

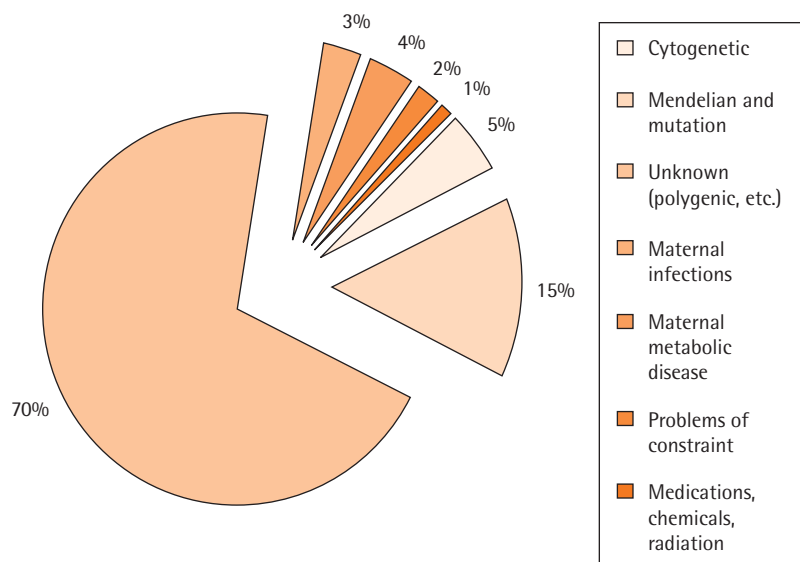
## 1

# Introduction to drugs in pregnancy

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Birth defects occur among 3.5–5 percent of infants examined at birth or neonatally (Polifka and Friedman, 2002) but prevalence of birth defects may be as high as 8 percent, according to a universal disease registry from British Columbia (Baird *et al.*, 1989). Using the estimated teratogenic causes of birth defects in Fig. 1.1, it may be extrapolated that as many as 1 percent of congenital anomalies are caused by drugs, chemicals and other exogenous agents (i.e., approximately one in 400 infants has a birth defect with a teratogenic etiology). These estimates have not changed over the past decade and a half, perhaps because genomic research eclipses research in clinical teratology, as suggested by a recent review (Polifka and Friedman, 2002). Nonetheless, much research remains to be done because the magnitude of the problem of medication use during pregnancy may be somewhat underestimated because 65–70 percent of birth defects have an unknown etiology. This may include unreported medically prescribed medication with teratogenic potential, use of alcohol and/or drugs of abuse, and other preventable causes of birth defects (i.e., congenital anomalies and other pregnancy complications due to drug and chemical exposure are unique because they are potentially preventable). Knowledge of the effects of prenatal exposure and the window of opportunity for intervention are the key factors in evaluation and prevention of morbidity and mortality due to drug and chemical exposure during pregnancy. Chapters 2–15 summarize information currently available regarding drug exposure during pregnancy, with detailed

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**Figure 1.1** Causes of birth defects

drug-specific information obtained from the current medical literature, clinical experience, and science.

Clinicians find it difficult to use the narrow window of opportunity to intervene in medication use during pregnancy because pregnant women do not present for prenatal care until embryogenesis is complete (i.e., after 58 days postconception). Intervention is further complicated because many women are not aware of the potential adverse effects of drugs and chemicals on pregnancy. For example, more than 60 percent of gravidas had never heard of fetal alcohol syndrome and were not aware of the adverse effects of alcohol on pregnancy in several surveys. Patient education prior to conception is obviously the best intervention, but very little funding is available for this. In addition, social and cultural barriers must also be overcome for the patient education process to be successful.

Even the most well-educated obstetrical patients have culturally based 'folk etiologies' that they believe explain the occurrence of birth defects and other adverse pregnancy outcomes that are usually not correlated with medically founded causes. The author has counseled gravid physicians who were not entirely correct in their understanding of prenatal development and how the environment can be a disruptive influence. Folk or culture-specific explanations and educational background must therefore be considered when counseling the obstetrical patient of specific risks to pregnancy, including exposures to medications, drugs, and chemicals.

### MAGNITUDE OF THE PROBLEM

Women ingest a variety of medications or drugs during pregnancy, usually related to a medical condition that was being treated before the pregnancy was recognized. Prevalence of medication use varied from less than 10 percent of pregnant women to

more than 95 percent. Frequently, more than one medication will be used. For example, in one comprehensive study in the United States of tens of thousands of patients, women received an average of 3.1 prescriptions for medications other than vitamins or iron during their pregnancies. Similar prevalences were observed in Brazil, Australia, New Zealand, and Egypt. The high end estimates are probably closer to the prevalence in 2004, and this is an international pattern and problem. Medication use during pregnancy is clearly a frequent event. However, safety may be questionable or simply unknown in many instances (Polifka and Friedman, 2002), primarily because of the paucity of clinical teratology research conducted over the last two decades (Lo and Friedman, 2002).

Three scenarios describe inadvertent drug exposure during pregnancy: (1) some medications are taken before the pregnancy is recognized; (2) some medications are taken without the physician's advice once the pregnancy is recognized; and (3) some are taken with physician's advice. In practice, the predominant case is for physicians to be faced with determining whether or not a medication or drug may be harmful to a pregnant woman or her unborn child after the exposure has occurred.

Also of concern are nonmedical exposures to drugs. Nonmedical exposures to drugs during pregnancy occur in suicide gestures (technically a subcategory of substance abuse) and substance abuse (i.e., recreational use). Suicide gestures occur among approximately 1 percent of pregnant women. Substance abuse during pregnancy is much more prevalent than suicide gestures, and is discussed in Chapter 15. Briefly, an estimated 10–20 percent of pregnant women use an illicit substance and/or alcohol during their pregnancies. Cocaine seems to be the most frequently used substance in 2004.

## CLINICAL EVALUATION

Clinical evaluation of potentially teratogenic and/or toxic exposures during pregnancy must consider three separate components of normal pregnancy: maternal, embryonic, and fetal. Marked differences in the physiology of these components exist because of differences in the purposes of the cells, or the end points of cell division (replacement versus morphogenesis versus hyperplastic growth) and the metabolic capabilities of the mother and the developing conceptus. In the embryo, organs are being formed, and drugs cannot be metabolized at adult or fetal rates, if at all. The embryo is not a little fetus. The fetus is not a little adult. Most of the fetal period is occupied with growth in size of organs, not usually their formation, and these are growing very rapidly. Exceptions exist (e.g., thyroid, sexual organs, brain cell 'arrangement'), but this is generally true for the fetus. Fetal enzyme systems involved in drug metabolism are only beginning to function, and some will not be active until after the neonatal period (e.g., cholinesterase). Pregnant women have the full enzyme complement for metabolizing drugs, but most such systems have lower activity during pregnancy, as does cholinesterase (Pritchard, 1955), which metabolizes cocaine. In addition, gender differences in the nonpregnant state also exist [e.g., alcohol dehydrogenase (ADH) among adult females is only 55 percent of adult males' activity]. Therefore, the responses of adults, fetuses, embryos, and pregnant women to drugs (pharmacodynamics, pharmacokinetics) differ markedly (Little, 1999). Therefore, it is important to differentiate the effects of drugs and chemicals upon these distinctly different components of pregnancy. We shall repeatedly observe that many drugs and chemicals have different effects on these three components of pregnancy.

