnostic radiography in pregnancy: risks and reality. *Aust N Z J Obstet Gynaecol.* 2004;44:191.

Therapeutic exposures for maternal thyroid ablation with I^{131} are rare but can cause fetal thyroid damage after 12 weeks of pregnancy.

Mutagenesis From Exposure

Mutagenic effects in the offspring of irradiated women may be manifested years after the birth of the infant. Mutagenic effects presumably explain the 50% increased risk of leukemia in children exposed in utero to radiation during maternal pelvimetry examinations compared with nonirradiated controls. However, the clinical consequence is almost nil. The absolute risk is approximately 1 in 2000 for exposed versus 1 in 3000 for unexposed children.

Lowe[89] estimates one additional cancer death per 1700 10 mGy (1 rad) exposures. If one were to recommend that pregnancies be terminated whenever exposure from diagnostic radiation occurred because of the increased probability of leukemia in the offspring, 1699 exposed pregnancies would have to be terminated to prevent a single case of leukemia. Radiation exposures should be minimized, but fear of radiation should never prevent a patient from having a necessary diagnostic procedure. A consent form has been developed for use with pregnant women.[91]

Questions have also been raised about potential risks to children associated with paternal occupational exposure to low-dose radiation. A case-control study by Gardner et al. in the area around the Sellafield Nuclear Facility in the United Kingdom found a statistically significant association between a paternal preconception radiation dose and childhood leukemia risk. A similar association had been observed between paternal preconception radiation and risk in workers at the Hanford Nuclear Facility in the United States. The finding regarding childhood leukemia risk is a particularly contentious issue, contradicting studies of the children born to atomic bomb survivors who do not show genetic effects, such as increased risks of childhood cancers. A study in the vicinity of nuclear facilities in Ontario also failed to demonstrate an association between childhood leukemia risk and paternal preconception radiation exposure.

Video Display Terminals

Concern about video display terminals linked to adverse reproductive outcomes now seems unwarranted. Early concern grew out of reports of spontaneous abortion clusters among groups of women who used video display terminals at work; some reported clusters included birth defects. Since then numerous reassuring papers have been published on this topic, along with a number of reviews.[92] **Video display terminal use does not increase the risk of adverse reproductive outcomes.**

Lead

Twenty-five years of public health efforts have produced a striking reduction in lead exposure in the United States. The average blood lead level has decreased to less than 20% of levels measured in the 1970s. However, elevated blood lead (>20 µg/dL) has a higher incidence among immigrants to southern California. In Los Angeles, 25 of the 30 cases of elevated blood lead level occurred in immigrants.

A high lead concentration in maternal blood is associated with an increased risk of delivery of a small-for-gestational-age infant. The frequency of preterm birth was also almost three times higher among women who had umbilical cord levels greater than or equal to 5.1 µg/dL compared with those who had levels below that cutoff. One study in Norway found an increased risk of low birthweight and also NTDs.[93]

Lead poisoning has been reported after a pregnant woman ingested Garbhpal Ras, an Asian Indian health supplement that contained extremely high levels of lead.[94]

Asking pregnant women about risk factors for lead exposure can aid in assessing prenatal exposure risk. A questionnaire that gathered information on housing conditions, smoking status, and consumption

of canned foods had a sensitivity of 89.2% and a negative predictive value of 96.4%.[95] Consumption of calcium and avoidance of the use of lead-glazed ceramics resulted in the lowering of blood lead, especially in pregnant women of low socioeconomic status in Mexico City.

Because the nervous system may be more susceptible to the toxic effects of lead during the embryonic and fetal periods than at any other time of life and because maternal and cord blood lead concentrations are directly correlated, lead concentrations in blood should not exceed 25 µg/dL in women of reproductive age.[96]

Ideally the maternal blood lead level should be less than 10 µg/dL to ensure that a child begins life with minimal lead exposure. A dose-response relationship is strongly supported by numerous epidemiologic studies of children showing a reduction in IQ with increasing blood lead concentrations above 10 µg/dL. Of note, these studies measured blood lead concentrations over time (often ≥2 years) and reported averaged values. **Other neurologic impairments associated with increased blood lead concentrations include attention deficit disorder ("hyperactivity"), hearing deficits, learning disabilities, and shorter stature.** Thus, for public health purposes, childhood lead poisoning has been defined as a blood lead level of 10 µg/dL or higher.

In occupational settings, federal standards mandate that women should not work in areas where air lead concentrations can reach 50 µg/cm, because this may result in blood concentrations above 25 to 30 µg/dL.[97] Subtle but permanent neurologic impairment in children may occur at lower blood lead concentrations.

Mercury in Fish

Fish and shellfish are an important part of a healthy diet, but some large fish contain significant amounts of mercury. **Mercury at high levels may harm the unborn baby or young child's developing nervous system.**[98]

Women who may become pregnant, pregnant women, and nursing mothers should avoid shark, swordfish, king mackerel, and tilefish because they contain high levels of mercury.[99] They may eat up to 12 oz a week of shrimp, canned light tuna, salmon, pollock, and catfish, all of which are very low in mercury. Albacore (white) tuna and tuna steaks have more mercury than canned light tuna, but an intake of 6 oz per week is allowed.

OBSTETRICIAN'S ROLE IN PATIENT ASSESSMENT AND EDUCATION

Most obstetricians will be faced with a variety of questions and concerns about the safety of medications and environmental agents in pregnancy. The assessment of the pregnant patient requiring medication involves a multidisciplinary approach, with the obstetrician at the center of the decision making and communication to the patient. Briefly, the assessment involves (1) a thorough physical exam and history with an understanding and prioritizing of various medical conditions that may affect the pregnancy; (2) a complete medication history and reconciliation of the medication regimen to establish current medications (including supplements and over-the-counter products), indications, and the patient's responses to these medications; (3) evaluation of all evidence related to the effects of the patient's medications on the fetus. Studies and databases referenced in this chapter can be used to assess these risks; (4) an open discussion with the patient on her current attitudes toward taking her medications during pregnancy along with their inherent risks; (5) determining medications to be continued during pregnancy with a clear description comparing benefits to the patient and risks to the fetus; (6) developing an ongoing monitoring plan to assess the efficacy of medications during pregnancy and evaluate the effects on the fetus. A variety of health care professionals such as nurses, pharmacists, therapists, and nutritionists can collect and analyze this information and provide a team recommendation to the obstetrician.

BOX 7.3 Teratogen Information Databases

- IBM Micromedex: 6200 South Syracuse Way, Suite 300, Greenwood Village, CO 80111-4740; 800-525-9083 (in US and Canada); http://www.micromedex.com
- REPROTOX (Reproductive Toxicology Center): 7831 Woodmont Avenue, Suite 375, Bethesda, MD 20814; 301-514-3081; http://www.reprotox.org
- Mother to Baby: 200 W. Arbor Drive, #8446, San Diego, CA 92103-9981; 886-626-6847; http://mothertobaby.org

To help in this assessment, a variety of teratology information services and computer databases are available to physicians who counsel pregnant women (Box 7.3). The options include personal computer software (Grateful Med, commercial services) and CD-ROM copies in medical libraries or leased from commercial versions. Information is available from a TOXNET representative, National Library of Medicine, Specialized Information Services, 8600 Rockville Pike, Bethesda, MD 20894, 301-496-6531.

The National Library of Medicine in Bethesda, Maryland, maintains several files on the TOXNET database system, including reproductive and developmental toxicology information in bibliographic or text form. Examples include Developmental and Reproductive Toxicology, GEN-TOX (genetic toxicology), LactMed and Environmental Mutagen Information Center. Other very useful sources are Reprotox (http://reprotox.org) and TERIS (depts.washington.edu/%7Eterisweb/teris/index.html). The book *Drugs in Pregnancy and Lactation*, 2014, 10th edition, by Briggs and Freeman, is now available both in print and online. The online version is updated quarterly.

Many medical conditions during pregnancy and lactation are best treated initially with nonpharmacologic remedies. Before a drug is administered in pregnancy, the indications should be clear and the risk/benefit ratio should justify the drug's use. **If possible, therapy should be postponed until after the first trimester**. In addition, patients should be cautioned about the risks of social drug use such as smoking, drinking alcohol, and using cocaine during pregnancy. Most drug therapy does not require cessation of lactation because the amount excreted into breast milk is sufficiently small to be pharmacologically insignificant.

KEY POINTS

- The critical period of organ development ranges from day 31 to day 71 from the first day of the last menstrual period.
- Assessment of the patient's drug therapy during pregnancy and breastfeeding must be done in a systematic manner to provide appropriate education on the risks and to ensure the prescribing of only necessary medications.
- Pharmacokinetic principles regarding the absorption, distribution, metabolism, and excretion of drugs should be applied in assessing drug therapy in pregnancy and breastfeeding.
- Most drugs cross the placenta and enter the breast milk, often in very small quantities that in most cases does not cause harm to the baby or fetus.

