

# Pharmacotherapeutics

MARY C. BRUCKER

TEKOA L. KING

## Introduction

Throughout history, pregnancy and midwifery have been surrounded in myths. One of the modern myths is that midwives eschew the use of drugs and only use, at most, herbal remedies. In reality, knowledge of pharmacology is necessary for the practice of midwifery in the twenty-first century so that midwives use pharmacotherapeutic agents appropriately. All 50 states grant some type of prescriptive authority to certified nurse-midwives.<sup>1</sup> Prescriptive authority remains less common for certified midwives, as their credential is newer and their numbers fewer. Prescriptive authority is controlled on the state level and ranges from very limited to relatively broad. Many states limit prescriptive authority according to the schedule of controlled substances described later in this chapter. Some prescriptive authority laws are based on specific wording in state licensing laws or practice sites.

As an increasing number of midwives attain prescriptive privileges, knowledge of pharmacology becomes even more important.<sup>1</sup> Although midwives may use a wide repertoire of nonpharmaceutical techniques, there are conditions and situations in which no effective substitutes exist for pharmacologic treatments. One of the greatest challenges to the midwife in clinical practice is maintaining current information about drug indications, doses, side effects, and contraindications.

Throughout this text, specific therapeutic agents are discussed as treatments for various conditions. However, the field of pharmacology is both expansive and ever-changing; thus this chapter presents a wide

overview that includes discussion of specific situations such as common drugs used for treating women who are pregnant or breastfeeding. Although many examples are included in the chapter as illustrations, it should not be assumed that they are exhaustive. Additionally, certain terms—including “drugs,” “agents,” “medications,” and “pharmaceuticals”—are used interchangeably throughout the chapter. The word “drug” does not connote an illicit substance or a licit substance being abused; rather, drugs with abuse potential are specifically designated as such. Drugs are listed by generic name followed by the most common brand name in parentheses.

This chapter has four sections. The first reviews fundamental concepts for midwives with prescriptive authority, including the drug development process, legal requirements for prescriptive authority, and essential information about drug–drug interactions and adverse effects of drugs. The second section reviews essential drug categories most commonly used in midwifery practice. The third and fourth sections describe pharmacologic essentials specific to prescribing drugs for women who are pregnant and women who are lactating.

## The Lexicon of Pharmacology

As knowledge in pharmacology has expanded, so has the accompanying lexicon. A prerequisite to understanding drug actions and their effects is the midwife’s ability to define the various terms used in pharmacology. Some of these terms are old and established. *Pharmacology* itself means the study of all

aspects of drugs. In addition, several more specific terms are employed in the field. *Pharmacokinetics* describes the absorption, distribution, metabolism (biotransformation), and excretion (clearance) of drugs. These factors then determine the amount of the agent available at the target sites for action. *Pharmacodynamics* refers to the action of drugs on the body. The pharmacodynamic action of a drug results from the drug's binding relationship at the receptor site as either an agonist or an antagonist. *Pharmacotherapeutics* is the field focusing on treatment effects of drugs. Additional terms can be found in the pharmacology glossary presented in **Box 5-1**.

### Drugs in Modern Society

More than 4 billion prescriptions are written each year in the United States. Each prescription filled can result in a 20% profit to the manufacturer, making the pharmaceutical industry highly profitable.

Most adults in the United States take at least one medication, and many take multiple pharmaceuticals daily.<sup>2</sup> The extensive use of drugs is related to several factors: the increase in their availability; the public belief that drugs are safe, especially over-the-counter products; and the plethora of healthcare providers, pharmacies, and Internet sites that supply drugs. These multiple options mean that an individual may receive drug prescriptions and recommendations from a variety of providers who may be unaware of the other prescribers' actions. Direct-to-customer advertising exposes many more individuals to prescription drugs and proposed therapeutic options of which they might have been previously unaware.<sup>3</sup> In addition to public acceptance of drugs to treat illnesses, there is a growing appreciation of how agents may be used for prophylaxis against various diseases or for general health maintenance. Drugs used for prophylaxis tend to be used for long periods of time. They include blockbuster drugs, such as atorvastatin (Lipitor).

Even individuals who avoid taking specific drugs or agents may constantly be exposed to pharmaceuticals through the food chain or in their daily environment.<sup>4</sup> The results of such exposure, including direct toxic reactions and reproductive toxicology, are beyond the scope of this chapter, although this area is likely to grow in importance.

### Drug Development and Regulation

Drugs are labeled in various ways. Specific drugs can be described by the physiochemical property of the

drug (e.g., an acid) or by pharmacotherapeutic indication (e.g., sedative). The same drug could be identified by its chemical name [e.g., 2-(2-methyl-5-nitro 1*H*-imidazol-1-yl)ethanol], its generic name (metronidazole), and its most common brand name (Flagyl).

Drugs formulated as medications are regulated in the United States by the Food and Drug Administration (FDA), one of 12 agencies within the U.S. Department of Health and Human Services. The pharmaceuticals for which the FDA has authority may be obtained by prescription or over the counter.

The FDA also regulates medical devices such as intrauterine contraceptive systems (e.g., ParaGard, Mirena) and biologic agents such as vaccines. The FDA does not regulate dietary supplements, such as St. John's wort, although the agency does track adverse reactions that occur following use of dietary supplements. Similarly, the FDA may require labeling to designate that safety has not been established for cosmetics, although recall of cosmetics is voluntary by the manufacturer.<sup>5</sup>

Drugs that are approved for specific use by the FDA must demonstrate both safety and efficacy for that indication in a series of preapproval studies that are submitted to the FDA for review. The regulation of drugs is administered by the Center for Drug Evaluation and Research (CDER), a subgroup within the FDA that oversees the research, development, manufacture, and marketing of both prescription and over-the-counter (OTC) drugs. After FDA approval, if unexpected risks are detected, CDER takes action to inform the public, change a drug's label, or, when necessary, remove the product from the market. The FDA itself does not develop, manufacture, or test drugs.

Drug manufacturers submit full reports of studies conducted on specific drugs, called clinical trials, so that CDER can evaluate the data and determine if the drug should be approved for a specific indication. This approval commonly is termed FDA labeling. The clinical trials are intended to be appropriately large enough to determine safety and effectiveness. However, sometimes the FDA approves a drug, only to remove it from the marketplace later due to adverse effects that emerge once the drug is in use by a large diverse population or when used in conjunction with other agents. **Box 5-2** identifies the sequencing of studies and subsequent clinical trials that are conducted prior to FDA approval, and **Figure 5-1** illustrates the process.<sup>6</sup>

Historically, women have not been participants in most drug development studies.<sup>7,8</sup> Although there are many reasons for this exclusion, one factor is the changing environment in a woman's body over

## BOX 5-1 A Brief Glossary of Pharmacology

**Adverse drug reaction** Response to a drug that is noxious and unintended, and that occurs at doses normally used for prophylaxis, diagnosis, or therapy of disease or for the modification of physiologic function.

**Agonist** A drug that binds to a receptor and activates it, producing a pharmacological response.

**Antagonist** A drug that attenuates the effects of an agonist. Antagonism can be competitive and reversible (i.e., the drug binds reversibly to a region of the receptor in common with the agonist) or competitive and irreversible (i.e., the antagonist binds covalently to the agonist binding site, and no amount of agonist can overcome the inhibition).

**Bioavailability** Percentage of an administered drug that is available to target tissues.

**Bioequivalent** Pharmacologically equivalent.

**Black box warning** A method that the FDA uses to identify unusual harm associated with an agent. Often this warning is added to package inserts after postmarketing studies identify unexpected risks linked to a drug.

**Brand name** A trademarked name assigned to a drug by its manufacturer. Some brand names are similar to the generic name (e.g., pseudoephedrine/Sudafed); others suggest their indications for use (e.g., Tamiflu).

**Chemical name** Although rarely used by prescribers and consumers, a name of a drug that describes its chemical composition.

**Compounding** Mixing or combining ingredients to produce a pharmaceutical agent. Pharmacists may perform compounding to change the form from solid pill to liquid, or it may be done to create a unique dose and combination of products for a specific individual.

**Controlled substance** Pharmaceuticals as listed in schedules found in U.S. Law 21 U.S.C. §802(32)(A). These agents include opiates as well as nonopiates but generally have a high risk of addiction, often without valid medicinal use. Examples include heroin.

**Cosmeceutical** A cosmetic product that has medicinal or druglike benefits.

**Direct-to-consumer advertising** Advertising of selected drugs placed in popular media and directed to the general public as opposed to providers in peer-reviewed journals.

**Dispense (furnish)** The process of giving a drug to a consumer.

**Ecopharmacology** Derivation of drugs from plants, especially those found in the rainforest, as well as exploration of pharmacologic implications of pollutants in water that exert pharmaceutical-like effects, most often estrogenic in nature. The latter substances also have been called ecoestrogens or xenoestrogens.

**Formulary** List of approved or available drugs. It is often used by insurers to identify agents that will be reimbursed or paid for by the insurer.

**Generic name** A formulation that contains the same active ingredients found in the original brand formulation and is bioequivalent to that formulation.

**Half-life** The period of time required for the concentration or amount of drug in the body to be reduced to exactly one-half of a given concentration or amount.

**Hypersensitivity reaction** A state of altered reactivity wherein the body reacts to a foreign substance with an exaggerated immune response; classified as Type I, II, III, or IV depending on the specific pathologic response.

**Immunotherapy** Treatment of disease by inducing, enhancing, or suppressing an immune response.

**Loading dose** A larger than normal dose administered as the first in a series of doses, with the other doses being equal to each other but smaller than the first. A loading dose is administered to achieve a therapeutic amount in the body more rapidly.

**Nutraceutical (functional food)** A food or supplement (e.g., folic acid) that has specific health benefits.

**Off-label use** Prescription or use of a drug for conditions other than those approved by the FDA.

**Over-the-counter (OTC)** Pharmaceuticals sold without prescriptions.

**Pharmacodynamics** How drugs produce their effects, such as interactions at a receptor site.

**Pharmacogenetics** The study of how drugs interact with the genetic makeup of an individual or the genetic response to a drug; this may be one of the first clinical applications derived from the Human Genome Project.