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### HUMAN TERATOLOGY – PRINCIPLES

A teratogen is usually defined as any agent, physical force, or other factor (e.g., maternal disease) that can induce a congenital anomaly through alteration of normal development during any stage of embryogenesis (Polifka and Friedman, 2002). Agents include drugs and other chemicals. Physical forces include ionizing radiation and physical restraint (e.g., amniotic banding). Teratogenic maternal diseases include disorders such as diabetes mellitus and phenylketonuria. Agents that cause defects during the postembryonic (fetal) period are termed to have the potential for producing adverse 'fetal effects.' However, not all agents or factors that are teratogens have adverse fetal effects, and vice versa.

A simplified overview of the differences between the embryonic and fetal periods should be presented during consultation to clarify status for the patient. The period of the embryo should be described as the growth of cells that all look alike (i.e., are undifferentiated) into specialized cells that are arranged in special ways (i.e., organs, specialized tissues). These specialized cell lines or lineages grow in number and change in structure and arrangement, giving rise to organs and tissues. Some organs and tissues are formed earlier than are others. For example, the brain and spine form earlier than do the face and endocrine system. After embryogenesis (58–60 days postconception) is completed, the conceptus is a fetus (Fig. 1.2). With few exceptions, the morphological architecture for a normal (or abnormal) human is laid down during the embryonic period, and these structures simply grow in size and develop normal physiologic function during the fetal period.

Congenital anomalies can be induced during the fetal period through a fetal effect, although they are usually induced during the critical embryonic period. For example, a structure that was formed normally during embryogenesis can be damaged during the fetal period, and the resulting malformation may appear to have arisen during morphogenesis. A classic example of a fetal effect is hemorrhaging due to Coumadin exposure, which may induce brain or eye defects despite the fact that these structures were formed normally during the embryonic period.

Of all the human teratogens, thalidomide is the most notorious and heuristic example of how such agents might not be identified. In the case of thalidomide, the animal models normally used in drug screening failed to identify this drug as a dangerous substance for use during pregnancy before it was released to the market. In the human experience, it was one of the most potent teratogens ever discovered. Although laboratory studies cannot replace large, well-controlled, human epidemiologic studies, they do play an important role in screening drugs and chemicals for their potential to cause human birth defects during pregnancy. Isotretinoin (Accutane) is the only human teratogen ever discovered through laboratory research. It was known before isotretinoin was ever released on the market that this drug had a high potential for inducing congenital anomalies and pregnancy loss, and this fact was clearly displayed on the manufacturer's package insert. Unfortunately, inadvertent exposures to isotretinoin during early human pregnancy have confirmed laboratory findings. More than 100 pregnancies have been exposed to date, and a pattern of anomalies known as isotretinoin embryopathy has been observed in more than 40 percent of the offspring. Other human teratogens were discovered by astute clinicians who recognized patterns or constellations of anomalies

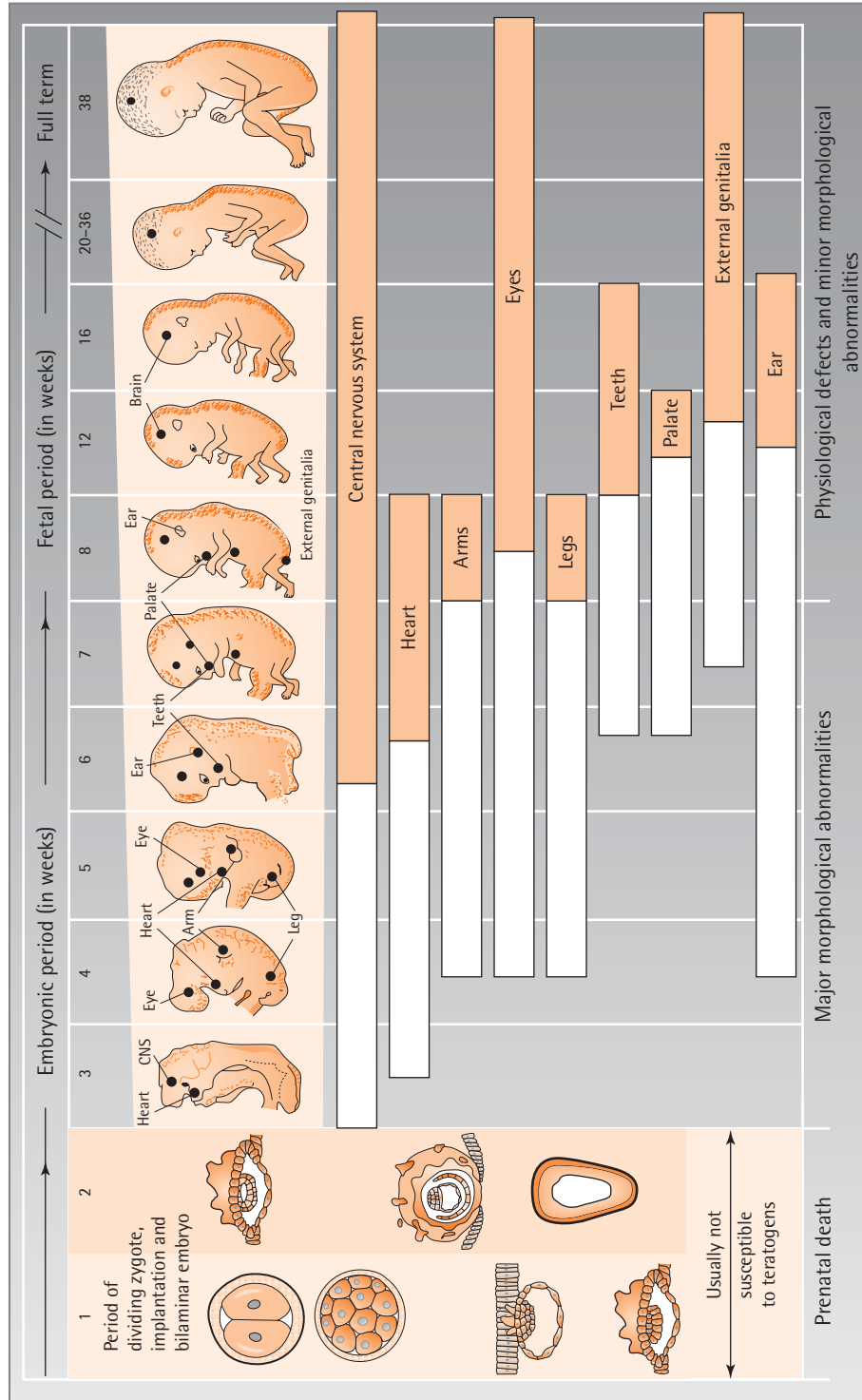


Figure 1.2 Critical times for the development of various organs and structures. Redrawn from Airrens ES, Simonis AM. *De invulsd Chemischestoffen op het angebaren kind*. Natuuren Technieke 1974; 43.