- Infants exposed to antiepileptic drugs, such as sodium valproate, are associated with twice the rate of malformations compared with unexposed infants. However, the risk of fetal hydantoin syndrome is less than 10% in babies exposed to phenytoin.
- The risk of malformations after in utero exposure to isotretinoin is 25%, with an additional 25% of exposed infants developing mental retardation and other cognitive delays.
- Heparin is the drug of choice for anticoagulation during pregnancy except for women with prosthetic heart valves, who should receive enoxaparin or warfarin. Warfarin therapy causes birth defects in 5% of the babies born to exposed women, and there is not clear consensus on its use with both new and older prosthetic heart valves. In addition, direct-acting oral anticoagulants are not recommended for therapeutic reasons.
- Angiotensin-converting enzyme inhibitors and angiotensin receptor blockers may cause fetal renal failure in the second and third trimesters, leading to oligohydramnios and hypoplastic lungs.
- Vitamin B_6 25 mg three times a day is a safe and effective therapy for first-trimester nausea and vomiting. Doxylamine 12.5 mg three times a day is also effective in combination with B_6. Ondansetron may pose an increased risk of congenital malformations.
- Most antibiotics are safe in pregnancy, although aminoglycosides are known to be ototoxic to the fetus. Trimethoprim may carry an increased risk in the first trimester, and tetracycline taken in the second and third trimesters may cause tooth discoloration due to the chelating properties of these drugs, which bind bone calcium specifically in the teeth.
- Aspirin in analgesic doses inhibits platelet function and prolongs bleeding time, increasing the risk of peripartum hemorrhage, but it is not associated with congenital defects.
- Fetal alcohol syndrome occurs in infants of mothers who drink heavily during pregnancy. A safe level of alcohol intake during pregnancy has not been determined.
- Cocaine use carries an increased risk of miscarriage, abruptio placentae, and congenital malformations, in particular microcephaly and limb defects.
- Only a small amount of prednisone crosses the placenta, so it is the preferred corticosteroid for most chronic maternal autoimmune diseases. In contrast, betamethasone and dexamethasone cross the placenta readily and are preferred for accelerating maturation of the fetal lung.
- Exposure to high-dose ionizing radiation at any stage during gestation causes microcephaly and mental retardation. Diagnostic exposures below 5 rad after 12 weeks of gestation do not pose increased teratogenic risks.
- Environmental lead exposure has decreased due to building regulations but may still be an issue with some immigrant populations. Blood levels below 25 µg/dL in women of reproductive age minimize the risk of fetal growth restriction during pregnancy.
- Mercury at high levels affects the fetal nervous system deleteriously. For this reason pregnant and nursing women should avoid shark, swordfish, king mackerel, and tilefish. Exposures to mercury can further be limited by restricting the ingestion of certain other seafoods (shrimp, canned tuna, salmon, pollock, and catfish) to 12 oz per week.

REFERENCES

1. Wilson JG, Fraser FC. *Handbook of Teratology*. New York: Plenum; 1979.
2. Teratology Society Public Affairs Committee. FDA Classification of drugs for teratogenic risk. *Teratol*. 1994;49:446.
3. Wilson JG. Current status of teratology—general principles and mechanisms derived from animal studies. In: Wilson JG, Fraser FC, eds. *Handbook of Teratology*. New York: Plenum; 1977:47.
4. Lenz W. Thalidomide and congenital abnormalities. *Lancet*. 1962;1:45.
5. Lammer EJ, Sever LE, Oakley GP Jr. Teratogen update: valproic acid. *Teratology*. 1987;35:465.
6. MRC Vitamin Study Research Group. Prevention of neural tube defects: results of the Medical Research Council Vitamin Study. *Lancet*. 1991;338:131.
7. Lieff S, Olshan AF, Werler M, et al. Selection bias and the use of controls with malformations in case-control studies of birth defects. *Epidemiology*. 1999;10:238.
8. Czeizel AE, Dudas I. Prevention of the first occurrence of neural-tube defects by periconceptional vitamin supplementation. *N Engl J Med*. 1992;327:1832.
9. Tetro N, Moushaev S, Rubinchick-Stern M, et al. The placental barrier: the gate and the fate in drug distribution. *Pharm Res*. 2018;35:71. doi:10.1007/s11095-017-2286-0.
10. Fowler DW, Eadie MJ, Dickinson RG. Transplacental transfer and bio transformational studies of valproic acid and its glucuronide in the perfused human placenta. *J Pharmacol Exp Ther*. 1989;249:318–323.
11. Tomson T, Marson A, Boon P, et al. Valproate in the treatment of epilepsy in girls and women of childbearing potential. *Epilepsia*. 2015;56:1006–1019.
12. Madadi P, Koren G, Cairns J, et al. Safety of codeine during breastfeeding: fatal morphine poisoning in the breastfed neonate of a mother prescribed codeine. *Can Fam Physician*. 2007;53:33–35.
13. Pekarek DM, Chapman VR, Neely CL, et al. Medication effects on midtrimester maternal serum screening. *Am J Obstet Gynecol*. 2009;201:622.e1–622.e5.
14. Einarson TR, Koren G, Mattice D, et al. Maternal spermicide use and adverse reproductive outcome: a meta-analysis. *Am J Obstet Gynecol*. 1990;162:665.
15. Meador KJ, Pennell PB, May RC, et al. Changes in antiepileptic drug-prescribing patterns in pregnant women with epilepsy. *Epilepsy Behav*. 2018;84:10–14.
16. Jentink J, Loane MA, Dolk H, et al. Valproic acid monotherapy in pregnancy and major congenital malformations. *N Engl J Med*. 2010;362:2185.
17. Holmes LB, Harvey EA, Coull BA, et al. The teratogenicity of anticonvulsant drugs. *N Engl J Med*. 2001;344:1132.
18. Biale Y, Lewenthal H. Effect of folic acid supplementation on congenital malformations due to anticonvulsive drugs. *Eur J Obstet Gynecol Reprod Biol*. 1984;18:211.
19. Jones KL, Lacro RV, Johnson KA, et al. Pattern of malformations in the children of women treated with carbamazepine during pregnancy. *N Engl J Med*. 1989;320:1661.
20. Buehler BA, Delimont D, VanWaes M, et al. Prenatal prediction of risk of the fetal hydantoin syndrome. *N Engl J Med*. 1990;322:1567.
21. GlaxoSmithKline International. Lamotrigine Pregnancy Registry, Final Report, July 2010.
22. Campbell E, Kennedy F, Russell A, et al. Malformation risks of antiepileptic drug monotherapies in pregnancy: updated results from the UK and Ireland epilepsy and pregnancy registers. *J Neurol Neurosurg Psychiatry*. 2014;doi:10.1136/jnnp-2013-306318.
23. Margulis AV, Mitchell AA, Gilboa SM, et al. Use of topiramate in pregnancy and risk of oral clefts. *Am J Obstet Gynecol*. 2012;207:405.e1–405.e7.