**Pharmacogenomics** Studies that illustrate similarities and differences in pharmacodynamic and pharmacokinetic mechanisms among various individuals and people of different ethnic backgrounds.

**Pharmacokinetics** The movement of drugs in the body, specifically encompassing the study of factors that determine the amount of chemical agents at their sites of biologic effect at various times after the agent is administered. Pharmacokinetics is composed of four specific factors: absorption, distribution, metabolism (biotransformation), and excretion (clearance).

**Pharmacotherapeutics** The field concentrating on the treatment effects of drugs. There are several subsections within pharmacotherapeutics.

**Polypharmacy** The practice of treating individuals using multidrug regimens. This term generally is accepted to mean administration of five or more drugs.

(continues)

## BOX 5-1 A Brief Glossary of Pharmacology (continued)

**Prescriptive authority** Legal ability to prescribe drugs, medical devices, or other regulated healthcare interventions.

**Side effect** A physiologic response unrelated to the desired drug effects that occurs with therapeutic doses of the medication. Side effects may be beneficial or negative.

**Therapeutic window** A point at which the plasma drug concentration is between the minimum effective concentration (MEC) in the plasma for obtaining the desired drug action and the mean toxic concentration (MTC).

**Toxicology** The branch of pharmacology that deals with the nature, effects, and treatments of poisons.

the course of the menstrual cycle, which could affect the pharmacokinetics and pharmacodynamics of a drug. Even when women have participated in clinical trials, it has been rare that an analysis of gender differences has been published. Moreover, clinical trials for contraceptives generally do not include many adolescents, as women younger than the age of 18 are considered pediatric patients. Pediatrics itself is a difficult area in which to conduct clinical trials because of the inherent problems obtaining informed consent.

Although the FDA approves drugs for specific indications, once it is marketed the same drug may be prescribed for another use—a phenomenon is called “off-label use.” Examples abound regarding off-label use.<sup>9</sup> For instance, the most commonly used tocolytic

in the United States is magnesium sulfate, yet it is not FDA approved for that indication. Methotrexate (Rheumatrex)—a folic acid antagonist used as a chemotherapeutic agent—has a marked predilection for destruction of trophoblastic tissue and is used off label for medical treatment of an unruptured ectopic pregnancy. Midwives should recognize that off-label use, though it remains common, should not be undertaken capriciously. A legal liability potentially exists, especially if the drug is not yet widely accepted in practice for the off-label indication.

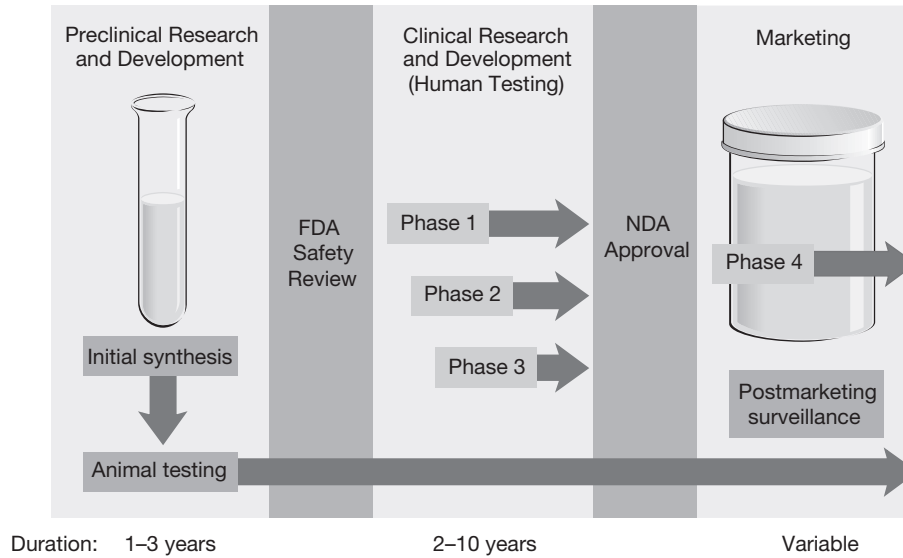
### Controlled Substances

The U.S. Drug Enforcement Administration (DEA) was established in 1973 within the Department of Justice. This agency has a special role in the regulation of prescription drugs that have the potential for abuse, under the 1970 Controlled Substance Act (CSA). The CSA has classified pharmaceuticals that can be abused into one of five schedules based on the substance’s medicinal value, harmfulness, and potential for abuse or addiction. Schedule I is reserved for the most dangerous drugs that have no recognized medical use, such as LSD and heroin. Schedule V is the classification used for the least dangerous drugs, such as brand-name antitussives containing small amounts of codeine. Meperidine (Demerol) is a Schedule II agent. Knowledge of these schedules is important for midwives with prescriptive authority because this authority is often limited to specific schedules. **Box 5-3** lists the five schedules for controlled substances.

A registration number issued by the DEA is needed to prescribe a controlled substance. In 1993, the DEA published a regulation that established a new category under which healthcare providers other than physicians, dentists, veterinarians, or podiatrists could receive individual DEA registration numbers

### BOX 5-2 Phases of the Food and Drug Administration Drug Approval Process

FDA	Phase Description
1	Designed to determine drug dynamics and identify drug metabolites. This phase is usually small and may be omitted if extensive international study has been conducted.
2	Controlled clinical trials to verify effectiveness and basic safety.
3	Randomized clinical trials, usually placebo controlled.
4	Postmarketing clinical trials, usually to gather information about adverse reactions, morbidity, and mortality that can be obtained only in larger groups.



**Figure 5-1** Steps required by the FDA for reviewing a new drug.

granting controlled substance prescribing privileges consistent with the authority granted them under state law.<sup>10</sup> Under this regulation, providers such as certified nurse-midwives were given authority to prescribe controlled substances if approved to do so by the state or jurisdiction in which they practice.

### The Prescription

Midwives with prescriptive authority have the legal ability to write prescriptions. Although many prescriptions are phoned into a pharmacy or, increasingly, transmitted by electronic means, a midwife needs to know the required components of a prescription.

#### BOX 5-3 FDA Classification of Controlled Substances

Schedule	Interpretation	Schedule	Interpretation
I	High potential for abuse and no current accepted medical use. Examples are heroin and LSD.	III (cont.)	are barbiturates and preparations containing small quantities of codeine. Prescriptions may be oral or written. Up to five renewals are permitted within 6 months.
II	High potential for abuse. Use may lead to severe physical or psychological dependence. Examples are opioids, amphetamines, short-acting barbiturates, and preparations containing codeine. Prescriptions must be written in ink or typewritten and signed by the practitioner. Verbal prescriptions must be confirmed in writing within 72 hours and may be given only in a genuine emergency. No renewals are permitted.	IV	Low potential for abuse. Examples include chloral hydrate, phenobarbital, and benzodiazepines. Use may lead to limited physical or psychological dependence. Prescriptions may be oral or written. Up to five renewals are permitted within 6 months.
III	Some potential for abuse. Use may lead to low-to-moderate physical dependence or high psychological dependence. Examples	V	Subject to state and local regulations. Abuse potential is low; a prescription may not be required. Examples are antitussive and antidiarrheal medications containing limited quantities of opioids.



All handwritten prescriptions must be legibly written in indelible ink. Every prescription must include the midwife's name, address, and contact information. It is optimal to have the midwife's prescriptive authority number or other identifying information appear either on the top of the prescription order or adjacent to the midwife's signature. In some states, the midwife's collaborating physician's numbers will also be placed on the prescription. All prescriptions are dated, and information about the prescription is placed in the woman's record so that if she loses the prescription, changes pharmacies, or moves, it can be easily retrieved. Only one drug can be written on each prescription blank. Refills, if any, are noted, especially as certain health plans limit coverage of monthly drugs. Permission to substitute a brand-name product for a generic drug is often included. Some authorities maintain lists of abbreviations, such as "TID" for "three times a day," although use of any abbreviations is increasingly discouraged.

The section of the prescription specific to the medication consists of four parts: (1) superscription, (2) inscription, (3) subscription, and (4) signature. The superscription includes the symbol "Rx," although according to World Health Organization guidelines, it is more proper to use the Latin "℞". In any case, the symbol is derived from the Latin word for "recipe" or "take." The inscription specifies the ingredients and their quantities (e.g., nitrofurantoin 100 milligram capsules). The subscription informs the pharmacist how to compound or dispense the medication (e.g., dispense 10 capsules). It is important to avoid decimals and, where necessary, write words in full to avoid misunderstanding. For example, write "levothyroxine 50 micrograms," not "0.050 milligram" or "50 mg." The signature, or "sig," is not that of the prescriber, but represents the Latin "signa" or "mark" that provides the instructions that enable the woman to understand dosages and when to take a drug. The sig should include route, frequency, duration, and any other specific information—for example, "Take 1 capsule by mouth at bedtime for 10 days."

Generally it is recommended that the generic or nonproprietary name be used when a prescription is written. Use of generic names enables the pharmacist to maintain a more limited stock of drugs and/or dispense the least expensive drug. However, if there is a particular reason to prescribe a brand-name drug, the trade name can be added. Some authorities allow generic substitution by the pharmacist and require the addition "Do not substitute," "Dispense as written," or "Brand medically necessary" if that brand, and no other, is to be dispensed. When a specific brand is

required, the midwife should document that instruction in the woman's chart along with the rationale. The documentation is created not only for completeness, but also may be necessary for the prescription to be covered by a public insurance program such as Medicaid, various managed care groups, or other types of health insurance. **Figure 5-2** illustrates a sample prescription written appropriately by a midwife.

### Adverse Drug Reactions and Adverse Drug Events

*Adverse drug reactions* (ADRs) are unintended responses to a drug that occur when normal dosing is used. ADRs are quite common.<sup>11,12</sup> The term *adverse drug events* (ADEs) is a more inclusive category connoting any injury that results from the administration of a drug. ADEs includes adverse drug reactions, medication errors, overdoses, and known dose-related side effects.