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in small clinical series of infants whose mothers used or were exposed to certain drugs or chemicals during early pregnancy. Epidemiological studies of infants whose mothers used certain drugs or chemicals during embryogenesis, as well as research with pregnant animals, have served primarily to confirm clinical observations.

Maternal complications and fetal effects due to drug or chemical exposures are not considered under the rubric of classical teratology, but the discovery of drugs and other agents with such potential adverse effects parallels the pattern of the discovery of human teratogens.

### ANIMAL STUDIES IN CLINICAL EVALUATION

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Animal models are poor predictors of whether or not a drug or chemical is teratogenic in humans. The accuracy and precision (sensitivity and specificity) of animal models in the prediction of human teratogenicity is dependent upon how close the experimental animal species is to humans. Nonhuman primates are better predictors of human teratogenicity and fetotoxicity than are rodent models because primates are genetically more closely related to humans. Animal teratology experiments are further complicated because doses used are many times greater than those given to humans, even approaching maternally toxic doses. Extremely high doses and toxic effects on the mother confound the interpretation of fetal outcome. Metabolism and absorption of drugs and chemicals are different between species because of differences in placentation, pharmacokinetics, pharmacodynamics, embryonic development timing, and innate predisposition to various congenital anomalies. Sensitivity and specificity of rodent studies are less than 60 percent (Schardein, 2000). Rodent animal teratology studies are undertaken by the US Food and Drug Administration (FDA) as part of an accepted drug-approval process to evaluate the safety of medications for use during human pregnancy, despite their very poor ability to predict human teratogens. Nonhuman primate teratology studies are considerably better predictors of which medications may be harmful when given during human pregnancy, with sensitivity and specificity of 90 percent or greater. Nonhuman primate studies are, however, orders of magnitude more expensive than rodent teratology studies, and few drugs are evaluated in primates. Unfortunately, the ultimate assessment of the safety of medication use in pregnancy must come from human studies (Schardein, 2000; Shepard, 2004). Human teratogens are discovered only after numerous children have been damaged, and an astute clinician recognizes a pattern (syndrome) of congenital anomalies, and makes the link to an exposure during pregnancy. These differences are well recognized. For example, of approximately 2000 drugs and chemicals tested in animal models, 55 percent were found to have teratogenic effects (Shepard, 2004). But the number of human teratogens is approximately 50.

### HUMAN STUDIES

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Human teratogens are identified through careful interpretation of data obtained from case reports, clinical series, and epidemiologic studies. A recurrent pattern of anomalies in babies who experienced similar well-defined exposures at similar points during embryogenesis are suggestive that the agent in question may be teratogenic. Case reports are important in raising causal hypotheses; however, most hypotheses are subsequently

proven incorrect. For example, a high incidence of environmental exposure to spermicides by pregnant women and congenital anomalies in offspring is a coincidental occurrence, despite what the legal literature states.

An example of a teratogen that was identified through epidemiologic studies, case reports, and animal studies is carbamazepine. For several decades, carbamazepine was assumed to be safer for the treatment of epilepsy during pregnancy than phenytoin or the other hydantoin. In 1993, a case report was published that reported a suicide attempt by a nonepileptic gravida during the period of spinal closure. The result was a fetus with a very large meningomyelocele (Little *et al.*, 1993). In 1989, Jones *et al.* published a case-control study of carbamazepine and concluded that the study drug was the cause of an increased frequency of birth defects. Other epidemiologic studies throughout the 1990s were conducted, and in 2006 the association of neural tube defects with carbamazepine exposure during early pregnancy is generally accepted as causal, and the risk is quantified at about 1 percent, compared to about 0.1 percent in the general population.

Quantitative estimates of risks for birth defects (strength and statistical significance of associations between agent exposures in pregnant women and abnormalities in their offspring) are obtained only through epidemiological studies. Human investigations are necessary to demonstrate that an agent is teratogenic. Unfortunately, such studies are not informative until the agent has already damaged a number of children. There are two types of epidemiology studies: cohort studies and case-control studies. In cohort studies the frequencies of certain anomalies in the offspring of women who are exposed are compared to the frequencies in those who are unexposed to the agent in question. A higher frequency of anomalies among exposed pregnancies indicates that the drug or agent should be scrutinized as a teratogen. In case-control studies the frequency of prenatal exposure to the agent is compared among children with and without a specific birth defect. If malformed children were more frequently exposed to a drug or agent than unaffected controls, then the drug or agent may be a teratogen. If an agent increases the risk of anomalies in the offspring only slightly, very large studies over a protracted period may be necessary to demonstrate that the increase is causal.

Epidemiologic studies have several limitations. Spurious associations often occur because many epidemiologists lack medical or biological training, and fail to scrutinize their 'statistical associations' for biological plausibility. Other confounders are sample size, investigations that involve small numbers of exposed or affected subjects, or situations in which the maternal disease or situation that led to the exposure may be responsible for an observed association with a congenital anomaly, rather than the agent itself. Of paramount importance is that the observed association makes biological sense. Exposures that produce malformations in the embryo should do so only during organogenesis or histogenesis. Affected structures should be susceptible to the teratogenic action of an agent only at specific gestational times. Systemic absorption of the agent by the mother and its presence at susceptible sites in the embryo or placenta should be demonstrable. Exposure to a greater quantity of the agent should be associated in a dose-response fashion with an increased frequency of abnormalities. Finally, a causal inference is supported if a reasonable pathogenic mechanism can be established for the observed effect. For example, lower birth weight is associated with maternal antihypertensive therapy, but maternal hypertension is itself strongly associated with decreased

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birth weight. Is lower birth weight associated with the blood pressure medication, or the disease of hypertension, or some combination?

### KNOWN HUMAN TERATOGENS

The list of known human teratogens is surprisingly small (Box 1.1). The most notorious human teratogen is thalidomide. It is currently available in the USA on a limited basis for treatment of several infectious diseases such as acquired immune deficiency syndrome (AIDS), tuberculosis, and leprosy. In 1996, a new thalidomide embryopathy epidemic was reported in Brazil and other South American countries (Castilla *et al.*, 1996).