24. Lammer EJ, Chen DT, Hoar RM, et al. Retinoic acid embryopathy. *N Engl J Med*. 1985;313:837.
25. Zalzstein E, Koren G, Einarson T, et al. A case-control study on the association between first trimester exposure to lithium and Ebstein's anomaly. *Am J Cardiol*. 1990;65:817.
26. Jacobson SJ, Jones K, Johnson K, et al. Prospective multi-centre study of pregnancy outcome after lithium exposure during first trimester. *Lancet*. 1992;339:530.
27. Newport DJ, Viguera AC, Beach AJ, et al. Lithium placental passage and obstetrical outcome: implications for clinical management during late pregnancy. *Am J Psychiatry*. 2005;162:2162–2170.
28. Way CM. Safety of Newer Antidepressants in Pregnancy. *Pharmacotherapy*. 2007;27:546.
29. Malm H, Artama M, Gissler M, et al. Selective serotonin reuptake inhibitors and risk for major congenital anomalies. *Obstet Obstet Gynecol*. 2011;118:111.
30. Yonkers KA, Wisner KL, Stewart DE, et al. The management of depression during pregnancy: a report from the American Psychiatric Association and the American College of Obstetricians and Gynecologists. *Obstet Gynecol*. 2009;114:703.
31. Rampono J, Simmer K, Ilett KF, et al. Placental transfer of SSRI and SNRI antidepressants and effects on the neonate. *Pharmacopsychiatry*. 2009;42:95–100.
32. Huybrechts KF, Palmsten K, Avorn J, et al. Antidepressant use in pregnancy and the risk of cardiac defects. *N Engl J Med*. 2014;370:2397–2407.
33. Stephansson O, Kieler H, Haglund B, et al. Selective serotonin reuptake inhibitors during pregnancy and risk of stillbirth and infant mortality. *JAMA*. 2013;309:48–54.
34. Zeskind PS, Stephens LE. Maternal selective serotonin reuptake inhibitor use during pregnancy and newborn neurobehavior. *Pediatrics*. 2004;113:368.
35. Chambers CD, Hernandez-Diaz S, Von Marter LJ, et al. Selective serotonin-reuptake inhibitors and risk of persistent pulmonary hypertension of the newborn. *N Engl J Med*. 2006;354:579.
36. Wilson KL, Zelig CM, Harvey JP, et al. Persistent pulmonary hypertension of the newborn is associated with mode of delivery and not with maternal use of selective serotonin reuptake inhibitors. *Am J Perinatol*. 2011;28:19.
37. Andersen JT, Andersen NL, Horwitz H, et al. Exposure to selective serotonin reuptake inhibitors in early pregnancy and the risk of miscarriage. *Obstet Gynecol*. 2014;124(4):655–661.
38. D'Souza R, Ostro J, Shah PS, et al. Anticoagulation for pregnant women with mechanical heart valves: a systematic review and meta-analysis. *Eur Heart J*. 2017;38:1509–1516.
39. McDonagh MS, Matthews A, Phillipi C, et al. Depression drug treatment outcomes in pregnancy and the postpartum period. A systematic review and meta-analysis. *Obstet Gynecol*. 2014;124(3):526–534.
40. Cooper DS. Antithyroid drugs. *N Engl J Med*. 2005;352:905.
41. Cooper DS, Rivkees SA. Putting propylthiouracil in perspective. *J Clin Endocrinol Metab*. 1881;94:2009.
42. De Groot L, Abalovich M, Alexander EK, et al. Management of thyroid dysfunction during pregnancy and postpartum: an Endocrine Society clinical practice guideline. *J Clin Endocrinol Metab*. 2012;97:2543–2564.
43. Alexander EK, Marqusee E, Lawrence J, et al. Timing and magnitude of increases in levothyroxine requirements during pregnancy in women with hypothyroidism. *N Engl J Med*. 2004;351:241.
44. Velinov M, Zellers N. The fetal mycophenolate mofetil syndrome. *Clin Dysmorphol*. 2008;17(1):77.
45. Nurmohamed L, Moretti ME, Schechter T, et al. Outcome following high-dose methotrexate in pregnancies misdiagnosed as ectopic. *Am J Obstet Gynecol*. 2011;205:533.e1–533.e3.
46. Hart CW, Naunton RF. The ototoxicity of chloroquine phosphate. *Arch Otolaryngol*. 1964;80:407.
47. Haagen Nielsen O, Loftus EV Jr, Jess T. Safety of TNF-α inhibitors during IBD pregnancy: a systematic review. *BMC Med*. 2013;11:174.
48. Koren G, Clark S, Hankins GD, et al. Effectiveness of delayed-release doxylamine and pyridoxine for nausea and vomiting of pregnancy: a randomized placebo controlled trial. *Am J Obstet Gynecol*. 2010;203(571): e1–e7.
49. Matok I, Gorodischer R, Koren G, et al. The safety of metoclopramide use in the first trimester of pregnancy. *N Engl J Med*. 2009;360: 2528.
50. Sullivan CA, Johnson CA, Roach H, et al. A pilot study of intravenous ondansetron for hyperemesis gravidarum. *Am J Obstet Gynecol*. 1996;174:2565.
51. Pasternak B, Svanstrom H, Hviid A. Ondansetron in pregnancy and risk of adverse fetal outcomes. *N Engl J Med*. 2013;368:814–823.
52. Deleted in review.
53. Deleted in review.
54. Ruigomez A, Garcia Rodriguez LA, Cattaruzzi C, et al. Use of cimetidine, omeprazole, and ranitidine in pregnant women and pregnancy outcomes. *Am J Epidemiol*. 1999;150:476.
55. Pasternak B, Hviid A. Use of proton pump inhibitors in early pregnancy and the risk of birth defects. *N Engl J Med*. 2010;363:2114.
56. Yau W-P, Mitchell AA, Lin KJ. Use of decongestants during pregnancy and the risk of birth defects. *Am J Epidemiol*. 2013;178(2):198–208.
57. Nordeng H, Lupattelli A, Romoren M, et al. Neonatal outcomes after gestational exposure to nitrofurantoin. *Obstet Gynecol*. 2013;121(2):306–313.
58. Stone KM, Reiff-Eldridge R, White AD, et al. Pregnancy outcomes following systemic prenatal acyclovir exposure: conclusions from the international acyclovir pregnancy registry, 1984–1999. *Birth Defects Res Part A. Clin Mol Teratol*. 2004;70:201.
59. Pasternak B, Hviid A. Use of acyclovir, valacyclovir and famciclovir in the first trimester of pregnancy and the risk of birth defects. *JAMA*. 2010;304:859.
60. Perinatal HIV Guidelines Working Group. Public Health Service Task Force. Recommendations for use of antiretroviral drugs in pregnant HIV-1-infected women for maternal health and interventions to reduce perinatal HIV-1 transmission in the United States. June 23, 2004. http://AIDSinfo.nih.gov.
61. Mastroiacovo P, Mazzone T, Botto LD, et al. Prospective assessment of pregnancy outcomes after first-trimester exposure to fluconazole. *Am J Obstet Gynecol*. 1996;175:1645.
62. Molgaard-Nielsen D, Pasternak B, Hviid A. Use of oral fluconazole during pregnancy and the risk of birth defects. *N Engl J Med*. 2013;369:830–839.
63. Feldkamp M, Meyer RE, Krikov S, et al. Acetaminophen use in pregnancy and risk of birth defects: findings from the National Birth Defects Prevention Study. *Obstet Gynecol*. 2010;115:109.
64. Nezvalova-Henriksen K, Spigset O, Nordeng H. Effects of ibuprofen, diclofenac, naproxen, and piroxicam on the course of pregnancy and pregnancy outcome: a prospective cohort study. *Brit J Obstet Gynecol*. 2013;120:948–959.
65. Hernandez RK, Werler MM, Romitti P, et al. Nonsteroidal antiinflammatory drug use among women and the risk of birth defects. *Am J Obstet Gynecol*. 2012;206:228.e1–228.e8.
66. Cunnington M, Ephross S, Churcill P. The safety of sumatriptan and naratriptan in pregnancy: what have we learned? *Headache*. 2009; 49:1414.
67. Loder E. Triptan therapy in migraine. *N Engl J Med*. 2010;363:63.
67a. Green SB, Pappas AL. Effects of maternal bisphosphonate use on fetal and neonatal outcomes. *Am J Health Syst Pharm*. 2014;71: 2028–2035.
68. Kahr MK, Padgett S, Shope CD, et al. A qualitative assessment of the perceived risks of electronic cigarette and hookah use in pregnancy. *BMC Public Health*. 2015;15:1273–1280.
69. Coleman T, Cooper S, Thornton JG, et al. A randomized trial of nicotine-replacement therapy patches in pregnancy. *N Engl J Med*. 2012;366:808–818.
70. ACOG Committee Opinion. Smoking cessation during pregnancy. *Obstet Gynecol*. 2010;116:1241.
71. Waterman EH, Pruett D, Caughey AB. Reducing fetal alcohol exposure in the United States. *Obstet Gynecol Survey*. 2013;68(5):367–378.

72. Acker D, Sachs BP, Tracey KJ, et al. Abruptio placentae associated with cocaine use. *Am J Obstet Gynecol*. 1983;146:220.
73. Volpe JJ. Effect of cocaine use on the fetus. *N Engl J Med*. 1992;327:399.
74. Brown HL, Britton KA, Mahaffey D, et al. Methadone maintenance in pregnancy: a reappraisal. *Am J Obstet Gynecol*. 1998;179:459.
75. Kalaitzopoulos DR, Chatzistergiou K, Amylidi AL, et al. Effect of methamphetamine hydrochloride on pregnancy outcome: a systematic review and meta-analysis. *J Addict Med*. 2018;12:220–226.
76. ACOG Committee Opinion. Moderate caffeine consumption during pregnancy. *Obstet Gynecol*. 2010;116:467.
77. Ito S, Blajchman A, Stephenson M, et al. Prospective follow-up of adverse reactions in breast-fed infants exposed to maternal medication. *Am J Obstet Gynecol*. 1993;168:1393.
78. Sachs HC, Committee on Drugs. The transfer of drugs and therapeutics into human breast milk: an update on selected topics. *American Academy of Pediatrics*. 2013;doi:10.1542/peds.2013-1985.
79. Committee on Drugs, American Academy of Pediatrics. The transfer of drugs and therapeutics into human breast milk. *Pediatrics*. 2013;132:e796–e809.
80. Nulman I, Koren G. The safety of fluoxetine during pregnancy and lactation. *Teratology*. 1996;53:304.

80a. Koren G, Cairns J, Chitayat D, et al. Pharmacogenetics of morphine poisoning in a breastfed neonate of a codeine-prescribed mother. *Lancet*. 2006;368:704.

81. Epperson CN, Anderson GM, McDougle CJ. Sertraline and breast-feeding. *N Engl J Med*. 1997;336:1189.
82. Orme ME, Lewis PJ, deSwiet M, et al. May mothers given warfarin breastfeed their infants? *Br Med J*. 1977;1:1564.
83. deSwiet M, Lewis PJ. Excretion of anticoagulants in human milk. *N Engl J Med*. 1977;297:1471.
84. Berlin CM Jr, Yaffe SJ. Disposition of salicylazosulfapyridine (Azulfidine) and metabolites in human breast milk. *Dev Pharmacol Ther*. 1980;1:31.
85. Little RE, Anderson KW, Ervin CH, et al. Maternal alcohol use during breastfeeding and infant mental and motor development at one year. *N Engl J Med*. 1989;321:425.
86. Mennella JA, Beauchamp GK. The transfer of alcohol to human milk. Effects on flavor and the infant's behavior. *N Engl J Med*. 1991;325:981.
87. Ryu JE. Effect of maternal caffeine consumption on heart rate and sleep time of breast-fed infants. *Dev Pharmacol Ther*. 1985;8:355.
88. Dekaban AS. Abnormalities in children exposed to x-radiation during various stages of gestation: tentative timetable of radiation injury to the human fetus. *J Nucl Med*. 1968;9:471.
89. Lowe SA. Diagnostic radiography in pregnancy: risks and reality. *Aust N Z J Obstet Gynaecol*. 2004;44:191.
90. Barish RJ. In-flight radiation exposure during pregnancy. *Obstet Gynecol*. 2004;103:1326.
91. El-Khoury GY, Madsen MT, Blake ME, et al. A new pregnancy policy for a new era. *Am J Roentgenol*. 2003;181:335.
92. Blackwell R, Chang A. Video display terminals and pregnancy. A review. *Br J Obstet Gynaecol*. 1988;95:446.
93. Irgens A, Kruger K, Skorve AH, et al. Reproductive outcome in offspring of parents occupationally exposed to lead in Norway. *Am J Ind Med*. 1998;34:431.
94. Shamshirsaz AA, Yankowitz J, Rijhsinghani A, et al. Severe lead poisoning caused by use of health supplements presenting as acute abdominal pain during pregnancy. *Obstet Gynecol*. 2009;114:448.
95. Stefanak MA, Bourguet CC, Benzies-Styka T. Use of the Centers for Disease Control and Prevention childhood lead poisoning risk questionnaire to predict blood lead elevations in pregnant women. *Obstet Gynecol*. 1996;87:209.
96. Centers for Disease Control. Preventing lead poisoning in young children. Atlanta, Department of Health and Human Services. Atlanta, Public Health Service, Centers for Disease Control, 1991, p 7.
97. Needleman HL, Schell A, Bellinger D, et al. The long-term effects of exposure to low doses of lead in childhood. An 11-year follow-up report. *N Engl J Med*. 1990;322:83.
98. Harada M. Congenital minamata disease: intrauterine methylmercury poisoning. *Teratology*. 1978;18:285.
99. Food and Drug Administration and the US Environmental Protection Agency. What you need to know about mercury in fish and shellfish. www.epa.gov/fishadvisories/advice/factsheet.html.

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BIBLIOGRAPHY

Teratogenesis

Blake DA, Niebyl JR. Requirements and limitations in reproductive and teratogenic risk assessment. In: Niebyl JR, ed. *Drug Use in Pregnancy*. Philadelphia: Lea & Febiger; 1988.

Lenz W, Knapp K. Foetal malformation due to thalidomide. *Geriatr Med Monthly*. 1962;7:253.