After a drug has been determined to be safe and effective in preapproval clinical trials, it is prescribed for individuals in a broader population—that is, for a more diverse group than the relatively select group who participated in the clinical trials. Thus adverse effects of drugs are primarily identified during the postmarketing period. The Adverse Event Reporting Program of the FDA collects reports of ADRs via the FDA MedWatch program. Details of how to report an adverse drug reaction are listed in **Box 5-4**.

Adverse drug reactions are classified as either immune or non-immune reactions. Non-immune reactions are predictable. They include drug–drug interactions, drug overdose, and drug toxicity, and commonly occur secondary to known pharmacologic effects or in a dose-related manner. Conversely, immune reactions, which are also called allergic reactions, are unpredictable. The four types of hypersensitivity reactions that cause a drug allergy are listed in **Table 5-1**.

### Drug–Drug Reactions

Although most drugs are therapeutic when used alone, adverse reactions may occur when certain drugs are used concomitantly. In some instances, reactions may occur when drugs are taken simultaneously with certain botanical/herbal therapies or even specific foods. It is important to consider such potential reactions when considering drugs for an individual woman.

Most drugs are metabolized via a group of liver enzymes called the cytochrome P-450 family. When a drug undergoes biotransformation via one of the cytochrome P-450 enzymes, it may be altered from a prodrug into an active drug, made inactive, or altered

Rose McNaught, CNM Certified Nurse-Midwife Dayton Women's Health UC # 54321 NPF: 2468-789		Kate Smith, MD Obstetrician/Gynecologist UCSF Women's Health BNDD No. AS345678 IL Lic. No. F28765	
Name	Susan Jones	Age:	24
Address	4265 Fruitvale Ave, Dayton, IL	Date:	May 5, 2013
<b>Rx</b>	Metronidazole 500 mg tablets sig: twice daily for 7 days disp: 14		
Indication: Bacterial vaginosis			
Refills: 0 <u>1</u> 2 3 4 5			
Allergies: None			
Dispense as written <input type="checkbox"/>			
Label: English <input checked="" type="checkbox"/> Spanish <input type="checkbox"/> Other _____			
<i>Rose McNaught</i> Signature			

**Figure 5-2** A sample prescription.

into a formulation that is more active. For example, codeine is metabolized by CYP2D6 into morphine (the active metabolite of codeine).

Assume drug A and drug B are both metabolized via the same cytochrome P-450 enzyme. When these drugs are taken at the same time, drug A either inhibits or enhances the activity of the cytochrome P-450 enzyme. In turn, metabolism of drug B is either inhibited, which results in higher plasma levels and perhaps overdose, or enhanced (i.e., it is metabolized more rapidly than usual), which results in a reduction of the plasma concentration of the drug, making it less effective. For example, the antifungal drug fluconazole (Diflucan) is an inhibitor of CYP2C9; when it is given to a person who is also taking tolbutamide (Micronase), the plasma concentration of tolbutamide increases and the individual becomes more likely to experience hypoglycemia.<sup>13</sup> In another example, cardiac arrhythmias may occur when one of the macrolides erythromycin (E-base), azithromycin (Zithromax), or clarithromycin (Biaxin) is taken simultaneously with the antifungal ketoconazole (Nizoral).

Some individuals have genetic mutations called polymorphisms that encode for the cytochrome P-450 enzymes. A common polymorphism of CYP2D6 inhibits function of this enzyme. Persons with this polymorphism are poor metabolizers and as such, they can have an exaggerated or toxic response to drugs

#### BOX 5-4 How to Report an Adverse Drug Reaction

In 1993, the FDA founded *MedWatch*, a reporting system for adverse events or sentinel events. This system includes a computerized information database designed to support postmarketing safety surveillance program for all FDA-approved drug and therapeutic biologic products. Any suspected adverse events or reactions to medications, drug products, or medical devices (other than vaccines or investigational drugs) should be reported using FDA Form 3500 (available online at <https://www.accessdata.fda.gov/scripts/medwatch/medwatch-online.htm>). Information re-garding the reporting of vaccine-related adverse event reports (VAERS) can be found at <https://vaers.hhs.gov/professionals/index>.

For individuals who prefer, the MedWatch program can be contacted by phone, fax, or mail, as well as online.

**Phone:** 1-800-332-1088

**Fax:** 1-800-FDA-0178

**Mail:** MedWatch  
 5600 Fishers Lane  
 Rockville, MD 20857

Table 5-1 Four Types of Hypersensitivity Reactions		
Type	Timing of Reaction	Examples
Type 1 (immediate)	Minutes to hours after drug exposure	<ul style="list-style-type: none"> <li>• Anaphylaxis from exposure to penicillin</li> <li>• Hives following exposure to sulfa drugs</li> <li>• Angioedema from ACE inhibitors</li> </ul>
Type 2 (cytotoxic)	Variable	<ul style="list-style-type: none"> <li>• Transfusion reaction</li> <li>• Hemolytic anemia from penicillin</li> </ul>
Type III (immune complex formed)	1–3 weeks after drug exposure	<ul style="list-style-type: none"> <li>• Drug-induced lupus caused by minocycline (Minocin)</li> <li>• Serum sickness caused by cefaclor (Ceclor)</li> </ul>
Type IV (delayed or cell mediated)	2–7 days after drug exposure	<ul style="list-style-type: none"> <li>• Ampicillin rash</li> <li>• Contact dermatitis caused by topical antihistamine</li> </ul>

that are metabolized by CYP2D6. For example, persons with this polymorphism have a fivefold increased risk of adverse reactions when taking metoprolol (Lopressor) compared to persons who do not have this polymorphism.<sup>14</sup> Approximately 5% to 14% of Caucasians, 0% to 5% of Africans, and 0% to 1% of Asians have the polymorphism that results in a lack of CYP2D6 activity.<sup>15</sup> Gene testing for this cytochrome P-450 mutation is available but not yet implemented commonly in practice. This is only one reason why it is important to know all of the medications, including herbs, that a woman is taking before prescribing or recommending other substances.

### Drug Resistance

Shortly after drug manufacturers began mass production of penicillin in the 1940s, infections secondary to resistant *Staphylococcus aureus* began to appear. The spread of resistance was rapid.<sup>16</sup> Between 1979 and 1987, only 0.02% of strains of pneumococcus were reported by the Centers for Disease Control and Prevention (CDC) as resistant; by 1994, 6.6% were reported to be resistant. Several factors account for the development and rapid rise of drug-resistant strains of bacteria. One factor is the human complacency that developed in the 1980s when many scientists and clinicians began to view bacterial infection as an easily curable condition. Antimicrobial agents were used liberally, even for conditions for which they were not indicated, such as the common cold.

When susceptible bacteria were eradicated, the few survivors were those that were resistant to the antimicrobial agent. Through natural selection, these microbes then became the predominant microorganism.

Resistant microbes have several mechanisms of action. For example, penicillin resistance is the result

of gene action. Because penicillin inhibits enzymes involved in cell wall synthesis, some of the organisms can alter their cell walls so that the antibiotic cannot bind to it. These organisms are called beta-lactamase inhibitors because they produce an enzyme called beta-lactamase that breaks open the beta-lactam ring of the penicillin molecule.<sup>17,18</sup> In contrast, resistance to quinolones involves altering the ability of the drug to penetrate its target.<sup>19</sup>

Bacteria can acquire genes that provide resistance to antimicrobial drugs in one of three ways: (1) spontaneous DNA mutation (e.g., drug-resistant tuberculosis); (2) transformation in which one bacterium assumes DNA from another bacterium (e.g., penicillin-resistant gonorrhea); and (3) resistance acquired from a small circle of DNA called a plasmid that can move from one type of bacterium to another (e.g., shigella). The third type is the most troublesome, because with plasmid acquisition, the bacteria may simultaneously become resistant to several types of drugs.

The rise in drug resistance directly correlates with the trend toward increased use of antimicrobials. Clinicians are advised to use antimicrobials only when these agents are clearly indicated, and to use narrow-spectrum agents when the microorganism is known. Clinicians should also educate women about the appropriate use of antimicrobials, including avoidance of antibacterial soaps and cleansers that may contribute to the problem. The antibacterial agents added to a variety of substances, such as soaps, lotions, and cleaning supplies, can act like antibiotics in the selection of resistant strains of microbes; these products are no more effective than similar agents without the antibacterial additives, and controversy has arisen regarding whether they may contribute to drug resistance.<sup>20</sup>



### Regulation of Herbal Therapies

More than 2000 years ago, Hippocrates documented the use of more than 200 herbal remedies. Today, many herbs and botanicals are sold as dietary supplements, even though their actions and safety largely remain unknown. Under the Dietary Supplement Health and Education Act of 1994 (DSHEA), a manufacturer must ensure that its dietary supplement is safe before the product is marketed in the United States.<sup>21</sup> The FDA is responsible for taking action against any unsafe dietary supplement product after it reaches the market. Generally, manufacturers do not register with the FDA, nor do they seek FDA approval before producing or selling dietary supplements. The FDA's postmarketing responsibilities include monitoring safety concerns, such as through voluntary dietary supplement adverse event reporting. The FDA also monitors product information, such as labeling, claims, package inserts, and accompanying literature. The Federal Trade Commission regulates dietary supplement advertising.

Many individuals consume nutritional supplements and herbs, often as a complementary therapy to pharmaceutical treatments. The use of herbs is challenging for midwives, as much of the information available on the Internet or in journals remains anecdotal or reflects expert opinion. Some evidence-based information can be obtained, however. In 1978, a regulatory agency was established in Germany to evaluate the effectiveness of herbal remedies. Called the German Commission E, the group of 24 scientists evaluated studies (clinical, case, field), and prepared scientific monographs. By 2004, only herbs that the German Commission E found to be effective and to carry a low risk of adverse effects were expected to be available in Germany. Although the work generally has been lauded, many common North American herbs are not included in the German registry.<sup>22</sup> The American Botanical Council, based in Texas, has published an English translation of the German monographs.<sup>23</sup>

Currently, the National Center for Complementary and Alternative Medicine (NCCAM) has approximately two dozen studies in process that are comparing herbal remedies to conventional pharmaceutical treatments for specific conditions, such as endometriosis. Publication of the results of these U.S. studies should expand knowledge in the area. Until such solid evidence becomes available, midwives must remain cautious regarding claims involving therapeutic uses of herbs. Many sources simply list possible indications for supplements without any accompanying scientific data.