The astute reader will note that some of the putative teratogens do not fit precisely the definition of teratogen (i.e., exposure is not strictly confined to the period of organogenesis).

#### Box 1.1 Known human teratogens

ACE inhibitors	Coumarin derivatives	Retinoids (oral)
Amiodarone	Cyclophosphamide	Tetracycline derivatives
Aminopterin	Danazol	Thalidomide
Antiepileptic drugs	Diethylstilbestrol	Fluconazole
Carbamazepine	Lithium	Methimazole
Clonazepam	Methotrexate	Misoprostol
Primidone	Methylene blue	Trimethadione, paramethadione
Phenobarbital	Penicillamine	Trimethoprim
Phenytoin/fosphenytoin	Quinine	
Valproic acid	Radioiodine	

ACE, Angiotensin converting enzyme

Adapted from Schardein (2000), Shepard (2004), and Polifka and Friedman (2002).

### CRITICAL TIME PERIODS

*In utero* development is divided into three time periods of development: (1) preimplantation; (2) period of the embryo; and (3) time of the fetus. Exposure to drugs during pregnancy must be separated into these time periods because the conceptus responds differently in each of the three stages of development.

#### Preimplantation

No physiologic interface between the mother and the conceptus exists at conception (ovum penetration by the spermatid to form a single diploid cell). Traditionally, the first week postconception (until the blastocyst attaches to the wall of the uterus forming chorionic villi) was considered protected from drugs or medications that may be in the maternal circulation because there is no formal biological interface between the blastocyst and the mother. However, recent evidence (e.g., mitomycin) indicates that the preimplantation embryo may not be as protected as previously thought.

## Embryonic development

The most critical stage of development for the induction of birth defects is the period of the embryo. The period of the embryo extends the time of implantation until 58–60 days postconception. The organs and tissues of the unborn baby are being formed (i.e., organogenesis) during this period. Mistakes which occur during the period of the embryo result in malformations (congenital anomalies) and are called birth defects. Teratogens are agents that cause abnormal embryonic physical or physiological development by acting during the period of the embryo, or organogenesis (Jones, 1988). Malformations lethal to the embryo present as spontaneous abortion, sometimes before pregnancy is recognized. Similarly, some substances that are directly toxic to the embryo, e.g., methotrexate, also present as spontaneous abortions. The critical times for the development of various organs and structures of the human embryo are given in Fig. 1.2 (p. 5).

## Fetal development

Important changes occur during the embryonic development that can also be damaged outside the period of the embryo. Traditionally, things that happened to a fetus were not considered a teratogenic effect, but some authorities have begun lumping fetal effects into this category. Changes in cellular structures such as the brain cell arrangements during neuronal migration occur during the fetal period. However, the predominant fetal event is hyperplastic growth (increase in cell number) with organs and other tissues becoming larger through cellular proliferation, and only secondarily through hypertrophy. An important example is the thyroid, which appears early in the fetal period, as does fetal endocrine function. Most of the potential adverse effects during fetal development are maldevelopment due to interrupted cell migration and growth retardation (Jones, 1988). If blood flow to an organ or structure is interrupted or obstructed, structures that were normally formed during embryogenesis may be malformed during the fetal period (e.g., vascular disruption and fetal cocaine or warfarin exposure). The structure deprived of blood flow would undergo necrosis and be resorbed. This would produce a defect that may mimic an embryonic effect. However, the true origin of the defect would be fetotoxicity.

The embryo and fetus are exposed to drugs through the placenta which can: (1) metabolize certain drugs before they reach the conceptus; (2) allow 99 percent of drugs to cross by simple diffusion; (3) not transport large molecules (i.e., larger than 1000 molecular weight), unless there is an active transport system (e.g., antibodies); (4) transport neutrally charged molecules; (5) easily transport lipid-soluble drugs; and (6) not transport charged (+ or -) molecules. Poor potential for transfer back to the maternal circulation occurs for some drugs (e.g., water-soluble drugs transfer back to the mother's circulation poorly), resulting in accumulation in the embryofetal compartment.

## POTENTIAL ADVERSE EFFECTS

### Spontaneous abortion

As many as 50 percent of early pregnancies (0–58 days) end in spontaneous abortion. Recent findings from *in vitro* fertilization studies suggest that the majority of these

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spontaneous abortuses are chromosomally abnormal. The risk of spontaneous abortion is 15–20 percent among fetuses surviving 59–126 days of gestation. The risk of spontaneous abortion/fetal death decreases to 1–2 percent by 18–20 weeks (127–140 days). Up to 28 weeks (196 days) postconception the risk for spontaneous abortion is approximately 2 percent.

### **Congenital anomalies**

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The frequency of congenital anomalies detected at birth is approximately 3.5–5 percent (Brent and Beckman, 1990). This figure is thought to underrepresent the true frequency of anomalies by as much as twofold because 100 percent detection of anomalies is not usually reached until about 5 years of age. The frequency of congenital anomalies is severalfold higher among stillbirths and miscarriages than live births, and is especially high among early (i.e., first-trimester) miscarriages.

### **Fetal effects**

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Fetal effects are of four primary types: (1) damage to structures or organs that are formed normally during embryogenesis; (2) damage to systems undergoing histogenesis during the fetal period; (3) growth retardation; or (4) fetal death or stillbirth. Any or all of these fetal effects can occur concomitantly. Fetal effects may be caused by a teratogen, but may also be caused by agents that have no apparent potential to produce abnormal embryonic development. Organs, structures, or functions formed normally during embryogenesis can be damaged by some environmental exposures during the fetal period.

Fetal growth retardation is the most frequently observed effect of agents given during pregnancy and outside the period of embryogenesis. Sometimes it is difficult to distinguish between the effects of the agents from those of the disease entity being treated. Propranolol, for example, is associated with fetal growth retardation, but the maternal disease for which the drug is given (hypertension) is also associated with fetal growth retardation in the absence of antihypertensive therapy. Some agents that are teratogenic may be associated with fetal growth retardation. Fetal growth retardation may also occur without embryonic damage. Risks of fetal death, stillbirth, and other adverse effects are increased with exposure to some agents during pregnancy (Table 1.1).

### **Neonatal and postnatal effects**

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Prenatal exposure to some drugs is associated with adverse neonatal effects, such as difficulty in adaptation to life outside the womb. Drugs associated with adverse neonatal are not usually associated with teratogenic effects. Transient metabolic abnormalities, withdrawal, and hypoglycemia are well-documented neonatal effects of certain medications and nonmedical drugs. Examples of other adverse neonatal effects are the floppy infant syndrome with the use of benzodiazepines near term, patent ductus arteriosus with the use of prostaglandin synthetase inhibitors (non-steroidal anti-inflammatory agents – or NSAIDs) such as aspirin or indomethacin, and gray baby syndrome with high-dose chloramphenicol near the time of delivery (Table 1.1). Developmental delay is frequently associated with the action of teratogens, but is also observed in association with the fetal effects of drugs that are apparently not teratogenic.