Sever LE. Neuroepidemiology of interuterine radiation exposure. In: Molgaard C, ed. *Neuroepidemiology: Theory Method*. San Diego: Academic Press; 1993:241.

Selevan SG, Lemasters GK. The dose-response fallacy in human reproductive studies of toxic exposures. *J Occup Med*. 1987;29:451.

Van Allen MI, Kalousek DK, Chernoff GF, et al. Evidence for multi-site closure of the neural tube in humans. *Am J Med Genet*. 1993;47:723.

van Gelder HJ, de Jong-van W, den Berg LT, Roeleveld N. Drugs associated with teratogenic mechanisms. Part II: a literature review of the evidence on human risks. *Hum Reprod*. 2014;29:168–183.

Epidemiology

Bracken MB. Design and conduct of randomized clinical trials in perinatal research. In: Bracken MB, ed. *Perinatal Epidemiology*. New York: Oxford University Press; 1984:397.

Centers for Disease Control and Prevention. Recommendations for the use of folic acid to reduce the number of cases of spina bifida and other neural tube defects. *MMWR Morb Mortal Wkly Rep*. 1992;41:1.

Gregg NM. Congenital cataract following German measles in the mother. *Ophthalmol Soc Aust*. 1941;3:35.

Mburia-Mwalili A, Yang W. Birth defects surveillance in the United States: challenges and implications of International Classification of Diseases, Tenth Revision, Clinical Modification Implementation. *International Scholarly Research Notices*. 2014;http://dx.doi.org/10.115/2014/212874.

McBride WG. Thalidomide and congenital abnormalities. *Lancet*. 1961;2: 1358.

Sever LE, Hessol NA. Overall design considerations in male and female occupational reproductive studies. *Prog Clin Biol Res*. 1984;160:15.

Pharmacokinetics

Faure-Bardon V, Mandelbrot L, Duro D, Dussaux C, Le M, Peytavin G. Placental transfer of elvitegravir and cobicistat in an ex-vivo human cotyledon double perfusion model. *AIDS*. 2018;32:321–325.

Feghali M, Venkataramanan R, Caritis S. Pharmacokinetics of drugs in pregnancy. *Semin Perinatol*. 2015;39:512–519.

Jauniaux E, Gulbis B. In vivo investigation of placental transfer early in human pregnancy. *Eur J Obstet Gynecol Reprod Biol*. 2000;92:45–49.

Jauniaux E, Johns J, Gulbis B, Spasic-Boskovic O, Burton GJ. Transfer of folic acid inside the first-trimester gestational sac and the effect of maternal smoking. *Am J Obstet Gynecol*. 2007;197:58.e1–58.e6.

Ke AB, Greupink R, Abduljalil K. Drug dosing in pregnant women: challenges and opportunities in using physiologically based pharmacokinetic modeling and simulations. *CPT Pharmacometrics Syst Pharmacol*. 2018;7:103–110.

Morgan JL, Kogutt BK, Meek C, et al. Pharmacokinetics of amlodipine besylate at delivery and during lactation. *Pregnancy Hypertens*. 2018;11:77–80.

Hormones

Brunskill PJ. The effects of fetal exposure to danazol. *Br J Obstet Gynaecol*. 1992;99:212.

Duck SC, Katayama KP. Danazol may cause female pseudohermaphroditism. *Fertil Steril*. 1981;35:230.

Pardthaisong T, Gray RH, McDaniel EB, Chandacham A. Steroid contraceptive use and exposed to depo-provera during pregnancy or lactation. *Contraception*. 1992;45:313.

Park-Wyllie L, Mazzotta P, Pastuszak A, et al. Birth defects after maternal exposure to corticosteroids: prospective cohort study and meta-analysis of epidemiological studies. *Teratology*. 2000;62:385.

Phillips OP, Simpson JL. Contraception and congenital malformations. In: Sciarra JJ, ed. *Gynecology and Obstetrics*. Vol. VI. Philadelphia: Lippincott, Williams and Wilkins; 2001:1.

Raman-Wilms L, Tseng AL, Wighardt S, et al. Fetal genital effects of first-trimester sex hormone exposure: a meta-analysis. *Obstet Gynecol*. 1995;85:141.

Tingi E, Syed AA, Kyriacou A, et al. Benign thyroid disease in pregnancy: a state of the art review. *J Clin Transl Endocrinology*. 2016;6:37–49.

Wilkins L. Masculinization of female fetus due to use of orally given progestins. *JAMA*. 1960;172:1028.

Antiepileptic Drugs

Callaghan N, Garrett A, Goggin T. Withdrawal of anticonvulsant drugs in patients free of seizures for two years. *N Engl J Med*. 1988;318:942.

Centers for Disease Control. Recommendations for the use of folic acid to reduce the number of cases of spina bifida and other neural tube defects. *MMWR Morb Mortal Wkly Rep*. 1992;41:1.

Dansky LV, Rosenblatt DS, Andermann E. Mechanisms of teratogenesis: folic acid and antiepileptic therapy. *Neurology*. 1992;42:32.

Deblay MF, Vert P, Andre M, et al. Transplacental vitamin K prevents haemorrhagic disease of infant of epileptic mother. *Lancet*. 1982;1:1247.

Gaily E, Granstrom M-L, Hiilesmaa V, et al. Minor anomalies in offspring of epileptic mothers. *J Pediatr*. 1988;112:520.

Hanson JW, Smith DW. The fetal hydantoin syndrome. *J Pediatr*. 1975;87:285.

Meador KJ, Baker GA, Browning N, et al. Cognitive function at 3 years of age after fetal exposure to antiepileptic drugs. *N Engl J Med*. 2009;360:1597.

Molgaard-Nielsen D, Hviid A. Newer-generation antiepileptic drugs and the risk of major birth defects. *JAMA*. 2011;305:1996.

Morrell MJ. The new antiepileptic drugs and women: efficacy, reproductive health, pregnancy, and fetal outcome. *Epilepsia*. 1996;37:S34.

Nakane Y, Okuma T, Tasashashi R, et al. Multi-institutional study on the teratogenicity and fetal toxicity of antiepileptic drugs: a report of a collaborative study group in Japan. *Epilepsia*. 1980;21:663.

Reinisch JM, Sanders SA, Mortensen EL, et al. In utero exposure to phenobarbital and intelligence deficits in adult men. *JAMA*. 1995;274:1518.

Richards N, Reith D, Stitely M, et al. Antiepileptic drug exposure in pregnancy and pregnancy outcome from national drug use data. *BMC Pregnancy Childbirth*. 2018;18:84. https://doi.org/10.1186/s12884-018-1728-y.

Rosa FW. Spina bifida in infants of women treated with carbamazepine during pregnancy. *N Engl J Med*. 1991;324:674.

Scolnik D, Nulman I, Rovet J, et al. Neurodevelopment of children exposed in utero to phenytoin and carbamazepine monotherapy. *JAMA*. 1994;271:767.

Strickler SM, Miller MA, Andermann E, et al. Genetic predisposition to phenytoin-induced birth defects. *Lancet*. 1985;2:746.

Van der Pol MC, Hadders-Algra M, Huisjes JH, et al. Antiepileptic medication in pregnancy: late effects on the children's central nervous system development. *Am J Obstet Gynecol*. 1991;164:121.

Vitamin A Derivatives

Adams J. High incidence of intellectual deficits in 5 year old children exposed to isotretinoin "in utero.". *Teratology*. 1990;41:614.

Collins M-K, Moreau JF, Opel D, et al. Compliance with pregnancy prevention measures during isotretinoin therapy. *J Am Acad Dermatol*. 2014;70(1):55–59.

Dai WS, Hsu M-A, Itri L. Safety of pregnancy after discontinuation of isotretinoin. *Arch Dermatol*. 1989;125:362.

Jick SS, Terris BZ, Jick H. First trimester topical tretinoin and congenital disorders. *Lancet*. 1993;341:1181.

McCauley ME, van den Broek N, Dou l, et al. Vitamin A supplementation during pregnancy for maternal and newborn outcomes. *Cochrane Database Syst Rev*. 2015;(10):CD008666, doi:10.1002/14651858.CD008666.pub3.

Mills JL, Simpson JL, Cunningham GC, et al. Vitamin A and birth defects. *Am J Obstet Gynecol*. 1997;177:31.

Rothman KJ, Moore LL, Singer MR, et al. Teratogenicity of high vitamin A intake. *N Engl J Med*. 1995;333:1369.

Psychoactive Drugs

Amitriptyline. In Briggs GG, Freeman RK. *Drugs in Pregnancy and Lactation*. 10th ed. Philadelphia, PA: Wolters Kluwer Health; 2014:58.
Ang MS, Thorp JA, Parisi VM. Maternal lithium therapy and polyhydramnios. *Obstet Gynecol*. 1990;76:517.
Bergman V, Rosa F, Baum C, et al. Effects of exposure to benzodiazepine during fetal life. *Lancet*. 1992;340:694.
Chambers CD, Johnson KA, Dick LM, et al. Birth outcomes in pregnant women taking fluoxetine. *N Engl J Med*. 1996;335:1010.
Cohen LS, Friedman MJ, Jefferson JW. A reevaluation of risk of in utero exposure to lithium. *JAMA*. 1994;271:146.
Czeizel A. Lack of evidence of teratogenicity of benzodiazepine drugs in Hungary. *Reprod Toxicol*. 1988;3:183.
Goldstein DJ, Corbin LA, Sundell KL. Effects of first-trimester fluoxetine exposure on the newborn. *Obstet Gynecol*. 1997;89:713.
Hendrick V, Smith LM, Suri R, et al. Birth outcomes after prenatal exposure to antidepressant medication. *Am J Obstet Gynecol*. 2003;188:812.
Imipramine. In Briggs GG, Freeman RK. *Drugs in Pregnancy and Lactation*. 10th ed. Philadelphia, PA: Wolters Kluwer Health; 2014:697.
Kallen B, Olaussan PO. Antidepressant drugs during pregnancy and infant congenital heart defect. *Reprod Toxicol*. 2006;21:221–222.
Krause S, Ebbesen F, Lange AP. Polyhydramnios with maternal lithium treatment. *Obstet Gynecol*. 1990;75:504.
Kulin NA, Pastuszak A, Sage SR, et al. Pregnancy outcome following maternal use of the new selective serotonin reuptake inhibitors: a prospective controlled multicenter study. *JAMA*. 1998;279:609.
Laegreid L, Olegard R, Wahlstrom J, et al. Abnormalities in children exposed to benzodiazepines in utero. *Lancet*. 1987;1:108.
Linden S, Rich CL. The use of lithium during pregnancy and lactation. *J Clin Psychiatry*. 1983;44:358.
Morales DR, Slattery J, Evans S, et al. Antidepressant use during pregnancy and risk of autism spectrum disorder and attention deficit hyperactivity disorder: systematic review of observational studies and methodological considerations. *BMC Med*. 2018;16:6. doi:10.1186/s12916-017-0993-3.
Nulman I, Rovert J, Stewart DE, et al. Neurodevelopment of children exposed in utero to antidepressant drugs. *N Engl J Med*. 1997;336:258.
Nulman I, Rowet J, Stewart DE, et al. Neurodevelopment of children exposed in utero to antidepressant drugs. *N Engl J Med*. 1997;336:258.
Pastuszak A, Schick-Boschetto B, Zuber C, et al. Pregnancy outcome following first-trimester exposure to fluoxetine (Prozac). *JAMA*. 1993;269:2446.
Weinstein MR, Goldfield MD. Cardiovascular malformations with lithium use during pregnancy. *Am J Psychiatry*. 1975;132:529.