### Pharmacotherapeutics in Primary Care

The drug categories most commonly used in primary care are analgesics, antihistamines, antimicrobials, hormonal formulations used for contraception, and immunizations. It is not possible to review these topics in depth here. Instead, this section simply introduces the reader to analgesics, antimicrobials, and antihistamines—key drug categories that incorporate the pharmacologic principles and clinical implications that are inherent in all drug categories and that are not covered in other chapters of this text. References that have more in-depth information are provided where relevant.

#### Analgesics

Analgesic medications are categorized as non-opioid analgesics and opioid analgesics. Non-opioid analgesics include aspirin, acetaminophen (Tylenol), and nonsteroidal anti-inflammatory drugs (NSAIDs).<sup>24</sup> Opioid analgesics are a family of drugs with an action similar to morphine.

In the outpatient setting, most of the prescriptions written for analgesia are for formulations that contain a mixture of non-opioid and opioid drugs. It is essential that the prescriber know the mechanism of action, predictable side effects/adverse effects, individual dose variations, maximum daily dose, important drug–drug interactions, and expected response for each medication that is prescribed.

Several different formulations combine an opiate with a non-opiate. For example, the combination of acetaminophen and codeine comes in different strengths of acetaminophen (e.g., Tylenol #1, #2, or #3). In this case, although the drug is usually prescribed on the basis of the 30 mg of codeine in each tablet, the maximum dose is actually limited by the maximum dose of acetaminophen that is safe to take in a 24-hour period. When choosing a specific formulation, the midwife will assess the analgesic capability of a particular formulation and match that to the pain control needs of the woman.<sup>18,25</sup>

Analgesics have pharmacologic effects that are broad and affect many physiologic functions. Consequently, this category of drugs requires that the prescriber be especially aware of side effects and adverse effects. NSAIDs mitigate pain via their ability to inhibit cyclooxygenase (COX), the enzyme responsible for synthesizing prostaglandins.<sup>26,27</sup> Prostaglandins protect gastric mucosa, inhibit platelet aggregation, and stimulate uterine contractions, in addition to mediating the inflammatory response and sensitizing pain receptors. Thus these drugs can

have multiple predictable side effects that can also be adverse effects.<sup>28,29</sup>

In the inpatient setting, midwives frequently manage pain as part of their care of women during labor. The analgesic options for this clinical setting are unique because the physiologic characteristics and function of both the parturient and the fetus must be taken into consideration. Until recently, meperidine (Demerol) was the drug most commonly administered to mitigate labor pain. This agent is very lipophilic, however, so it transfers across the placenta readily. Meperidine also has an active metabolite that can cause significant respiratory depression in the neonate several hours after the drug was administered to the laboring woman.<sup>29</sup> Today, short-acting opioids such as fentanyl (Sublimaze) and morphine, which has predictable pharmacokinetics, are used, but only for specific indications.<sup>30</sup> Most women who desire significant pain control during labor rely on epidural analgesia.

Both gender differences and individual differences are noted in the pain response and in the response to many analgesics.<sup>31,32</sup> The various hormonal and genetic reasons underlying these differences have yet to be fully elucidated, and the clinical implications of this knowledge have not yet been fleshed out. In any event, when prescribing analgesic medications, it is important to assess response and be available to change the recommended therapy as needed.

### Antimicrobials

Antimicrobial drugs include agents directed against bacteria, fungi, viruses, and parasites. Each type of microorganism targeted by these drugs has a different biochemical structure, and consequently each type of antimicrobial has a different chemical structure and biochemical action. In general, antifungal and antiviral drugs attack protein structures that are not present in human cells, so these drugs are less likely to have adverse side effects. At the other end of the spectrum are parasites, which are multicellular organisms that share many similarities with human cells. Safe and effective antiparasitic drugs are particularly difficult to create.

Antimicrobials and analgesics are the most common prescriptions written in primary care practice. It is important to note that the increasingly problematic rise in drug resistance is directly related to the overuse of antibiotics for conditions that do not actually require an antimicrobial agent.<sup>20,33</sup> Thus the first step when using these agents is to make sure they are required. Eight principles describe the critical

clinical considerations prior to prescribing an antimicrobial drug:

1. Confirmation of the presence of an infection through history and physical exam
2. Identification of the pathogen when possible
3. Confirmation of need for antimicrobial as opposed to palliative therapies and infection control measures
4. Understanding of host factors that may influence pharmacodynamics as well as the individual's concerns and resources
5. Selection of an appropriate antimicrobial agent using the dual principles of narrowest spectrum and shortest effective duration possible
6. Knowledge of the pharmacokinetics and pharmacodynamics of selected medications
7. Education of individual and family regarding appropriate use of antimicrobial
8. Appropriate monitoring of the therapeutic response<sup>34</sup>

Antibacterial drugs are either bacteriostatic (i.e., they inhibit bacterial growth) or bacteriocidal (i.e., they kill bacteria) in nature. More generally, these agents are classified by their mechanism of action: (1) they attack the cell wall (penicillins, cephalosporins, and vancomycin); (2) they inhibit or alter protein synthesis (macrolides, tetracycline, and aminoglycosides); or (3) they interfere with bacterial DNA (fluoroquinolones, antiprotozoan drugs, and isoniazid [INH]).

Inappropriate prescribing of antibiotics for viral infections and use of third- and fourth-generation broad-spectrum agents when a narrow-spectrum agent is available are by far the most important problems facing midwives who may be prescribing these agents. There are two critical components to the solution to these problems. First, clinical guidelines are available from most professional associations as well as individual institutions; these guidelines can help the prescriber choose the correct therapy. Second, thorough health education that is both culturally competent and provided at the correct health literacy level is essential. As a corollary to this general rule, when an antimicrobial agent is prescribed, detailed information on dose, timing, specific rules about taking with food or drink, and possible side effects or adverse effects is also part of the required health education.

### Antihistamines

Four different types of histamine receptors ( $H_1$ ,  $H_2$ ,  $H_3$ ,  $H_4$ ) are found in multiple tissue sites within the body. Thus antihistamine drugs have a wide range of actions and uses. These agents are commonly used over-the-counter medications.

$H_1$  receptors are found in the muscles that line blood vessels (vascular smooth muscle) and in nervous tissue. These receptors are involved in the inflammatory response and allergic reactions.  $H_2$  receptors are located in gastric mucosa. Stimulation of these receptors causes secretion of gastric acid.  $H_3$  and  $H_4$  receptors are found in the brain, heart, eye, breast tissue, and immune cells. These receptors appear to be involved in circadian rhythms, allergic reactions, and perhaps carcinomas, although their exact functions are not yet well elucidated.

Antihistamines that are antagonists at  $H_1$  receptors are used to treat allergic reactions, nausea and vomiting, and motion sickness. First-generation  $H_1$  antihistamines have a duration of action of approximately 4–6 hours. Also, because they cross the blood–brain barrier, they cause sedation—the most common side effect. When sedation is the desired effect, it is important to note that tolerance to sedation develops within a few days. Thus drugs such as diphenhydramine hydrochloride (Benadryl) and doxylamine succinate (Unisom Sleep Tabs) should be taken for a few days only. The other side effect of antihistamines that is of clinical concern relates to their anticholinergic effects. This action causes a drying of mucous membranes, which is helpful in treating allergies, but can also cause urinary retention and blurred vision. The primary contraindications to antihistamines are those wherein sedation or anticholinergic effects would cause adverse outcomes. For example, persons with glaucoma or hyperthyroidism should not use antihistamines.

The second-generation  $H_1$  antihistamines have a longer duration of action, which can be as long as 24 hours. In addition, they are more selective for peripheral  $H_1$  receptors and, therefore, do not cause sedation. The second-generation  $H_1$  antihistamines, however, have more drug–drug interactions than do the first-generation drugs in this category.<sup>35</sup>

The  $H_2$  antihistamines are used to treat gastric disorders wherein hyperacidity is a problem. These antihistamines have very few side effects. Cimetidine (Tagamet) has many drug–drug interactions and, for this reason, is not considered the first  $H_2$  antihistamine of choice. Famotidine (Pepcid AC) is more potent than cimetidine (Tagamet) or ranitidine

(Zantac). The most common side effect of these drugs is headache, which occurs in 3% to 5% of persons who take these medications.

### Use of Drugs During Pregnancy

#### Pharmacokinetics in Pregnancy

Pharmacokinetics encompasses the absorption, distribution, metabolism, and excretion of drugs. The myriad physiologic changes that occur during pregnancy affect the pharmacokinetics of any drugs and herbs that the pregnant woman uses.<sup>36</sup> Pregnancy-related changes in pharmacokinetics are summarized in Table 5-2.

#### Transport of Drugs Across the Placenta

Drug distribution is complex during pregnancy, as four separate compartments exist: (1) the fetus, (2) the amniotic fluid, (3) the placenta, and (4) the mother. Each of the compartments affects movement of drugs, and occasionally certain drugs can have a higher concentration in a specific compartment.<sup>37</sup> Placental transfer of drugs can be accomplished by any of the traditional drug transfer methods, whether passive or active.

Passive transfer includes simple diffusion and facilitated diffusion. Neither of these two methods requires energy or allows an agent to be transferred across the membrane to an area of higher drug concentration. Most drugs move across the placenta by simple diffusion, although some take advantage of carrier-mediated mechanisms or use facilitated diffusion. Glucocorticoids and cephalexin (Keflex), for example, are transported via facilitated diffusion. One can assume that this mechanism is intended for endogenous compounds such as hormones and, therefore, is also used to transport drugs that are structurally similar to naturally occurring hormones.<sup>38</sup>

Active transport requires energy; the most common method is pinocytosis, a process during which a portion of the plasma membrane engulfs the drug molecule, creating a type of intracellular vesicle. Because of the energy and time required for pinocytosis, the small number of drugs that cross the placenta using active transport are also similar in structure to endogenous compounds that cross the placenta this way. Digoxin (Lanoxin) and valproic acid (Depakene), for example, cross the placenta via active transport.