**Table 1.1** Adverse effects other than birth defects on the human fetus associated with drugs

Maternal medication	Fetal/neonatal effect
Acetaminophen	Renal failure
Adrenocortical hormones	Adrenocortical suppression; electrolyte imbalance
Alcohol	Muscular hypotonia: hypoglycemia (?); withdrawal; intrauterine growth restriction (IUGR); blood changes; affect mental ability
Alphaprodine	Platelet dysfunction
Amitriptyline	Withdrawal
Ammonium chloride	Acidosis
Amphetamines	Withdrawal
Antihistamines	Infertility(?)
Antineoplastics	Transient pancytopenia IUGR
Antithyroid drugs	Hypothyroidism
Barbiturates/diphenylhydantoin	Coagulation defects; withdrawal (barbiturates only); IUGR
Chloral hydrate, excess	Fetal death
Chloramphenicol	Death ('gray baby syndrome')
Chlordiazepoxide	Withdrawal(?)
Chloroquine	Death(?)
Chlorpropamide	Prolonged hypoglycemia; fetal death
Cocaine	Vascular disruption, withdrawal, IUGR
Coumarin anticoagulants	Hemorrhage, death, IUGR
Diazepam	Hypothermia; hypotonia; withdrawal
Diphenhydramine	Withdrawal
Ergot	Fetal death
Erythromycin	Liver damage(?)
Gold salts	Complications; kernicterus
Glutethimide	Withdrawal
Heroin/morphine/methadone	Withdrawal; neonatal death
Hexamethonium bromide	Neonatal ileus
Hykinone	Blood changes; jaundice
Immunosuppressants	Transient immune system depression, danger of infection
Insulin (shock)	Fetal loss
Intravenous fluids, excess	Fluid and electrolyte abnormalities
Iophenoxic acid	Evaluation of serum protein-bound iodine (PBI)
Lithium	Cyanosis, flaccidity, polyhydramnios, toxicity
Magnesium sulfate	Central depression and neuromuscular block
Meperidine	Neonatal depression
Mepivacaine	Fetal brachycardia and depression
Meprobamate	Retarded development(?)
Nitrofurantoin	Hemolysis
Novobiocin	Hyperbilirubinemia(?)
Oral progestogens, androgens, and estrogens	Advanced bone age
Phenformin	Lactic acidosis(?)
Phenobarbital, excess	Neonatal bleeding; death
Phenothiazines	Hyperbilirubinemia(?), depression, hypothermia(?), withdrawal
Polio vaccine, live	Fetal loss(?)

*continued*

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**Table 1.1** *Continued*

Maternal medication	Fetal/neonatal effect
Prednisolone	Acute fetal distress, fetal death (?)
Primaquine, pentaquine	Hemolysis(?)
Primidone	Withdrawal(?)
Propoxyphene	Withdrawal
Quinine	Thrombocytopenia
Reserpine	Nasal congestion, lethargy, respiratory depression, brachycardia
Salicylates, excess	Bleeding, fetal death
Sedatives	Behavioral changes
Smoking	Premature births, IUGR, perinatal loss(?)
Sulfonamides	Kernicterus(?), anemia(?)
Tetracyclines	Deposition in bone, inhibition of bone growth in premature infants, discoloration of teeth
Thiazide diuretics	Thrombocytopenia, salt and water depletion, neonatal death(?)
Thioureas	Blood changes, affect mental ability
Tolbutamide	Thrombocytopenia, fetal death
Vaccinations	Fetal vaccinia
Verapamil	Transient fetal-neonatal cardiovascular
Vitamin K analogs, excess	Hyperbilirubinemia

Adapted from Schardein, 2000.

## MATERNAL PHYSIOLOGY DURING PREGNANCY

Profound physiological changes occur during pregnancy. Maternal enzymes, particularly cholinesterases (Pritchard, 1955), have lowered activity. Maternal blood volume increases dramatically during pregnancy, by perhaps 40–50 percent, to support the requirements of the developing fetus (Cunningham *et al.*, 2001). Distribution of drugs in this increased blood volume may lower serum concentrations. Absorption of drugs occurs with about the same kinetics as in the nonpregnant adult; however, renal clearance is increased and enzyme activity is downregulated. Decreased enzyme activity levels are exacerbated somewhat by the increased blood volume, decreasing the overall effective serum concentration of a given dose. In turn, increased renal output may effect an increased clearance index for most drugs. Drugs that are tightly bound to the serum proteins have little opportunity to cross the placenta or enter breast milk. Consequently, increased demands are placed on cardiovascular, hepatic, and renal systems. In addition, the gravid uterus is vulnerable to a variety of effects not present in the nonpregnant state, such as hemorrhage, rupture, or preterm contraction.

Increased demands imposed on these physiological systems by pregnancy may, under normal conditions, be dealt with in an uncomplicated manner. However, conditions of disease or other stress weaken these key systems and they may be unable to function normally. For example, cocaine abuse during pregnancy actually targets these key systems that are already stressed from the gravid state of the woman. Hence, it would be expected that cocaine use during pregnancy would place cardiovascular, renal, and hepatic systems at greater risk than those of the nonpregnant

adult. Indeed, these expectations are borne out in the observations of cocaine use during pregnancy.

## PHARMACOKINETICS IN PREGNANCY

The quantity of pharmacokinetic data during pregnancy is extremely limited. Only two investigations examined for this review made explicit quantitative recommendations for dose or schedule during pregnancy (Caritis *et al.*, 1989; Wisner *et al.*, 1993). Frequently, results are conflicting between studies of the same drug. Across all investigations reviewed, area under the curve was decreased in 41 percent of the studies, volume of distribution was increased in 30 percent, and peak plasma concentration was decreased in 34 percent. Steady-state plasma concentration was decreased in 44 percent of the studies, as was half-life in 41 percent. Clearance was increased in 55 percent of the studies (Table 1.2).