Anticoagulants

Barbour LA, Kick SD, Steiner JF, et al. A prospective study of heparin-induced osteoporosis in pregnancy using bone densitometry. *Am J Obstet Gynecol*. 1994;170:862.
Brill-Edwards P, Ginsberg JS, Gent M, et al. Safety of withholding heparin in pregnant women with a history of venous thromboembolism. *N Engl J Med*. 2000;343:1439.
Casele HL, Laifer SA, Woelkers DA, et al. Changes in the pharmacokinetics of the low-molecular-weight heparin enoxaparin sodium during pregnancy. *Am J Obstet Gynecol*. 1999;181:1113.
Chan WS, Ray JG. Low molecular weight heparin use during pregnancy: issues of safety and practicality. *Obstet Gynecol Surv*. 1999;54:649.
Cotrufo M, De Feo M, De Santo LS, et al. Risk of warfarin during pregnancy with mechanical valve prostheses. *Obstet Gynecol*. 2002;99:35.
D'Souza R, Ostro J, Shah PS, et al. Anticoagulation for pregnant women with mechanical heart valves: a systematic review and meta-analysis. *Eur Heart J*. 2017;38:1509–1516.
Dahlman TC. Osteoporotic fractures and the recurrence of thromboembolism during pregnancy and the puerperium in 184 women undergoing thromboprophylaxis with heparin. *Am J Obstet Gynecol*. 1993;168:1265.
deSwiet M, Ward PD, Fidler J, et al. Prolonged heparin therapy in pregnancy causes bone demineralization. *Br J Obstet Gynaecol*. 1983;90:1129.
Ginsberg JS, Hirsh J. Use of antithrombotic agents during pregnancy. *Chest*. 1998;114:524S.
Hill RM, Stern L. Drugs in pregnancy: effects on the fetus and newborn. *Drugs*. 1979;17:182.
Nelson-Piercy C, Letsky EA, deSwiet M. Low-molecular-weight heparin for obstetric thromboprophylaxis: experience of sixty-nine pregnancies in sixty-one women at high risk. *Am J Obstet Gynecol*. 1997;176:1062.
Sbarouni E, Oakley CM. Outcome of pregnancy in women with valve prostheses. *Br Heart J*. 1994;71:196.
Tengborn L, Bergqvist D, Matzsch T, et al. Recurrent thromboembolism in pregnancy and puerperium: is there a need for thromboprophylaxis? *Am J Obstet Gynecol*. 1989;160:90.
Vitale N, De Feo M, De Santo LS, et al. Dose-dependent fetal complications of warfarin in pregnant women with mechanical heart valves. *J Am Coll Cardiol*. 1637;33:1999.

Thyroid and Antithyroid Drugs

Blazer S, Moreh-Waterman Y, Miller-Lotan R, et al. Maternal hypothyroidism may affect fetal growth and neonatal thyroid function. *Obstet Gynecol*. 2003;102:232.
Burrow GN. Thyroid diseases. In: Burrow GN, Ferris TF, eds. *Medical Complications During Pregnancy*. Philadelphia: WB Saunders Company; 1988:229.
Casey BM, Dashe JS, Wells CE, et al. Subclinical hypothyroidism and pregnancy outcomes. *Obstet Gynecol*. 2005;105:239.
Haddow JE, Palomaki GE, Allan WC, et al. Maternal thyroid deficiency during pregnancy and subsequent neuropsychological development of the child. *N Engl J Med*. 1999;341:549.
l'Allemand D, Gruters A, Heidemann P, et al. Iodine-induced alterations of thyroid function in newborn infants after prenatal and perinatal exposure to povidone iodine. *J Pediatr*. 1983;102:935.
Mandel SJ, Larsen PR, Seely EW, et al. Increased need for thyroxine during pregnancy in women with primary hypothyroidism. *N Engl J Med*. 1990;323:91.
Wing DA, Millar LK, Koonings PP, et al. A comparison of propylthiouracil versus methimazole in the treatment of hyperthyroidism in pregnancy. *Am J Obstet Gynecol*. 1994;170:90.

Cardiac and Antihypertensive Medications

Armenti VT, Ahlswede BA, Ahlswede JR, et al. National transplantation pregnancy registry: analysis of outcome/risks of 394 pregnancies in kidney transplant recipients. *Transplant Proc*. 1994;26:2535.
Aselton P, Jick H, Milunsky A, et al. First-trimester drug use and congenital disorders. *Obstet Gynecol*. 1985;65:451.
Azathioprine. In Briggs GG, Freeman RK. *Drugs in Pregnancy and Lactation*. 10th ed. Philadelphia, PA: Wolters Kluwer Health; 2014:113.
Basle EV, Conard JV, Weiss L. Adult and two children with fetal methotrexate syndrome. *Teratology*. 1998;57:51.
Cooper WO, Hernandez-Diaz S, Arbogast PG, et al. Major congenital malformations after first-trimester exposure to ACE inhibitors. *N Engl J Med*. 2006;354:2443.
Cyclophosphamide. In Briggs GG, Freeman RK. *Drugs in Pregnancy and Lactation*. 10th ed. Philadelphia, PA: Wolters Kluwer Health; 2014:335.
Hanssens M, Keirse MJNC, Vankelecom F, et al. Fetal and neonatal effects of treatment with angiotensin-converting enzyme inhibitors in pregnancy. *Obstet Gynecol*. 1991;78:128.
Heinonen OP, Slone S, Shapiro S. *Birth Defects and Drugs in Pregnancy*. Littleton, MA: Publishing Sciences Group; 1977.
Kozlowski RD, Steinbrunner JV, MacKenzie AH, et al. Outcome of first-trimester exposure to low-dose methotrexate in eight patients with rheumatic disease. *Am J Med*. 1990;88:589.
Levy M, Buskila D, Gladman DD, et al. Pregnancy outcome following first trimester exposure to chloroquine. *Am J Perinatol*. 1991;8:174.
Orbach H, Matok I, Gorodischer R, et al. Hypertension and antihypertensive drugs in pregnancy and perinatal outcomes. *Am J Obstet Gynecol*. 2013;208:301.e1–301.e6.
Piper JM, Ray WA, Rosa FW. Pregnancy outcome following exposure to angiotensin-converting enzyme inhibitors. *Obstet Gynecol*. 1992;80:429.

Pruyn SC, Phelan JP, Buchanan GC. Long-term propranolol therapy in pregnancy: maternal and fetal outcome. *Am J Obstet Gynecol*. 1979;135:485.
Redmond GP. Propranolol and fetal growth retardation. *Semin Perinatol*. 1982;6:142.
Rubin PC, Clark DM, Sumner DJ. Placebo-controlled trial of atenolol in treatment of pregnancy-associated hypertension. *Lancet*. 1983;1:431.
Takahashi N, Nishida H, Hoshi J. Severe B cell depletion in newborns from renal transplant mothers taking immunosuppressive agents. *Transplantation*. 1617;57:1994.
Weiner CP, Landas S, Persoon TJ. Digoxin-like immunoreactive substance in fetuses with and without cardiac pathology. *Am J Obstet Gynecol*. 1987;157:368.
Weiner CP, Thompson MIB. Direct treatment of fetal supraventricular tachycardia after failed transplacental therapy. *Am J Obstet Gynecol*. 1988;158:570.
Zemlickis D, Lishner M, Degendorfer P, et al. Fetal outcome after in utero exposure to cancer chemotherapy. *Arch Intern Med*. 1992;152:573.

Bronchodilators

Blais L, Kettani FZ, Forget A, et al. Long-acting β_2-agonists and risk of hypertensive disorders in pregnancy: a cohort study. *J Allergy Clin Immunol Pract*. 2018;6:555–561.
Carmichael SL, Shaw GM. Maternal corticosteroid use and risk of selected congenital anomalies. *Am J Med Genet*. 1999;86:242.
Cromolyn. In Briggs GG, Freeman RK. *Drugs in Pregnancy and Lactation*. 10th ed. Philadelphia, PA: Wolters Kluwer Health; 2014:332.
Isoproterenol. In Briggs GG, Freeman RK. *Drugs in Pregnancy and Lactation*. 10th ed. Philadelphia, PA: Wolters Kluwer Health; 2014:742.
Main EK, Main DM, Gabbe SG. Chronic oral terbutaline therapy is associated with maternal glucose intolerance. *Obstet Gynecol*. 1987;157:644.