Table 5-2 Pregnancy-Related Changes in Pharmacokinetics		
Pharmacokinetic Phase	Pregnancy Changes	Clinical Implications
<b>Absorption</b>	Increased progesterone production causes decreased intestinal motility and 30%–50% increase in gastric emptying time Gastric pH increases at midgestation	Gestational nausea and vomiting may impair absorption Slower gastric emptying time may delay onset of drug response Increased exposure to bacteria in intestine may decrease bioavailability of some drugs Calcium and iron bind when ingested concurrently, thereby decreasing absorption of both minerals
Lung absorption	Respiratory minute volume increases approximately 50%	Dose requirements for inhaled drugs are decreased
Transdermal, subcutaneous absorption	Skin perfusion and skin hydration are both increased Enhanced perfusion to muscles	Both lipophilic drugs and hydrophilic drugs are more rapidly absorbed transcutaneously Intramuscular absorption of drugs is more rapid and complete compared to absorption in nonpregnant individuals
<b>Distribution</b>	Plasma volume is expanded by approximately 50% Body fat stores increase by 3–4 kg	Hydrophilic drugs have reduced plasma concentration and need to be given in higher doses Lipophilic drugs that concentrate in body fat may accumulate and prolonged effects could be seen following long-term use
Protein binding	Plasma albumin concentrations are reduced secondary to increased plasma volume	Increased free drug is available for pharmacologic effects Drugs that are highly protein bound will have more pharmacologic activity in a pregnant woman
Fetal–maternal distribution	Fetal compartment available for distribution of drugs Fetal circulation is more acidic than the maternal circulation Fetal albumin concentration in plasma increases throughout pregnancy and is 20% higher than maternal concentrations at term	Highly lipophilic drugs of low molecular weight and that have low protein binding can accumulate in the fetal compartment Basic drugs such as meperidine (Demerol) can have higher concentrations in the fetal compartment than in the maternal circulation secondary to “ion trapping” Drugs that are highly bound to albumin can concentrate in the fetus at term Most drugs in the fetal compartment tend to be 50%–100% of the concentration in the maternal compartment
<b>Metabolism</b>	Changes in estrogen and progesterone affect cytochrome P-450 enzyme activity CYP1A2 is inhibited CYP3A4 and CYP2C9 are increased	Metabolism of caffeine and theophylline (Theo-Dur) is inhibited or slower Metabolism of sertraline (Zoloft) and metoprolol (Lopressor) is enhanced or faster
<b>Elimination</b>	Glomerular filtration rate increases by 50% throughout pregnancy	More rapid clearance of most all drugs that are eliminated renally

Drug transfer is facilitated by various characteristics of the drug, including its size (molecular weight), lipid solubility, plasma protein binding, and acid versus basic properties. Most drugs have a small molecular weight, usually less than 500 daltons (Da), so they are easily transferred easily across the placenta. Drugs with a molecular weight greater than

500 Da transfer incompletely; those like heparin and insulin, which have a molecular weight greater than 1000 Da, transfer very poorly.<sup>38</sup> Drugs that are more lipophilic cross the placenta more readily than those that are hydrophilic, as the placenta is lipoid in character. A non-ionized state facilitates transfer. When ionized basic drugs such as meperidine (Demerol)

cross the placenta, they can accumulate in the fetal liver and adrenal glands and become ion-trapped in the fetus because the fetal circulation is more acidic than the maternal circulation.

Once a drug enters the fetal circulation, it is free to bind with proteins in the fetal plasma. Albumin concentrations in the fetal compartment are higher than in the maternal compartment. Thus some highly protein-bound drugs such as diazepam (Valium) may have an increased fetal effect when compared with their maternal effects.

### Drug Dose Alterations in Pregnancy

Some medications may need dosage adjustments over the course of pregnancy. For example, aminoglycosides such as gentamicin (Garamycin), as well as other agents such as ampicillin (Omnipen, Polycillin, Principen) and cefazolin (Rocephin), have lower serum concentrations during pregnancy and therefore, to be effective, the doses of these medications may need to be increased for pregnant women. Ampicillin, in particular, has serum concentrations in pregnant women that are 50% of the serum concentrations seen in nonpregnant women. The clinician may also need to decrease theophylline (Theolair) doses for the asthmatic woman, as serum concentrations of this agent rise in pregnancy.

### Teratogenic and Fetotoxic Effects of Drugs

Although most women are aware that they should not take drugs during pregnancy, 50% of all pregnancies are unintended and awareness of pregnancy typically occurs only after embryogenesis has begun.<sup>38</sup> Approximately 20% of pregnant women use a medication at least once that is known to have a risk for causing fetal harm.<sup>29</sup> One of the major concerns specific to pregnancy is whether the drugs used are teratogenic.

*Teratology* is essentially the study of congenital anomalies and teratogens or any agent that irreversibly alters growth, structure, or function in a developing embryo or fetus. Teratogens include viruses such as rubella, chemicals such as mercury, and drugs such as diethylstilbestrol (DES).<sup>36,39</sup> The term *fetotoxic* is used to describe agents, such as tobacco, that have toxic effects on the fetus and adversely affect growth or development.<sup>36,40</sup> The fetus is mostly likely to be exposed to teratogenic agents in the first trimester and to fetotoxic agents in the second and third trimesters.

Overall, birth defects occur in approximately 1% to 3% of all births. This percentage is often called the “background risk” upon which additional risks are

calculated based on family history, past history, and environmental exposure. Only 10% of birth defects can be associated with environmental factors, and the majority of environmental factors are not pharmaceuticals. Drugs and chemical agents such as mercury and pesticides account for approximately 45% of the environmental teratogens involved in congenital anomalies. Drugs alone account for only 2% to 3% of all birth defects.<sup>40,41</sup>

The unique fact about teratogenic medications is that avoiding the teratogen can prevent the associated congenital anomaly. Thus knowledge of teratogenic drugs is essential for the practicing midwife. Fortunately, the number of these agents is relatively small, and even fewer are in common use.

The preimplantation period is considered the “all or nothing” period. If a small number of cells are damaged during this time period, the fetus usually compensates without any damage. Conversely, if a large number of cells are damaged, the embryo will be lost and a spontaneous abortion will occur. The period of organogenesis—between 2 and 8 weeks post fertilization, or 4 to 10 gestational weeks—is the most critical period wherein teratogenic exposures can cause fetal malformations<sup>40</sup> (Figure 5-3). A list of drugs that are known to have teratogenic or fetotoxic effects is presented in Table 5-3.

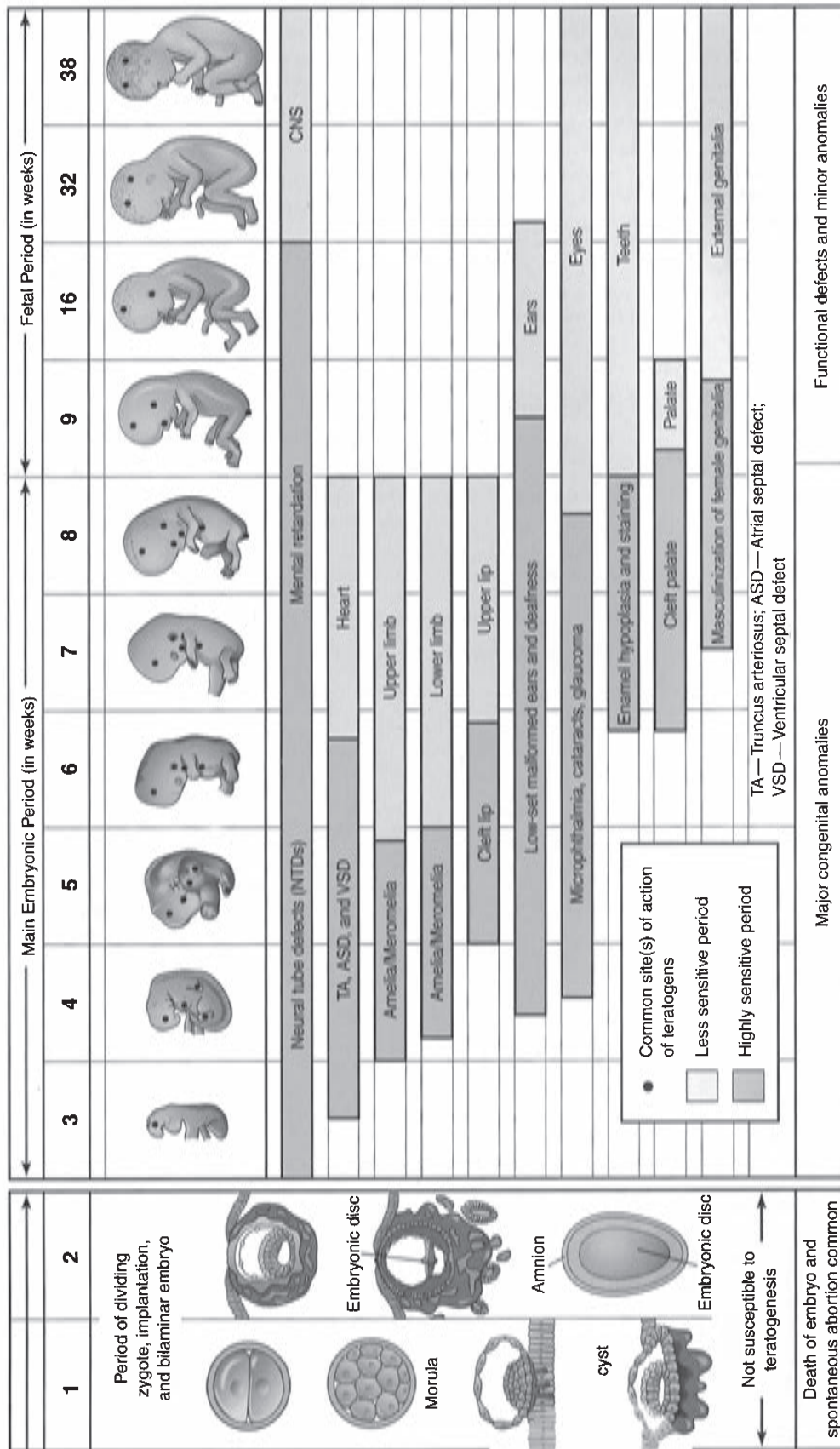
### FDA Drug Categories

In 1979, the FDA published a list of pregnancy risk categories for prescription and nonprescription drugs, including those with known teratogenic effects. These categories are listed in Table 5-4.<sup>42</sup> Although the FDA created the drug categories, the drug manufacturer usually determines which category a particular drug will be assigned.<sup>6</sup>

Unfortunately, these FDA pregnancy categories oversimplify the complexity of what is known and what is not known about drug effects on human fetuses, in several different ways.<sup>43</sup> First, the FDA pregnancy categories suggest that the level of risk increases from Category A to Category X. This is only true somewhat true for Categories A, B, and C. Categories D and X are based on the risk weighed against the evidence of benefit. Thus drugs in Categories D, X, and to some extent C may be associated with a similar risk but are categorized differently based on their different risk–benefit calculations.