No general statement about pharmacokinetic changes during pregnancy can be made. The individual drug must be considered. These changes in pharmacokinetics cause decreases in drug plasma concentrations. When pharmacokinetic data are altered in this way, increased doses or schedules are needed to maintain effective systemic drug levels. However, this summary information is biased by a lack of information on many therapeutic agents used during pregnancy and because some drugs are represented more than once among the investigations reviewed. Still, the physiologic changes during pregnancy and their effects on the disposition of medications given during gestation found in this review are consistent with previous surveys of the literature (Amon and Hüller, 1984a, b; Cummings, 1983; Kafetzis *et al.*, 1983; Mattison *et al.*, 1992; Philipson 1978; Reynolds 1991). Multiple confounders make it difficult to interpret available pharmacokinetic data in pregnancy. Many studies have had very small sample sizes, frequently fewer than 10 pregnant women. Comparison groups have varied in composition. Studies have used nonpregnant women, adult males, the same patients 6–8 weeks postpartum, or published pharmacokinetic data. None of the studies reviewed gave maternal weight-

**Table 1.2** Pharmacokinetics in pregnancy

Index	Studies reporting pharmacokinetic data changes associated with pregnancy				Studies not reporting pharmacokinetic data (%)
	<i>n</i>	Decrease	No change	Increase	
AUC	17	7	5	5	44 (72.1)
$V_d$	23	3	11	9	38 (62.3)
$C_{max}$	30	10	17	3	31 (50.8)
$C_{ss}$	42	19	4	19	19 (31.1)
$t_{1/2}$	39	16	17	6	22 (36.1)
$t_{max}$	9	3	4	2	52 (85.2)
Cl	44	5	15	24	17 (27.9)
PPB	7	6	1	0	54 (88.5)

Source: Little BB. *Obstet Gynecol* 1999; **93**: 858.

AUC, area under the curve;  $V_d$ , volume of distribution;  $C_{max}$ , maximum concentration;  $C_{ss}$ , steady state concentration;  $t_{1/2}$ , half-life;  $t_{max}$ , time to plasma concentration; Cl, clearance; PPB, plasma protein bound.

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adjusted values, despite the strong influence this variable might have on area under the curve, volume of distribution, peak plasma concentration, steady-state plasma concentration, half-life, and time to peak plasma concentration. Route of administration also varied, even with the same drug, and is also known to be an important influence on peak plasma concentration, steady-state plasma concentration, half-life, time to peak plasma concentration, and area under the curve. Another important confounder is estimated gestational age. Most pharmacokinetic measures differ by the stage of gestation, and the method of determining estimated gestational age was not reported in any of the studies reviewed. A lack of consistency in the method of quantitative assay of drug levels and interlaboratory variation further confound the studies. The empiric effect of pharmacogenetic variation on drug disposition during pregnancy has been reported by only one group of investigators (Bardy *et al.*, 1982). Polymorphisms in enzymes are known to exist and might result in lower enzyme activity in 10–20 percent of the population, including pregnant women (Vesell, 1997). No data are available to address this variation directly among gravidas, although pharmacogenetic differences must affect drug disposition during pregnancy.

### PRENATAL DIAGNOSIS

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Medication exposure or substance use during pregnancy, including that which is chronic, is not necessarily an indication for pregnancy termination, although this is a common reaction among patients and physicians. Such exposure is, however, an indication for prenatal diagnosis. Prenatal diagnosis cannot rule out defects that are not related to gross structural abnormalities, but major congenital anomalies, such as spina bifida, structural heart defects, and limb reduction, can usually be determined prenatally.

Prenatal diagnosis can be used to screen for congenital anomalies and other fetal complications following use of medications or drugs during pregnancy. Commonly available prenatal diagnosis procedures include: (1) high-resolution ultrasound; (2) maternal serum alpha-fetoprotein (MSAFP); and (3) fetal echocardiography. Ultrasound studies are informative in assessment of fetal growth and in possible detection of specific structural anomalies of major organs. MSAFP is important for screening pregnancies for open neural tube or other open defects (e.g., gastroschisis). Amniocentesis may be performed to assess an abnormal alpha-fetoprotein level, but a karyotype study is not indicated by drug or alcohol exposure *per se*, except for colchicine. Fetal echocardiography is used to screen for cardiovascular defects that cannot be detected with the basic ultrasound four-chamber view of the heart, for example, valvular defects and vascular stenosis.

The patient should be advised of the limitations of prenatal diagnosis not only in the constraints on what can be detected (i.e., gross structural abnormalities), but also in its reliability in detecting defects prenatally (ranging from 40 to 90 percent).

### COUNSELING AND EVALUATION OF THE DRUG-EXPOSED PREGNANT PATIENT

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Counseling patients who have been exposed to drugs or other environmental agents during pregnancy is difficult for several reasons. Many patients have anxiety regarding the exposure because they fear their child will be born with birth defects. Anxiety is height-

ened because the mother frequently feels guilt, believing she may have damaged her baby through some action of her own. Cultural beliefs regarding the causes of congenital anomalies differ from scientific explanations, placing blame on the mother. Other factors, such as the patient's educational background, socioeconomic status, and ethnic-specific folklore, may also pose an obstacle to communication during counseling. These influences come into play when counseling patients exposed to potential teratogens.

Rapport with the patient is important, assuring confidentiality and establishing a basis for the patient's trust. The counselor must convey to the patient his or her understanding of the patient's concerns, and explain that the purpose of the consultation is to deal directly with those concerns by ascertaining the magnitude of the risk for an adverse pregnancy outcome arising from the drug exposure.

### General principles of counseling

Many patients are not satisfied with the counseling they receive for exposure to potential teratogens during pregnancy. Dissatisfaction stems largely from two major issues that both cause patient anxiety. First, the physician is frequently unable to obtain adequate information to make meaningful statements regarding the medical risks of whether the pregnancy was adversely affected by the drug exposure. Second, most patients do not understand the difference between an embryo and a fetus. Consequently, patients may not be able to grasp the importance of the concept of 'critical periods' unless they have been given a proper briefing during the consultation.

It is our policy to explain that there are two distinct phases involved in the growth of a baby, as shown in Fig. 1.2. The first phase is the embryonic development, and it is during this period that the structure or architecture for the baby is laid down. Embryonic age should be differentiated from menstrual age, which is 2 weeks greater than embryonic age. Briefly, we explain to our patients that organs take shape and the body assumes the form it will have thereafter by day 58 postconception. All major structures, such as the heart, brain, liver, kidneys, and limbs, have formed by this time. Fetal development during the remainder of pregnancy, the second phase of development, is primarily devoted to the growth of these organs and structures, and to augmenting their function.

It is through this heuristic approach to counseling that the patient understands that most congenital anomalies are caused by early exposures, often before the pregnancy was recognized. This ameliorates anxiety and guilt. This component is included early in the consultation; patients then understand why certain questions are important and having such knowledge increases their cooperation and rapport.

### Preconceptional counseling

Ideally, all counseling regarding drug or medication use during pregnancy should occur before conception, because the opportunity to prevent possible adverse effects is then optimal. Preconceptional counseling should include all the components of a consultation during the pregnancy, with one exception. Recommendations regarding medication or drug use during pregnancy will be *prospective* for a preventive purpose, and only medically indicated drugs and medications known to be safe will be recommended for continued use while attempting to conceive.