Antiemetics

Borrelli F, Caspasso R, Aviello G, et al. Effectiveness and safety of ginger in the treatment of pregnancy-induced nausea and vomiting. *Obstet Gynecol*. 2005;105:849.
Cartwright EW. Dramamine in nausea and vomiting of pregnancy. *West J Surg Obstet Gynecol*. 1951;59:216.
Chlorpromazine. In Briggs GG, Freeman RK. *Drugs in Pregnancy and Lactation*. 10th ed. Philadelphia, PA: Wolters Kluwer Health; 2014:252.
Diggory PLC, Tomkinson JS. Nausea and vomiting in pregnancy: a trial of meclozine dihydrochloride with and without pyridoxine. *Lancet*. 1962;2:370.
Diphenhydramine. In Briggs GG, Freeman RK. *Drugs in Pregnancy and Lactation*. 10th ed. Philadelphia, PA: Wolters Kluwer Health; 2014:414.
Fischer-Rasmussen W, Kjaer SK, Dahl C, et al. Ginger treatment of hyperemesis gravidarum. *Eur J Obstet Gynecol Reprod Biol*. 1990;38:19.
Lavecchia M, Chair R, Campbell S, et al. Ondansetron in pregnancy and the risk of congenital malformations: a systematic review. *J Obstet Gynaecol Can*. 2018;doi:10.1016/j.jogc.2017.10.024.
Meclizine. In Briggs GG, Freeman RK. *Drugs in Pregnancy and Lactation*. 10th ed. Philadelphia, PA: Wolters Kluwer Health; 2014:848.
Milkovich L, Van Den Berg BJ. An evaluation of the teratogenicity of certain antinauseant drugs. *Am J Obstet Gynecol*. 1976;125:244.
Niebyl JR. Nausea and Vomiting in Pregnancy. *N Engl J Med*. 2010;363:1544.
Prochlorperazine. In Briggs GG, Freeman RK. *Drugs in Pregnancy and Lactation*. 10th ed. Philadelphia, PA: Wolters Kluwer Health; 2014:1155.
Promethazine. In Briggs GG, Freeman RK. *Drugs in Pregnancy and Lactation*. 10th ed. Philadelphia, PA: Wolters Kluwer Health; 2014:1159.
Sahakian V, Rouse D, Sipes S, et al. Vitamin B_6 is effective therapy for nausea and vomiting of pregnancy: a randomized double-blind, placebo-controlled study. *Obstet Gynecol*. 1991;78:33.
Vutyavanich T, Wongtra-Rjan S, Ruangsri R. Pyridoxine for nausea and vomiting of pregnancy: a randomized double-blind placebo-controlled trial. *Am J Obstet Gynecol*. 1995;173:881.
Yost NP, McIntire DD, Wians FH Jr, et al. A randomized, placebo-controlled trial of corticosteroids for hyperemesis due to pregnancy. *Obstet Gynecol*. 2003;102:1250.

Antihistamines and Decongestants

Golembesky A, Cooney M, Boev R, et al. Safety of cetirizine in pregnancy. *J Obstet Gynaecol*. 2018;doi:10.1080/01443615.2018.1441271.
Pastuszak A, Schick B, D'Alimonte D, et al. The safety of astemizole in pregnancy. *J Allergy Clin Immunol*. 1996;98:748.
Terfenadine. In Briggs GG, Freeman RK. *Drugs in Pregnancy and Lactation*. 10th ed. Philadelphia, PA: Wolters Kluwer Health; 2014:1407.
Werler MM, Mitchell AA, Shapiro S. First trimester maternal medication use in relation to gastroschisis. *Teratology*. 1992;45:361.
Zierler S, Purohit D. Prenatal antihistamine exposure and retrolental fibroplasia. *Am J Epidemiol*. 1986;123:192.

Antibiotics and Antiinfective Agents

Andrews EB, Yankaskas BC, Cordero JF, et al. Acyclovir in pregnancy registry: six years' experience. *Obstet Gynecol*. 1992;79:7.
Antiretroviral Pregnancy Registry Steering Committee. Antiretroviral pregnancy Registry International Interim Report for 1 January 1989 through 31 January 2004. Wilmington, NC: Registry Coordinating Center; 2004. Available from URL: www.apregistry.com.
Berkovitch M, Pastuszak A, Gazarian M, et al. Safety of the new quinolones in pregnancy. *Obstet Gynecol*. 1994;84:535.
Bookstaver PB, Bland CM, Griffin B, et al. A review of antibiotic use in pregnancy. *Pharmacotherapy*. 2015;35:1052–1062.
Bristol-Myers Squibb. Important drug warning. Available at: http://www.fda.gov/medwatch/safety/2001/zerit&videx_letter.htm.
Burtin P, Taddio A, Ariburnu O, et al. Safety of metronidazole in pregnancy: a meta-analysis. *Am J Obstet Gynecol*. 1995;172:525.
Cephalexin. In Briggs GG, Freeman RK. *Drugs in Pregnancy and Lactation*. 10th ed. Philadelphia, PA: Wolters Kluwer Health; 2014:235.
Ciprofloxacin. In Briggs GG, Freeman RK. *Drugs in Pregnancy and Lactation*. 10th ed. Philadelphia, PA: Wolters Kluwer Health; 2014:275.
Clavulanate, Potassium. In Briggs GG, Freeman RK. *Drugs in Pregnancy and Lactation*. 10th ed. Philadelphia, PA: Wolters Kluwer Health; 2014:289.
Cohlan SQU, Bevelander G, Tiamsic T. Growth inhibition of prematures receiving tetracycline. *Am J Dis Child*. 1963;105:453.
Culnane M, Fowler MG, Lee SS, et al. Lack of long-term effects of in utero exposure to zidovudine among uninfected children born to HIV-infected women. *JAMA*. 1999;281:151.
Czeizel A. A case-control analysis of the teratogenic effects of co-trimoxazole. *Reprod Toxicol*. 1990;4:305.
Czeizel AE, Rockenbauer M, Sorensen HT, et al. Use of cephalosporins during pregnancy and in the presence of congenital abnormalities: a population-based, case-control study. *Am J Obstet Gynecol*. 2001;184:1289.
Czeizel AE, Rockenbauer M. Teratogenic study of doxycycline. *Obstet Gynecol*. 1997;89:524.
Einarson A, Phillips E, Mawji F, et al. A prospective controlled multicentre study of clarithromycin in pregnancy. *Am J Perinatol*. 1998;15:523.
Hailey FJ, Fort H, Williams JR, et al. Foetal safety of nitrofurantoin macrocrystals therapy during pregnancy: a retrospective analysis. *J Int Med Res*. 1983;11:364.
Harris RC, Lucey JF, MacLean JR. Kernicterus in premature infants associated with low concentration of bilirubin in the plasma. *Pediatrics*. 1950;23:878.
Hernandez-Diaz S, Werler MM, Walker AM, et al. Folic acid antagonists during pregnancy and the risk of birth defects. *N Engl J Med*. 2000;343:1608.
Jick SS. Pregnancy outcomes after maternal exposure to fluconazole. *Pharmacotherapy*. 1999;19:221.
Kenyon S, Boulvain M, Neilson J. Antibiotics for preterm rupture of the membranes: a systematic review. *Obstet Gynecol*. 2004;104:1051.
Kenyon SL, Taylor DJ, Tarnow-Mordi W, ORACLE Collaborative Group. Broad-spectrum antibiotics for preterm, prelabour rupture of fetal membranes: the ORICLE I randomized trial. *Lancet*. 2001;357:979.
L'Hommedieu CS, Nicholas D, Armes DA, et al. Potentiation of magnesium sulfate–induced neuromuscular weakness by gentamicin, tobramycin, and amikacin. *J Pediatr*. 1983;102:629.
Lenke RR, VanDorsten JP, Schifrin BS. Pyelonephritis in pregnancy: a prospective randomized trial to prevent recurrent disease evaluating

suppressive therapy with nitrofurantoin and close surveillance. *Am J Obstet Gynecol*. 1983;146:953.
Loebstein R, Addis A, Ho E, et al. Pregnancy outcome following gestational exposure to fluoroquinolones: a multicenter prospective controlled study. *Antimicrob Agents Chemother*. 1998;42:1336.
Marynowski A, Sianozecka E. Comparison of the incidence of congenital malformations in neonates from healthy mothers and from patients treated because of tuberculosis. *Ginekol Pol*. 1972;43:713.
Miconazole. In Briggs GG, Freeman RK. *Drugs in Pregnancy and Lactation*. 10th ed. Philadelphia, PA: Wolters Kluwer Health; 2014:913.
Muanda FT, Sheehy O, Anick B. Use of antibiotics during pregnancy and the risk of major congenital malformations: a population based cohort study. *Br J Clin Pharmacol*. 2017;83:2557–2571.
Nishimura H, Tanimura T. *Clinical Aspects of the Teratogenicity of Drugs*. Amsterdam: Excerpta Medica; 1976.
Piper JM, Mitchel EF, Ray WA. Prenatal use of metronidazole and birth defects: no association. *Obstet Gynecol*. 1993;82:348.
Pursley TJ, Blomquist IK, Abraham J, et al. Fluconazole-induced congenital anomalies in three infants. *Clin Infect Dis*. 1996;22:336.
Robinson GC, Cambon KG. Hearing loss in infants of tuberculous mothers treated with streptomycin during pregnancy. *N Engl J Med*. 1964;271:949.
Rosa FW, Baum C, Shaw M. Pregnancy outcomes after first trimester vaginitis drug therapy. *Obstet Gynecol*. 1987;69:751.
Sulfonamides. In Briggs GG, Freeman RK. *Drugs in Pregnancy and Lactation*. 10th ed. Philadelphia, PA: Wolters Kluwer Health; 2014:1297.
Trimethoprim. In Briggs GG, Freeman RK. *Drugs in Pregnancy and Lactation*. 10th ed. Philadelphia, PA: Wolters Kluwer Health; 2014:1406.
Wolfe MS, Cordero JF. Safety of chloroquine in chemosuppression of malaria during pregnancy. *Br Med J*. 1985;290:1466.