Second, the pregnancy categories imply that drugs within one category have a similar risk for reproductive harm to the fetus. This is particularly problematic for Category C, which includes drugs that have demonstrated risks in animal studies and





**Figure 5-3** Early stages of development.

Source: Reproduced by permission from Moore KL, Persaud TVN. *The Developing Human: Clinically Oriented Embryology*. 6th ed. Philadelphia, PA: W.B. Saunders; 1998.

Table 5-3 Drugs That Have a Teratogenic or Fetotoxic Effect		
Drug Category Name (Brand Name)	Teratogenic or Fetotoxic Effects	Comments
<b>Androgens and testosterone derivatives:</b> Danocrine (Danazol)	Virilization of females Advanced genital development of males	Dose dependent and based on critical period. Brief exposure rarely is significant. Before 9 weeks' gestation, labioscrotal fusion is common. Incidental, brief exposure usually has minimal risk.
<b>Antibiotics:</b> <b>Tetracyclines:</b> Tetracycline (Terramycin) Doxycycline (Adoxa)	Abnormalities of teeth discoloration	Critical period is after first trimester. Discoloration of permanent teeth is possible if exposure occurs after 24 weeks' gestation.  No well-controlled studies of doxycycline have been performed, but case-controlled studies suggest it is not associated with teratogenic risk. Recommend that doxycycline be used only if it is the only effective agent.
<b>Sulfonamides:</b> Sulfamethoxazole (Bactrim, Septra)  Chloramphenicol	Hyperbilirubinemia in neonate  Grey syndrome in neonate 2–9 days after therapy administered	Contraindicated in third trimester.  Oral chloramphenicol is contraindicated in pregnancy.
<b>Aminoglycosides:</b> Gentamycin (Garamycin) Streptomycin	Neonatal ototoxicity	Streptomycin in high doses used to treat tuberculosis has a clear risk of fetal ototoxicity. The risk associated with gentamycin may be smaller, but this agent is not recommended for use in pregnancy.
<b>Anticonvulsants:</b> Carbamazepine (Tegretol) Phenytoin (Dilantin) Trimethadione (Tridione) Valproic acid (Depakene) Valproate (Depacon)	1% risk of neural tube defect, cardiovascular defects, developmental delays, intrauterine growth restriction  Reduced intelligence associated with use of valproic acid or valproate  Phenytoin is specifically associated with cardiac defects and cleft palate	Critical period is all trimesters. Risk of neural tube defect is increased, especially when used with other antiepileptic drugs.  Risk of neural tube defects is decreased with increased folic acid supplementation.  Polytherapy with more than one anticonvulsant increases risk.  Newer anticonvulsants such as gabapentin (Neurontin) do not appear to engender a risk of congenital anomaly.
<b>Angiotensin-converting enzyme (ACE) inhibitors:</b> Captopril (Capoten) Enalapril (Vasotec) Lisinopril (Prinivil)	Intrauterine growth restriction Oligohydramnios Renal failure Decreased skull ossification Renal tubular dysgenesis	Risk of growth restriction is approximately 25%, with fetal morbidity of approximately 30%. Risk of adverse effects increases in second and third trimesters (probably due to decreased uteroplacental flow).  Beta blockers such as labetalol (Trandate) are safe in pregnancy.
<b>Antidepressants:</b> Fluoxetine (Prozac) Paroxetine (Paxil) Sertraline (Zoloft)	Paroxetine increases risk of cardiac defects 1.5- to 2-fold; the other SSRI-type antidepressants do not appear to have teratogenic effects  Exposure in third trimester associated with neonatal withdrawal  Persistent pulmonary hypertension noted in case reports	Overall, risks of teratogenic and fetotoxic effects are low. Antidepressants should not be discontinued during pregnancy. If starting antidepressant therapy during pregnancy, avoid paroxetine.

(continues)

Table 5-3		Drugs That Have a Teratogenic or Fetotoxic Effect (continued)	
Drug Category	Name (Brand Name)	Teratogenic or Fetotoxic Effects	Comments
<b>Antineoplastic drugs:</b>			
	Cyclophosphamide (Cytoxan)	Multiple birth defects and spontaneous abortion if used in first trimester	If a woman needs one of these drugs, refer her for consultation with perinatologists and oncologists.
	Methotrexate (Rheumatrex)		Methotrexate is used to treat ectopic pregnancy.
<b>Angiotensin II receptor blockers:</b>			
	Losartan (Cozaar)	Prolonged renal failure and hypotension in the newborn, decreased skull ossification, renal tubular agenesis	Critical period is all trimesters.
<b>Antithyroid drugs:</b>			
	Propylthiouracil (PTU)	Fetal and neonatal goiter, fetal hypothyroidism, and aplasia cutis are associated with methimazole but not propylthiouracil	Critical period is all trimesters. Women who need to take antithyroid drugs will generally be counseled to take propylthiouracil. The risk of fetal goiter is approximately 1%–5%.
	Methimazole		
	Aspirin	More than 150 mg/day is associated with prolonged gestation, prolonged labor, bleeding complications in the neonate, premature closure of the ductus arteriosus, and intrauterine growth restriction	Critical period is all trimesters. Although low-dose aspirin may be of benefit for women with antiphospholipid syndrome or lupus, normal adult doses should be avoided.
<b>Benzodiazepines:</b>			
	Alprazolam (Xanax)	Increased risk of neonatal withdrawal	Early data on oral cleft association are controversial. Benzodiazepines are highly lipophilic and have a long half-life in the neonate.
	Chlordiazepoxide (Librium)	Some studies show increased risk of oral clefts with first-trimester exposure to diazepam	
	Diazepam (Valium)		
<b>Corticosteroids:</b>			
	Methyl prednisone (Medrol)	Possibly increased risk of oral and cleft defects	Critical period is first trimester. Because the risk is low, oral corticosteroids are used in the first trimester to treat hyperemesis gravidarum and other medical conditions. No risk associated with topical use.
	Coumarin (Warfarin)	Bone defects Growth restriction Central nervous system (CNS) defects Developmental delays	15%–25% risk when anticoagulants that impair vitamin K are used, especially between 6 and 9 weeks of gestation. Later use in pregnancy is associated with abruption, CNS defects, stillbirth, and hemorrhage of the fetus/newborn.
<b>Ergot alkaloids:</b>			
	Ergotamine (Cafergot)	Spontaneous abortion Mobius syndrome Intestinal atresia Cerebral developmental abnormalities Low birth weight and preterm birth	Critical period is all trimesters. Sumatriptan (Imitrex): alternative to ergotamine for acute migraine treatment.
<b>Folic acid antagonists:</b>			
	Methotrexate (Rheumatrex)	Spontaneous abortion	Drugs in many different drug categories are folic acid antagonists.
	Carbamazepine (Tegretol)	Neural tube defects	Some suggest that risk can be decreased with folic acid supplementation.
	Phenytoin (Dilantin)	Cardiovascular defects	
	Phenobarbital (Solfoton)	Urinary tract defects	Trimethoprim is a component of trimethoprim-sulfamethoxazole (Septra), which is commonly used to treat urinary tract infections. This drug should not be given in the first and third trimesters.
	Primidone (Mysoline)		
	Trimethoprim (Trimpex)		

Table 5-3 Drugs That Have a Teratogenic or Fetotoxic Effect (continued)		
Drug Category Name (Brand Name)	Teratogenic or Fetotoxic Effects	Comments
Lithium (Lithobid)	Cardiac defects Epstein's anomaly	Absolute risk is small, but alternative drugs should be recommended if possible.
Mifepristone (RU-486)	Antiprogesterone; used as an abortifacient Human data are limited	Primarily used for abortion in combination with misoprostol. Less effective when used alone.
Misoprostol (Cytotec)	Abortion Moebius sequence (brain stem ischemia, vascular disruption) for misoprostol	Potent uterostimulant capable of initiating uterine contractions at all gestational ages.
<b>Nonsteroidal anti-inflammatory drugs:</b> Ibuprofen (Advil) Naproxen (Aleve)	Theorized premature closure of the ductus arteriosus Necrotizing enterocolitis	Contraindicated in general but especially in third trimester.
<b>Retinoids:</b> Isotretinoin (Accutane)	Multiple birth defects, including CNS, cardiac, and endocrine damage	Oral isotretinoin is contraindicated in pregnancy. Topical preparations are unlikely to have serious teratogenic effects but are still contraindicated because other agents can be used.
<b>Statins:</b> Atorvastatin (Lipitor) Lovastatin (Mevacor)	Interfere with cholesterol production Primarily theoretical adverse effects on the fetus	Contraindicated in pregnancy.
Streptomycin and kanamycin	Hearing loss Eighth nerve damage	No ototoxicity has been found with gentamicin or vancomycin.
Thalidomide	Limb deficiencies Cardiac and GI abnormalities	20%–30% risk during critical period (very potent). Used for years before teratogenic effects became obvious. Has caused the belief that all drugs have the potential to be a “new thalidomide.” Back on market for oral lesions in HIV, Hansen's disease, TB, and multiple myeloma. STEPS (System for Thalidomide Education and Prescribing Safety) is available online from the manufacturer, Celgene.