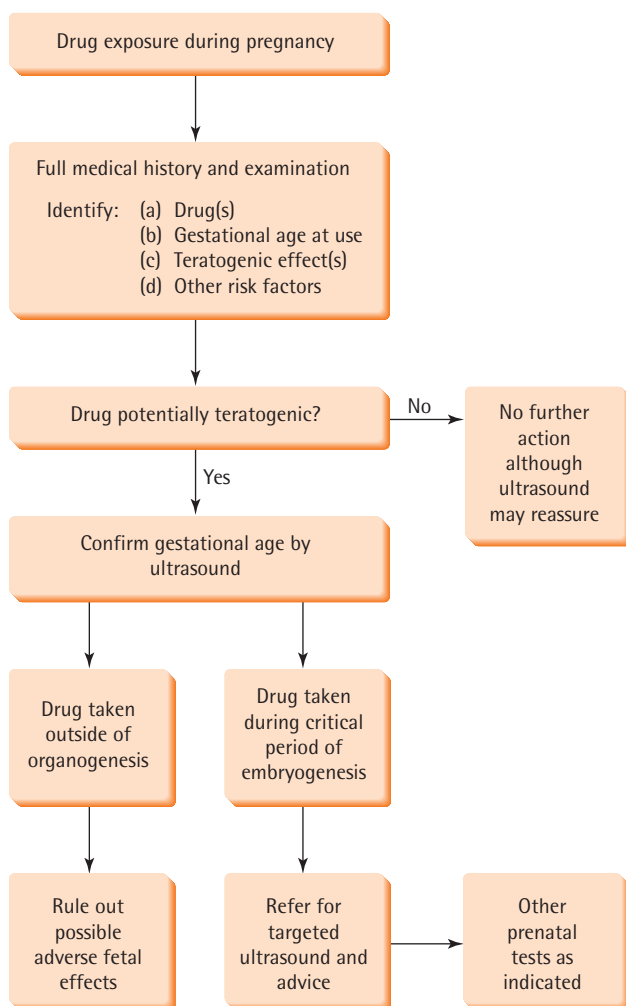
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### Counseling the exposed gravida

Counseling for drug or medication exposures during pregnancy should follow a protocol as laid out in Fig. 1.3. The concept of background risk for major congenital anomalies should be explained in a manner tailored to the patient’s level of understanding. This concept is especially important because it conveys to the patient that, even if the drug exposure is harmless, no guarantee can be given that the fetus she carries will not have a congenital anomaly. Notwithstanding other risk factors, the risk for major congenital anomalies is approximately 3.5–5 percent. Other identified risks are generally considered to be additive to background risk.

A usual component of counseling is the determination of exactly what drugs were taken, the dosage, the timing and duration of the exposure(s), the patient’s health history and present state of health. A thorough physical examination should be used to determine the present state of health. Also, a medical genetic pedigree, including the patient’s

Figure 1.3 Flow diagram



parents as well as the baby's father's parents, brothers and sisters, and nieces and nephews, should be constructed. The current state of health of all people in the pedigree should also be elicited. For those individuals in the pedigree who are no longer living, whether death was due to a birth defect or to a heritable disorder should be determined. It is also important to ask whether the patient's family or the baby's father's family has any member who was mentally retarded, or has a chromosomal abnormality, Down syndrome, congenital heart disease, spina bifida or another neural tube defect, or any other inherited disease. When such risk factors are discovered, it is important to explore these avenues further. It is desirable to refer the patient for a medical genetic consultation and evaluation when a risk increase above background is other than zero.

The next step in the consultation is to determine whether or not the agent(s) has known teratogenic potential. This is the most difficult part of the evaluation because there is insufficient information to make such a determination for more than 60 percent of medications. Currently, the most reliable source of information regarding drug or medication use during pregnancy is TERIS (Teratogen Information System), a computerized database available for use either on IBM-compatible personal computers or

### Box 1.2 Sources of information on drugs and medications during pregnancy

#### Databases

TERIS, Department of Pediatrics, University of Washington, Seattle, WA 206-543-4365  
<http://depts.washington.edu/~terisweb/>

Note: Individual summaries may be purchased for clinical use

REPROTOX, An independent non-profit organization: [reprotox@reprotox.org](mailto:reprotox@reprotox.org); <http://reprotox.org/>

#### Hotlines

MotheRisk Program +1-416-813-6780

Teratogen Information Service (TIS) +1-800-532-3749 or +1-619-294-6084

Organization of Teratology Information Services (OTIS) +1-888-285-3410

#### Textbooks

*Catalog of Teratogenic Agents*. 10th edn. T.H. Shepard. Baltimore: Johns Hopkins University Press, 2001.

*Drugs in Pregnancy and Lactation*. 6th edn. G.G. Briggs, R.K. Freeman, S.J. Yaffe. Baltimore: Williams & Wilkins, 2002.

*Chemically Induced Birth Defects*. 3rd edn. J.L. Schardein. New York: Marcel Dekker, 2002.

*Drugs and Pregnancy*. 2nd edn. L.C. Gilstrap, B.B. Little. New York: Chapman and Hall, 1998.

*Management of Psychiatric Disorders in Pregnancy*. K.A. Yonkers, B.B. Little. London: Arnold Press, 2001.

*The Effects of Neurologic and Psychiatric Drugs on the Fetus and Nursing Infant: A Handbook for Health Care Professionals*. J.M. Friedman, J.E. Polifka. Baltimore: Johns Hopkins University Press, 1998.

*Teratogenic Effects of Drugs: A Resource for Clinicians*, 2nd edn. J.M. Friedman, J.E. Polifka. Baltimore: Johns Hopkins University Press, 2000.

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online by subscription (Box 1.2). If it can be documented that the agent has no teratogenic risks or adverse fetal effects associated with its use during pregnancy, then no further action is required except to document this in the medical record and counsel the patient accordingly. Some patients may benefit from reassurance offered by high-resolution ultrasound to confirm fetal well-being, and this procedure should be offered if the patient's anxiety is not relieved through counseling. The limitations of diagnostic ultrasound should also be included in the consultation.

If the drug is known not to be safe for use during pregnancy, or if there are reasons to suspect that a drug with unknown risks is associated with congenital anomalies, then gestational age should be confirmed by ultrasound. It is of utmost importance to base the risk assessment and counseling upon embryonic age, not menstrual age. If the exposure occurred during embryogenesis, then it is necessary to undertake high-resolution ultrasound in an attempt to detect damage to specific organ systems or structures that were being formed during the time of the exposure. If the ultrasound scan is normal, then it is reasonable to reassure the patient of normal fetal structure within the limits of the sensitivity and specificity of ultrasound, which range from 40 to 90 percent for gross structural abnormalities when the procedure is performed by an experienced sonographer. If the exposure occurred during the fetal period, it is likewise important to evaluate the possible fetal effects of the medication.