Ovulation Induction Medications

Asch RH, Greenblatt RB. Update on the safety and efficacy of clomiphene citrate as a therapeutic agent. *J Reprod Med*. 1976;17:175.
Riuz-Velasco V, Tolis G. Pregnancy in hyperprolactinemic women. *Fertil Steril*. 1984;41:793.
Scaparrotta A, Chiarelli F, Verrotti A. Potential teratogenic effects of clomiphene citrate. *Drug Saf*. 2017;40:761–769.

Mild Analgesics

Areilla RA, Thilenius OB, Ranniger K. Congestive heart failure from suspected ductal closure in utero. *J Pediatr*. 1969;75:74.
Broussard CS, Rasmussen SA, Reefhuis J, et al. Maternal treatment with opioid analgesics and risk for birth defects. *Am J Obstet Gynecol*. 2011;204:314–e1.
Collins E, Turner G. Salicylates and pregnancy. *Lancet*. 1973;2:1494.
Ibuprofen. In Briggs GG, Freeman RK. *Drugs in Pregnancy and Lactation*. 10th ed. Philadelphia, PA: Wolters Kluwer Health; 2014:682.
Naproxen. In Briggs GG, Freeman RK. *Drugs in Pregnancy and Lactation*. 10th ed. Philadelphia, PA: Wolters Kluwer Health; 2014:955.
Price HR, Collier AC. Analgesics in pregnancy: an update on use, safety and pharmacokinetic changes in drug disposition. *Curr Pharm Des*. 2017;23:6098–6114.
Stuart JJ, Gross SJ, Elrad H, et al. Effects of acetylsalicyclic acid ingestion on maternal and neonatal hemostasis. *N Engl J Med*. 1982;307:909.
Thulstrup AM, Sorensen HT, Nielsen GL, et al. Fetal growth and adverse birth outcomes in women receiving prescriptions for acetaminophen during pregnancy. *Am J Perinatol*. 1999;16:321.
Tyson HK. Neonatal withdrawal symptoms associated with maternal use of propoxyphene hydrochloride (Darvon). *J Pediatr*. 1974;85:684.
Waltman T, Tricomi V, Tavakoli FM. Effect of aspirin on bleeding time during elective abortion. *Obstet Gynecol*. 1976;48:108.
Werler MM, Mitchell AA, Shapiro S. The relation of aspirin use during the first trimester of pregnancy to congenital cardiac defects. *N Engl J Med*. 1989;321:1639.

Drugs of Abuse

Alberman E, Creasy M, Elliott M, et al. Maternal factors associated with fetal chromosomal anomalies in spontaneous abortions. *J Obstet Gynecol*. 1976;83:621.
Bingol N, Fuchs M, Diaz V, et al. Teratogenicity of cocaine in humans. *J Pediatr*. 1987;110:93.
Bupropion Pregnancy Registry. Interim Report: 1 September 1997 through 28 February 2002. Wilmington, NC, PharmaResearch Corporation, June 2002.
Carter RC, Wainwright H, Molteno CD, et al. Alcohol, methamphetamine, and marijuana exposure have distinct effects on the human placenta. *Alcohol Clin Exp Res*. 2016;40:753–764.
Chasnoff IJ, Chisum GM, Kaplan WE. Maternal cocaine use and genitourinary tract malformations. *Teratology*. 1988;37:201.
Chasnoff IJ, Griffith DR, MacGregor S, et al. Temporal patterns of cocaine use in pregnancy. *JAMA*. 1989;261:1741.
Day NL, Richardson GA. Prenatal alcohol exposure: a continuum of effects. *Semin Perinatol*. 1991;15:271.
Dolan-Mullen P, Ramierez G, Groff JY. A meta-analysis of randomized trials of prenatal smoking cessation interventions. *Am J Obstet Gynecol*. 1994;171:1328.
Fergusson DM, Horwood LJ, Nortstone K. Maternal use of cannabis and pregnancy outcome. *Br J Obstet Gynecol*. 2002;109:21.
Finnegan LP, Wapner RJ. Narcotic addiction in pregnancy. In: Niebyl JR, ed. *Drug Use in Pregnancy*. Philadelphia: Lea & Febiger; 1988:203.
Handler A, Kistin N, Davis F, et al. Cocaine use during pregnancy: perinatal outcomes. *Am J Epidemiol*. 1991;133:818.
Jones HE, Kaltenbach K, Heil SH, et al. Neonatal abstinence syndrome after methadone or buprenorphine exposure. *N Engl J Med*. 2010;353:2320.
Jones KL, Smith DW, Streissguth AP, et al. Outcome of offspring of chronic alcoholic women. *Lancet*. 1974;2:1076.
Jones KL, Smith DW, Ulleland CN, et al. Patterns of malformation in offspring of chronic alcoholic mothers. *Lancet*. 1973;2:1267.
Keith LG, MacGregor S, Friedell S, et al. Substance abuse in pregnant women: recent experience at the perinatal center for chemical dependence of Northwestern Memorial Hospital. *Obstet Gynecol*. 1989;73:715.
Kwiatkowski MA, Donald KA, Stein DJ, et al. Cognitive outcomes in prenatal methamphetamine exposed children aged six to seven years. *Compr Psychiatry*. 2018;80:24–33.
Linn S, Schoenbaum SC, Monson RR, et al. The association of marijuana use with outcome of pregnancy. *Am J Public Health*. 1983;73:1161.
Little BB, Snell LM, Klein VR, et al. Cocaine abuse during pregnancy: maternal and fetal implications. *Obstet Gynecol*. 1989;73:157.
Little BB, Snell LM. Brain growth among fetuses exposed to cocaine in utero: asymmetrical growth retardation. *Obstet Gynecol*. 1991;77:361.
MacGregor SN, Keith LG, Chasnoff IJ, et al. Cocaine use during pregnancy: adverse perinatal outcome. *Am J Obstet Gynecol*. 1987;157:686.
Marcus BH, Albrecht AE, King TK, et al. The efficacy of exercise as an aid for smoking cessation in women. *Arch Intern Med*. 1999;159:1229.
Martin TR, Bracken MB. Association of low birth weight with passive smoke exposure in pregnancy. *Am J Epidemiol*. 1986;124:633.
Mills JL, Graubard BI. Is moderate drinking during pregnancy associated with an increased risk of malformations? *Pediatrics*. 1987;80:309.
Ogburn PL, Hurt RD, Croghan IT, et al. Nicotine patch use in pregnant smokers: nicotine and cotinine levels and fetal effects. *Am J Obstet Gynecol*. 1999;181:736.
Ouellette EM, Rosett HL, Rosman NP, et al. Adverse effects on offspring of maternal alcohol abuse during pregnancy. *N Engl J Med*. 1977;297:528.
Rosett HL. A clinical perspective of the fetal alcohol syndrome. *Alcohol Clin Exp Res*. 1980;4:119.
Shah NR, Bracken MB. A systematic review and meta-analysis of prospective studies on the association between interval cigarette smoking and preterm delivery. *Am J Obstet Gynecol*. 2000;182:465.
Sokol RJ, Martier SS, Ager JW. The T-ACE questions: practical prenatal detection of risk-drinking. *Am J Obstet Gynecol*. 1989;160:863.
Tonnesen P, Norregaard J, Simonsen K, et al. A double-blind trial of a 16-hour transdermal nicotine patch in smoking cessation. *N Engl J Med*. 1991;325:311.
Van den Berg BJ. Epidemiologic observations of prematurity: effects of tobacco, coffee and alcohol. In: Reed DM, Stanley FJ, eds. *The Epidemiology of Prematurity*. Baltimore: Urban & Schwarzenberg; 1977.

Visscher WA, Feder M, Burns AM, et al. The impact of smoking and other substance use by urban women on the birthweight of their infants. *Subst Use Misuse*. 2003;38:1063.
Warton FL, Taylor PA, Warton CMR, et al. Prenatal methamphetamine exposure is associated with corticostriatal white matter changes in neonates. *Metab Brain Dis*. 2018;33:507–522.
Zuckerman B, Frank DA, Hingson R, et al. Effects of maternal marijuana and cocaine use on fetal growth. *N Engl J Med*. 1989;320:762.

Caffeine

Beaulac-Baillargeon L, Desrosiers C. Caffeine-cigarette interaction on fetal growth. *Am J Obstet Gynecol*. 1987;157:1236.
Infante-Rivard C, Fernandez A, Gauthier R, et al. Fetal loss associated with caffeine intake before and during pregnancy. *JAMA*. 1993;270:2940.
Linn S, Schoenbaum SC, Monson RR, et al. No association between coffee consumption and adverse outcomes of pregnancy. *N Engl J Med*. 1982;306:141.
Martin TR, Bracken MB. The association between low birth weight and caffeine consumption during pregnancy. *Am J Epidemiol*. 1987;126:813.
Mills JL, Holmes LB, Aarons JH, et al. Moderate caffeine use and the risk of spontaneous abortion and intrauterine growth retardation. *JAMA*. 1993;269:593.
Munoz LM, Lonnerdal B, Keen CL, et al. Coffee consumption as a factor in iron deficiency anemia among pregnant women and their infants in Costa Rica. *Am J Clin Nutr*. 1988;48:645.