drugs for which no animal studies have been conducted.<sup>40,43–45</sup> In fact, each of the categories is heterogeneous with regard to clinical interpretation. For example, only 0.7% of drugs are classified into Category A.<sup>40</sup> Randomized controlled trials (RCTs) of pregnant women to assess risks associated with drugs are ethically questionable and, therefore, are rarely performed. In addition, Category A may suffer from the problem of publication bias, as studies with negative findings are not published as often as studies with positive outcomes. Thus Category A may be used less often than it should secondary to

research constraints. Category B has another problem. Classification of a drug into this category can be based on animal studies that document no harm and failure of human studies to document harm or no human studies that show harm.<sup>42</sup> The rigor of safety information based on some human studies or no human studies is not equal, however, so the drugs in this category may have significantly different safety profiles. Categories D and X both include teratogens but differ according to the supposed risks and benefits of their member drugs. For example, some Category D drugs are antiepileptic drugs (AEDs) with known

Table 5-4	FDA Pregnancy Risk Categories for Prescription and Nonprescription Drugs
Category	Description
A	Controlled studies in women fail to demonstrate a risk to the fetus in the first trimester (and there is no evidence of a risk in later trimesters), and the possibility of fetal harm appears remote.
B	Either animal reproduction studies have not demonstrated a fetal risk but there are no controlled studies in pregnant women or animal reproduction studies have shown an adverse effect (other than a decrease in fertility) that was not confirmed in controlled studies in women in the first trimester (and there is no evidence of a risk in later trimesters).
C	Either studies in animals have revealed adverse effects on the fetus (teratogenic, embryocidal, or other) or controlled studies in women and animals are not available. Drugs should be given only if the potential benefit justifies the potential risk to the fetus.
D	There is positive evidence of human fetal risk, but the benefits from use in pregnant women may be acceptable despite the risk (e.g., if the drug is needed in a life-threatening situation or for a serious disease for which safer drugs cannot be used or are ineffective).
X	Studies in animals or human beings have demonstrated fetal abnormalities or there is evidence of fetal risk based on human experience, or both, and the risk of the use of the drug in pregnant women clearly outweighs any possible benefit. The drug is contraindicated in women who are or may become pregnant.
Source: Pregnancy labeling. <i>FDA Drug Bull.</i> 1979;9:23-24.	

teratogenic effects. Even so, these AEDs may be prescribed during pregnancy if they are the only agents effective in controlling seizure activity. Category X is reserved for drugs that are known teratogens and are used to treat disorders for which safe and effective alternative nonteratogenic therapies are available.

In 2008, the FDA proposed a pregnancy and lactation section of drug labeling that omits the letter categories and replaces them with text that is divided into sections addressing clinical considerations, detailed data about risks, and lactation information.<sup>46</sup> It is believed that this system will be adopted in the near future and will replace the current pregnancy categories A, B, C, D, and X.

Despite the fact that the current FDA pregnancy categories lack sufficient specificity, multiple evidence-based sources of reliable information about specific drugs are available on several different websites including the FDA, the Teratogen Information System (TERIS), and the Organization of Teratology Information Specialists (OTIS).

### Pharmaceuticals Commonly Used During Pregnancy

At least 50% of all pregnant women are prescribed one or more drugs during pregnancy.<sup>47</sup> Although the majority of these medications are classified into FDA Category A, B, or C, approximately 5% are members of Category D or X.<sup>47</sup> The drug classifications most commonly used during pregnancy include vitamins, antimicrobials, analgesics, and blood

glucose regulators. The sections that follow present a brief review of these categories of pharmaceuticals from which midwives often prescribe or recommend treatments, in order of most frequently to least frequently used.

### Vitamins

Prenatal vitamins are multivitamin supplements formulated to provide the vitamins and minerals needed most by pregnant women. In fact, prenatal vitamins are one of the universal symbols of prenatal care, considered essential by both women and their health-care providers. However, the actual value of vitamin and micronutrient supplements for pregnant women is more nuanced and complex. Although a balanced diet generally provides all the nutrients needed for health during pregnancy, a majority of the women in the United States do not consume a diet that provides all the vitamins and micronutrients needed during pregnancy.<sup>48</sup> This fact is the overall reason why prenatal vitamins are recommended. In addition, evidence indicates that prenatal multivitamins containing additional folic acid have a positive effect in lowering the incidence of several congenital anomalies in addition to neural tube defects.<sup>49</sup>

*Multivitamins* do have some problems. Calcium interferes with iron absorption, so placing both of these minerals in one vitamin may obviate the overall goal. Many women report significant nausea or gastric upset secondary to the iron in prenatal



vitamins—a problem that can be resolved by discontinuing the multivitamin for a period of time, switching to a multivitamin without iron, or sometimes using a different formulation of iron.<sup>50</sup>

The specific vitamins and micronutrients that have documented adverse effects on fetal development if present in insufficient amounts in the diet are folic acid, iron, and iodine.<sup>51</sup> Women who follow vegetarian or vegan diets also need supplemental vitamin B<sub>12</sub>. There is some evidence that vitamin D supplements may be necessary for women who do not get enough exposure to sunlight<sup>52</sup> and that additional omega-3 fatty acids may improve fetal growth as well as neonatal cognition and visual function although the evidence is not robust enough to recommend either for all women at the time of this writing.<sup>53</sup>

It has been definitively proven that *folic acid* supplementation taken during the 3 months prior to conception and for the first 2 months after conception can reduce the incidence of neural tube defects by approximately 50%.<sup>49,54</sup> Although many dietary sources of folic acid exist, this is the one nutrient that women absorb from supplements better than from dietary sources.<sup>55</sup> Routine supplementation with folic acid is recommended for all women of childbearing years.<sup>56</sup>

*Iron* is the single most difficult nutrient to obtain via the diet during pregnancy, and iron needs are approximately doubled during pregnancy.<sup>57–59</sup> However, unlike folic acid, routine iron supplementation is controversial. The CDC recommends routine iron supplementation, but other organizations recommend that supplementation be started only for women who do not have normal hemoglobin values.<sup>57–59</sup> Iron supplementation will increase plasma hemoglobin levels but does not have any effect on overall maternal and neonatal outcomes unless iron is used specifically to treat anemia during pregnancy. Iron supplements frequently cause gastrointestinal distress.

*Iodine* deficiency can cause significant intellectual impairment but is rare in the United States given that table salt and many common foods are routinely fortified with iodine. Nevertheless, many multivitamins contain amounts of iodine that are less than the amount recommended by the American Thyroid Association.<sup>60,61</sup>

Vitamins are not always positive supplements. For example, vitamin A in large doses can be a teratogen. Initially the threshold for adverse effects was thought to be more than 25,000 IU of vitamin A daily, but studies have since shown that cranial neural crest anomalies occur with as little as 10,000 IU daily.<sup>62</sup> Routine supplementation of vitamin A is unnecessary, and, if supplementation is used, it

should not exceed 5000 IU daily. Typical prenatal multivitamins contain at least 800 IU of vitamin A. Women should be cautioned not to double or triple their intake of multivitamins in an attempt to get additional folic acid or calcium. Increasing intake of a multiple vitamin increases intake of all of that product's constituents, including vitamin A.

### Antimicrobials

*Penicillins* and *cephalosporins* are among the most commonly prescribed antimicrobials for treatment of various female reproductive infections. Few studies of cephalosporins have been conducted in the first trimester of pregnancy, but no adverse effects have been reported and cephalosporins, like penicillin, belong to the beta-lactam classification of antimicrobial agents. However, because the penicillins and erythromycin have been studied extensively and not found to be associated with teratogenic effects, many experts advocate using them as first-line therapies whenever possible.

*Metronidazole* (Flagyl) is a well-established antiprotozoal agent and the treatment of choice for *Trichomonas vaginalis* infection and bacterial vaginosis. No teratogenic effect has been found with metronidazole, even though its mechanism of action involves bacterial mutation.<sup>63</sup> The drug is assigned to FDA Category B, yet many providers are hesitant to administer it during the first trimester. Although evidence does not support withholding the drug, the conditions for which it is used generally are not life threatening. Because metronidazole is the most effective drug for the treatment of trichomoniasis, it should be prescribed when indicated.<sup>64</sup>

*Quinolones* are FDA Category C drugs, but are rarely used in pregnancy because animal studies have demonstrated drug accumulation in the joints with subsequent damage.<sup>65</sup>

*Sulfonamides* are not teratogenic but require attention to timing. These agents are highly protein bound and can displace bilirubin from binding sites. The most commonly used agents in this category are a combination of sulfamethoxazole and trimethoprim (Bactrim, Septa). Administration of sulfonamides becomes problematic when they are administered near the time of birth because the free bilirubin that is displaced will be in the newborn's circulation. The immature liver is unable to compensate and kernicterus may result from these high plasma levels. Thus sulfonamides should be avoided in the third trimester. One sulfonamide, sulfasalazine (Azulfidine), appears to be an exception. This drug is used primarily for the treatment of ulcerative colitis and Crohn's disease and has a weak effect (if any) on bilirubin.

*Tetracyclines* are contraindicated in pregnancy because they concentrate in teeth. Children exposed in utero to tetracyclines may have yellowed teeth with poor enamel and vulnerability to caries as well as potential problems with bone growth.

*Aminoglycosides* include streptomycin, gentamycin (Garamycin), and kanamycin (Kantrex). All are ototoxic drugs that can cause permanent eighth cranial nerve damage. These agents are reserved for grave situations in which their benefits outweigh their risks.

### **Analgesics**

The category of *nonsteroidal anti-inflammatory drugs* technically includes acetaminophen, ibuprofen, and aspirin. In general use, the term NSAIDs refers specifically to the family of drugs similar to ibuprofen (Advil); this is how the term is used in this chapter. Aspirin and NSAIDs have been implicated in disruption of the prostaglandin cascade involved in initiation of labor and, therefore, are linked to post-term pregnancy. NSAIDs can cause premature closure of the ductus arteriosus; indeed, they are employed neonatally for that specific therapeutic effect. Aspirin has been associated with fetal vascular disruptions as well as competition with bilirubin for albumin binding sites. NSAIDs and aspirin should be avoided in pregnancy, especially in the first and third trimesters. An alternative agent without anti-inflammatory action is acetaminophen (Tylenol).<sup>64</sup> Acetaminophen is the analgesic of choice for minor pain during pregnancy.