If defects are detected, it is necessary to describe them in detail to the patient and to give a prognosis, as far as available medical knowledge will allow, regarding the outcome of pregnancy and postnatal development. To assist the patient in making a decision on the disposition of the pregnancy, prognostication should include medically documented risk figures. Ethically, pregnancy termination should not be a recommendation made to the patient and her family and significant others. This option should be discussed, but the ultimate decision of whether to continue the pregnancy should be left to the patient and her family and significant others. The role of teratogen counseling is ultimately to provide the patient with as much information as possible and encourage her to make her own decision regarding whether to continue the pregnancy.

Drug- or chemical-related causes of maternal complications, congenital anomalies, and fetal toxicity are almost unique among adverse pregnancy outcomes because they are potentially preventable, given the window of opportunity to do so. These problems are also exceptional among obstetric complications in that they are often the focus of malpractice litigation. Attorneys recognize that such adverse outcomes could have been prevented, and litigation ensues despite the fact that the window of opportunity to intervene prudently may not have existed for the physician and, more importantly, the drug exposure may not be teratogenic at any time during the pregnancy.

## FOOD AND DRUG ADMINISTRATION CLASSIFICATION OF DRUGS AND INFORMED CONSENT

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Until 1979, most drugs and medications were accompanied by disclaimers, the most common of which were the 'safe use in pregnancy has not been established' and such a medication 'should not be used in pregnant women unless, in the judgment of the physician, the potential benefits outweigh the possible hazards' (Brent, 1982). The major drawback with such disclaimers was that there existed little to no information upon

which to 'weigh the possible hazards'. Such disclaimers would make defense of a litigation case involving a drug or medication extremely difficult for the physician because benefits are not easily weighed against unknown possible hazards. With no scientific data relating a specific malformation to a given drug, it is nearly impossible to 'prove' in the courtroom that a drug is not a teratogen and is safe for use during pregnancy. Thus a jury may be asked to consider the important question of why a physician would utilize a medication that carried the warning 'safe use in pregnancy has not been established'. The disclaimer itself implies that a medication may indeed be a teratogen, although the warning is actually little more than legally formulated rhetoric designed to protect the pharmaceutical company (Brent, 1982). There have been many efforts to encourage the FDA to change the nature of the labeling on the package insert and to change the manner in which drugs are classified with regard to their reproductive risks (Brent, 1982).

In 1979, the FDA attempted to improve labeling policies for the use of medications during pregnancy. Five risk categories that addressed potential adverse fetal effects, including congenital anomalies, were developed. Although an improvement over the previous labeling disclaimers, this classification is less than perfect (Brent, 1982).

According to the *Physicians' Desk Reference* (2005), the categories devised by the FDA are 'based on the degree to which available information has ruled out risk to the fetus, balanced against the drug's potential benefits to the patient'. Although intended to provide management guidance about teratogenic risks, a recent study found that FDA categories have little, if any, correlation to teratogenic risk. Friedman and colleagues (1990) compared the teratogenic risk of 157 most frequently prescribed drugs according to TERIS, a computerized database of clinical teratology information, to the FDA pregnancy categories, where available. These authors pointed out that 'any classification of agents according to teratogenic risk is incomplete because the risk to a given patient is determined by all of the conditions of exposure'. Paramount importance must also be ascribed to drug dose, route of administration, and timing of exposure, as well as exposure to multiple agents during the pregnancy (Friedman *et al.*, 1990). The information on the package insert, a joint effort of the FDA and the pharmaceutical company, fails to provide information about risks that are known, does not discuss the option of pregnancy interruption, and provides anxiety-provoking information that is irrelevant, such as 'this drug crosses the placental barrier' (Brent, 1982).

## INFORMED CONSENT AND POST-EXPOSURE COUNSELING

Before initiating informed consent regarding medication exposure during pregnancy, the factors of dose, route of administration, and timing must be ascertained as accurately as possible. Even if an agent is a potential teratogen of significant risk or even a proven teratogen such as thalidomide, the actual risk to the fetus may be minimal to none if the timing of exposure occurred during late pregnancy or after the period of organogenesis. In contradistinction, some teratogens, such as radioactive iodine or the angiotensin-converting enzyme inhibitors may be harmful only after early organogenesis (Brent and Beckman, 1990).

After a detailed history is obtained, the patient should be given 'full disclosure' regarding the known or suspected risk of the agent, as well as the various therapeutic and

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diagnostic options available. This information should be accurate, yet easily understandable. All such information and counseling should be well documented in the patient's chart.

All counseling regarding a drug or medication exposure should be performed by a clinician knowledgeable in both teratology and in counseling. Taking the whole clinical picture into account, one should utilize a resource such as TERIS as well as other teratogen information resources as sources of the most recent and accurate information on the potential teratogenic effects of a specific agent.

The TERIS summaries are available for a nominal fee by fax from the Department of Pediatrics, University of Washington, Seattle, WA, USA. The contact is Dr. Janine Polifka at +1-206-543-2465. The TERIS website is <http://www.depts.washington.edu/~TERISweb/TERIS>.

Experienced counselors may also have their own personal reprint collection dealing with teratogens. We include all such information, especially the TERIS summary in exposure cases, in the patient's chart, and it is used as an adjunct in counseling of each drug- or chemical-exposed pregnant patient.

In counseling, one could also make this statement: 'Although this agent may be associated with an increased risk of malformation when utilized in the first 8–10 (menstrual) weeks of pregnancy, it would not be expected to be associated with significant risk when given in the latter half of pregnancy'. In the case of an agent such as tetracycline, one might state: 'It is logical to conclude that tetracycline would not be expected to cause yellow-brown discoloration of the teeth when given during the first 16–20 weeks of pregnancy'.

Another suggested statement would be as follows: 'Although the actual teratogenic risk of this agent is unknown, given the dose and route of administration, the fetal risk of this preparation is negligible to nonexistent, since little to none of it reaches the fetus'.

Other sources of information regarding the teratogenic risk of specific agents that may be useful in counseling patients, in addition to the present text and TERIS, include Shepard's *Catalog of Teratogenic Agents, Drugs in Pregnancy and Lactation: A Reference Guide to Fetal and Neonatal Risk, Chemically Induced Birth Defects* and other similar texts.

## SUMMARY

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The clinician must be cognizant of the fact that many patients, as well as attorneys, believe that most congenital malformations must be secondary to a drug or medication taken during gestation. Counseling of such patients requires a significant degree of both knowledge and skill. Physicians must also realize that erroneous counseling by inexperienced health professionals is one of the leading stimuli for nonmeritorious litigation (Brent, 1977). Moreover, the clinician must be aware that drugs and medications represent a bountiful field for litigation, since there is a reasonable likelihood that, once the family and the attorney have concluded that there is merit to their allegation, they can locate experts who will support the nonmeritorious allegation. Thus, physicians may focus their attention on attorneys as the cause of the plethora of litigation, when in reality they could not proceed without the assistance of unknowledgable or unscrupulous experts.

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- Further references are available on the book's website at <http://www.drugsandpregnancy.com>