Drugs in Breast Milk

ACOG Practice Bulletin #121, Long-acting reversible contraception: implants and intrauterine devices. *Obstet Gynecol*. 2011;118:184.
Allaire AD, Kuller JA. Psychotropic drugs in pregnancy and lactation. In: Yankowitz J, Niebyl JR, eds. *Drug Therapy in Pregnancy*. 3rd ed. New York: Lippincott Williams & Wilkins; 2001.
Anderson PO, Salter FJ. Propranolol therapy during pregnancy and lactation. *Am J Cardiol*. 1976;37:325.
Anderson PO. Drug use during breast-feeding. *Clin Pharm*. 1991;10:594.
Bauer JH, Pope B, Zajicek J, et al. Propranolol in human plasma and breast milk. *Am J Cardiol*. 1979;43:860.
Brambel CE, Hunter RE. Effect of dicumarol on the nursing infant. *Am J Obstet Gynecol*. 1950;59:1153.
Burch KJ, Wells BG. Fluoxetine/norfluoxetine concentrations in human milk. *Pediatrics*. 1992;89:676.
Canales ES, Garcia IC, Ruiz JE, et al. Bromocriptine as prophylactic therapy in prolactinoma during pregnancy. *Fertil Steril*. 1981;36:524.
Celiloglu M, Celiker S, Guven H, et al. Gentamicin excretion and uptake from breast milk by nursing infants. *Obstet Gynecol*. 1994;84:263.
Chisolm CA, Kuller JA. A guide to the safety of CNS-active agents during breastfeeding. *Drug Saf*. 1997;17:127–142.
Cooper DS. Antithyroid drugs: to breast-feed or not to breast-feed. *Am J Obstet Gynecol*. 1987;157:234.
Devlin RG, Fleiss PM. Selective resistance to the passage of captopril into human milk. *Clin Pharmacol Ther*. 1980;27:250.
Ehrenkranz RA, Ackerman BA, Hulse JD. Nifedipine transfer into human milk. *J Pediatr*. 1989;114:478.
Findlay JWA, Butz RF, Sailstad JM, et al. Pseudoephedrine and triprolidine in plasma and breast milk of nursing mothers. *Br J Clin Pharmacol*. 1984;18:901.
Grimes DA, Wallach M. *Modern Contraception*. Totowa, NJ: Emron; 1997:249.
Hartikainen-Sorri AL, Heikkinen JE, Koivisto M. Pharmacokinetics of clonidine during pregnancy and nursing. *Obstet Gynecol*. 1987;69:598.
Hosbach RE, Foster RB. Absence of nitrofurantoin from human milk. *JAMA*. 1967;202:1057.
Illingsworth RS. Abnormal substances excreted in human milk. *Practitioner*. 1953;171:533.
Johns BG, Rutherford CD, Laighton RC, et al. Secretion of methotrexate into human milk. *Am J Obstet Gynecol*. 1972;112:978.
Kampmann JP, Hansen JM, Johansen K, et al. Propylthiouracil in human milk. *Lancet*. 1980;1:736.
Katz FH, Duncan BR. Entry of prednisone into human milk. *N Engl J Med*. 1975;293:1154.
Kelsey JJ, Moser LR, Jenning JC, et al. Presence of azithromycin breast milk concentrations: a case report. *Am J Obstet Gynecol*. 1994;170:1375.
Klebanoff MA, Levine RJ, DerSimonian R, et al. Maternal serum paraxanthine, a caffeine metabolite, and the risk of spontaneous abortion. *N Engl J Med*. 1639;341:1999.
Labrecque M, Marcoux S, Weber J-P, et al. Feeding and urine cotinine values in babies whose mothers smoke. *J Pediatr*. 1985;107:816.
Linden S, Rich CL. The use of lithium during pregnancy and lactation. *J Clin Psychiatry*. 1983;44:358.
Loughnan PM. Digoxin excretion in human breast milk. *J Pediatr*. 1978;92:1019.
Luck W, Nau H. Nicotine and cotinine concentrations in serum and urine of infants exposed via passive smoking or milk from smoking mothers. *J Pediatr*. 1985;107:816.
MacKenzie SA, Seeley JA, Agnew JE. Secretion of prednisolone into breast milk. *Arch Dis Child*. 1975;50:894.
Meyer LJ, de Miranda P, Sheth N, et al. Acyclovir in human breast milk. *Am J Obstet Gynecol*. 1988;158:586.
Miller ME, Cohn RD, Burghart PH. Hydrochlorothiazide disposition in a mother and her breast-fed infant. *J Pediatr*. 1982;101:789.
Moretti ME, Ito S, Koren G. Disposition of maternal ketoconazole in breast milk. *Am J Obstet Gynecol*. 1995;173:1625.
Niebyl JR, Blake DA, Freeman JM, et al. Carbamezapine levels in pregnancy and lactation. *Obstet Gynecol*. 1979;53:139.
Nilsson S, Nygren KG, Johansson EDB. Transfer of estradiol to human milk. *Am J Obstet Gynecol*. 1978;132:653.
Ost L, Wettrell G, Bjorkhem I, et al. Prednisolone excretion in human milk. *J Pediatr*. 1985;106:1008.
Phenytoin. In Briggs GG, Freeman RK. *Drugs in Pregnancy and Lactation*. 10th ed. Philadelphia, PA: Wolters Kluwer Health; 2014:1116.
Propranolol. In Briggs GG, Freeman RK. *Drugs in Pregnancy and Lactation*. 10th ed. Philadelphia, PA: Wolters Kluwer Health; 2014:1164.
Pynnonen S, Sillanpaa M. Carbamazepine and mother's milk. *Lancet*. 1975;2:563.
Sachs HC, Committee on Drugs. The transfer of drugs and therapeutics into human breast milk: an update on selected topics. *Pediatrics*. 2013;132:e796–e809.
Schmimmel MS, Eidelman AJ, Wilschanski MA, et al. Toxic effects of atenolol consumed during breast feeding. *J Pediatr*. 1989;114:476.
Weithmann MW, Krees SV. Excretion of chlorothiazide in human breast milk. *J Pediatr*. 1972;81:781.
White WB, Andreoli JW, Wong SH, et al. Atenolol in human plasma and breast milk. *Obstet Gynecol*. 1984;63:42S.
Wilson JT, Brown RD, Cherek DR, et al. Drug excretion in human breast milk: principles of pharmacokinetics and projected consequences. *Clin Pharmacokinet*. 1980;5:1.
Yoshioka H, Cho K, Takimoto M, et al. Transfer of cefazolin into human milk. *J Pediatr*. 1979;94:151.

Radiation

Brent RL. The effects of embryonic and fetal exposure to x-ray, microwaves, and ultrasound. *Clin Perinatol*. 1986;13:615.
Damilakis J, Perisinakis K, Voloudaki A, et al. Estimation of fetal radiation dose from computed tomography scanning in late pregnancy: depth-dose data from routine examinations. *Invest Radiol*. 2000;35:527.
Gardner MJ, Hall AJ, Snee MP, et al. Methods and basic data of case-control study of leukaemia and lymphoma among young people near Sellafield nuclear plant in West Cumbria. *Br Med J*. 1990;300:429.
Gardner MJ, Snee MP, Hall AJ, et al. Results of case-control study of leukaemia and lymphoma among young people near Sellafield nuclear plant in West Cumbria. *Br Med J*. 1990;300:423.
Giles D, Hewitt D, Stewart A, et al. Malignant disease in childhood and diagnostic irradiation in utero. *Lancet*. 1956;271:447.
Gold EB, Tomich E. Occupational hazards to fertility and pregnancy outcome. *Occup Med*. 1994;9:435.
Krisch-Volders M. *Mutagenicity, Carcinogenicity, and Teratogenicity of Industrial Pollutants*. New York: Plenum; 1984.
Marcus M. Epidemiologic studies of VDT use and pregnancy outcome. *Reprod Toxicol*. 1990;4:51.

McLaughlin JR, King WD, Anderson TW, et al. Paternal radiation exposure and leukaemia in offspring: the Ontario case-control study. *Br Med J*. 1993;307:959.

Miller RW. Delayed effects occurring within the first decade after exposure of young individuals to the Hiroshima atomic bomb. *Pediatrics*. 1956;18:1.

Miller RW. Effects of ionizing radiation from the atomic bomb on Japanese children. *Pediatrics*. 1968;41:257.

Neel JV. Problem of "false positive" conclusions in genetic epidemiology: lessons from the leukemia cluster near the Sellafield nuclear installation. *Genet Epidemiol*. 1994;11:213.

Sever LE, Gilbert ES, Hessol NA, et al. A case-control study of congenital malformations and occupational exposure to low-level ionizing radiation. *Am J Epidemiol*. 1988;127:226.

Sever LE. Parental radiation exposure and children's health: are there effects on the second generation? *Occup Med*. 1991;6:613.

Stewart A, Kneale GW. Radiation dose effects in relation to obstetric x-rays and childhood cancers. *Lancet*. 1970;1:1185.

Stewart A, Webb J, Hewett D. A survey of childhood malignancies. *Br Med J*. 1958;30:1495.

Wood JW, Johnson KG, Omori Y, et al. Mental retardation in children exposed in utero to the atomic bombs in Hiroshima and Nagasaki. *Am J Public Health Nations Health*. 1967;57:1381.

Lead

Bellinger D, Leviton A, Waternaux C, et al. Longitudinal analyses of prenatal and postnatal lead exposure and early cognitive development. *N Engl J Med*. 1987;316:1037.

Centers for Disease Control. Preventing lead poisoning in young children—United States. *MMWR Morb Mortal Wkly Rep*. 1985;34:66.

Creason JP, Svensgaard DJ, Baumgarner JE. Maternal-fetal tissue levels of sixteen trace elements in eight communities. *USEPA Report EPA No. 600*. 1978;1:78.

Farias P, Borja-Aburto VH, Rios C, et al. Blood lead levels in pregnant women of high and low socioeconomic status in Mexico City. *Environ Health Perspect*. 1996;104:1070.

Occupational Safety and Health Administration. Occupational exposure to lead. *Fed Reg*. 1978;43:52952.

Pietrzyk JJ, Nowak A, Mitkowska Z, et al. Prenatal lead exposure and the pregnancy outcome. A case-control study in southern Poland. *Przegl Lek*. 1996;53:342.

Rothenberg SJ, Manalo M, Jiang J, et al. Maternal blood lead level during pregnancy in South Central Los Angeles. *Arch Environ Health*. 1999;54:151.

Sandstead HH, Doherty RA, Mahaffey KA. Effects and metabolism of toxic trace metals in the neonatal period. In: Clarkson TW, Nordberg GFSRP, eds. *Reproductive and Developmental Toxicology of Metals*. New York: Plenum; 1983:207.

Torres-Sanchez LE, Berkowitz G, Lopez-Carrillo L, et al. Intrauterine lead exposure and preterm birth. *Environ Res*. 1999;81:297.

U.S. Environmental Protection Agency, March 2004, website: www.cfsan.fda.gov/.

Patient Education

Medicine and pregnancy. FDA Office of Women's Health. www.fda.gov/pregnancy.