*Opiate* analgesics have not been implicated as having teratogenic effects. Caution with their use in pregnancy is based upon fear of addiction, not teratogenicity.

### **Drugs Used for the Treatment of Medical Conditions During Pregnancy**

Although midwives care independently for women without medical or obstetrical complications, they often consult and collaborate in the care of women with medical or obstetrical complications. Thus knowledge of drugs that have teratogenic or fetotoxic effects and that are used in the care of pregnant women who have medical complications is necessary.

*Antiepileptic agents* pose a distinct challenge to the healthcare provider.<sup>65</sup> Seizure disorders themselves may contribute to teratogenic outcomes. Several older antiepileptic drugs (AEDs) are teratogenic, although the absolute risk of congenital malformations following prenatal exposure is low.<sup>66</sup> Phenytoin (Dilantin) is associated with midline cardiac defects,

hypospadias, neonatal coagulopathy, and neurobehavioral impairment. Carbamazepine (Tegretol), valproate (Depacon), and valproic acid (Depakene) can cause a dysmorphic pattern of minor anomalies, including neural tube defects and midline cardiac defects. Valproate and valproic acid are associated with intellectual impairment, and the congenital anomalies related to this drug appear to be dose dependent.<sup>67</sup> Phenobarbital (Solfoton) has been associated with neurobehavioral impairment and newborn withdrawal syndrome. Newborns exposed in utero to phenytoin (Dilantin), carbamazepine (Tegretol), or phenobarbital (Luminal) are at risk of coagulation problems secondary to drug-induced vitamin K deficiency, and need prompt supplemental vitamin K. Newer-generation antiepileptic drugs such as gabapentin (Neurontin) and lamotrigine (Lamictal) do not appear to have teratogenic effects.<sup>68</sup>

Many mechanisms have been proposed to explain the teratogenicity of anticonvulsant agents. Several of the drugs appear to have antifolate characteristics, and some authorities recommend that women on AEDs should be treated with 4 mg of folic acid both prior to conception and in early pregnancy.<sup>69</sup> The midwife should work closely with maternal-fetal specialists when caring for a woman with a seizure disorder, as treatment requires the choice of the least risky drug, at the lowest dose that controls seizures.

*Antidepressants* represent another drug category used by many women during pregnancy. The most widely used class of medications to treat depression, bipolar disorder, and anxiety disorders are the selective serotonin reuptake inhibitors (SSRIs) such as fluoxetine (Prozac), paroxetine (Paxil), and sertraline (Zoloft).<sup>70</sup> Untreated depression is associated with several adverse pregnancy outcomes, including preterm birth, postpartum depression, and poor behavioral and mental health outcomes in children.<sup>71</sup> Thus treatment of depression during pregnancy is recommended.<sup>72</sup> Although knowledge about the teratogenic and fetotoxic effects of SSRIs and serotonin norepinephrine reuptake inhibitors (SNRIs) is still being elucidated, there are some associations that women need to be apprised of prior to initiating or continuing therapy during pregnancy.<sup>72,73</sup> Midwives who choose to add these drugs to their individual formulary or manage women who are taking these drugs must know the required screening and diagnostic criteria for depression and other related mental disorders, understand the side effects and adverse effects associated with these agents, appreciate the FDA's "black box" warnings for these drugs, and practice within a setting that provides access to psychiatric services.

*Thyroid agents* are commonly used during pregnancy. The most common cause of hyperthyroidism is Graves' disease, which occurs secondary to the development of autoantibodies. These autoantibodies bind to the thyroid-stimulating hormone (TSH) receptor on the thyroid gland, which results in excessive production of thyroid hormone. Untreated hyperthyroidism has been linked to spontaneous abortion. The most popular treatment for hyperthyroidism is radioiodine (RAI), which is radioactive iodine that concentrates in the thyroid and destroys thyroid tissue. Radioiodine is contraindicated in pregnancy because it can cross the placenta and destroy the fetal thyroid. Traditionally, propylthiouracil (PTU) has been the drug of choice for hyperthyroidism in pregnancy, as methimazole (Tapazole) has been linked to aplasia cutis in the newborn. More recently this neonatal association has been called into question.<sup>73</sup> Moreover, PTU may result in fetal hypothyroidism when the drug is used in high doses, so close monitoring is required. Women who are taking PTU should be seen by an obstetrician to establish a plan for ultrasound monitoring to assess the fetal thyroid.

The most common etiology of hypothyroidism is Hashimoto's disease, also known as autoimmune thyroiditis. Untreated hypothyroidism can cause fetal mental retardation, preeclampsia, stillbirth, and other adverse obstetric outcomes.<sup>74</sup> Hypothyroidism is treated with levothyroxine (Synthroid), which is synthetic thyroid hormone. Levothyroxine has no adverse effects on the fetus, but the maternal dose may need to be increased by as much as 45% during pregnancy; thus thyroid stimulating hormone (TSH) and free thyroxine (T4) levels are typically assessed once each trimester. The goal is to maintain a euthyroid state during pregnancy.

*Antihypertensives* are prescribed for women with chronic hypertension. Chronic hypertension is defined as a systolic blood pressure of at least 140 mm Hg or a diastolic blood pressure of 90 mm Hg before pregnancy or in pregnant women prior to 20 weeks' gestation.<sup>75</sup> Angiotensin-converting enzyme (ACE) inhibitors and angiotensin-receptor blockers (ARBs) are contraindicated in pregnancy secondary to an increased risk for teratogenic effects. Use of these drugs in the second and third trimesters is associated with low birth weight, oligohydramnios, and hypoplastic fetal lung development.<sup>75</sup> Atenolol (Tenormin) has been associated with intrauterine growth restriction (IUGR) secondary to reduced placental function. This problem has not been noted following use of the other beta blockers; thus, with the exception of atenolol, beta blockers are the first-line drugs used to treat chronic hypertension in pregnancy. Labetalol

(Trandate) is the most commonly used antihypertensive prescribed in the United States today.<sup>75</sup> The other category of antihypertensive drugs that appear safe in pregnancy is the calcium-channel blockers, which include agents such as nifedipine (Procardia XL). Nifedipine is also used as a tocolytic because it inhibits uterine contractions.

*Anticoagulants*, if needed during pregnancy, should consist of heparin, either regular or low molecular weight, as the drug of choice.<sup>76</sup> Coumarins, including warfarin (Coumadin), easily cross the placenta; when pregnant women take these drugs, approximately one-fourth of their embryos are born with fetal warfarin syndrome (i.e., nasal hypoplasia, optic atrophy, and mental retardation). When the fetus is exposed to coumarins, the results may include cataracts, microcephaly, and microphthalmia, as well as fetal and maternal hemorrhage.

*Hypoglycemic agents* are another drug category of interest given that women with type 2 diabetes typically use oral hypoglycemic agents when not pregnant. Untreated diabetes is associated with multiple adverse outcomes for both the pregnant woman and her fetus, most of which occur secondary to hyperglycemia. Therefore close glucose control is essential during pregnancy.<sup>77,78</sup> Traditionally women with type 2 diabetes who are pregnant are treated as though they have gestational diabetes and managed with diet, exercise, and injectable insulin. In contrast to oral hypoglycemic agents, insulin is a large molecule and has difficulty crossing the placenta. Therefore, it has been the drug of choice for management of diabetes mellitus during pregnancy.<sup>79</sup> Glyburide (Micronase, Diabeta) and metformin (Glucophage) have recently been the subject of research for treatment of diabetes during pregnancy.<sup>79,80</sup> Glyburide is extensively protein bound and does not cross the placenta in sufficient amounts to affect the fetus. Both glyburide and metformin appear to be safe and effective when used to treat diabetes in pregnancy, but neither is fully endorsed or established in clinical practice as yet.<sup>81</sup>

## Pharmaceuticals and Breastfeeding

There is no doubt that breastfeeding is the best method of feeding newborns and young infants. For many lactating women, the need to take a medication during this time presents a concern about infant exposure through their breast milk. Knowledge of how drugs transfer into breast milk and access to reliable resources specific to breastfeeding and drug compatibility will help midwives who care for women during

the postpartum period.<sup>82,83</sup> For the majority of drugs, less than 1% of the maternal plasma level of the drug crosses into the breast milk. In addition, binding to the milk proteins or onto the surface of the milk fat globule deters neonatal exposure further, as bound drugs do not passively diffuse out of the newborn's stomach.<sup>84</sup> Other factors that affect the likelihood of drug transfer into breast milk include lipid solubility, low molecular weight, long half-life, and the capacity to remain unbound and non-ionized in the maternal plasma.

The excretion of drugs into breast milk primarily involves passive diffusion through the alveolar/lactocyte cells that line the alveoli, which make up the glandular/secretory tissue within the breast. Most drugs move through these alveolar cells via passive diffusion. Active transport is used by a small number of drugs (e.g., ranitidine [Zantac], nitrofurantoin [Macrobid], acyclovir [Zovirax]). During the first few weeks postpartum, large gaps exist between alveolar cells, facilitating easy transfer of various agents including immunoglobulins. As milk production is established and the alveolar cells expand, the intracellular gaps to close, making drug transfer more difficult.<sup>83</sup> Also, because the majority of milk is produced at the time of feeding and blood flow to the breast is maximized at this time, women should be educated about the timing of peak plasma levels for specific drugs used and counseled to avoid breastfeeding during these times.

One of the most popular approaches used in clinical practice to evaluate drug concentration in breast milk is the milk plasma ratio (M/P). This ratio varies over time as both drug amount and type of milk vary over time, so most drug kinetics is based on a time-averaged ratio or range.<sup>82</sup> The M/P has been calculated for many agents. The majority of drugs have an M/P of 1 or less, indicating that the level of drug in the breast milk is the same as or less than the level in maternal plasma. For example, an M/P of 0.10 indicates that the breast milk contains 10% of the amount of the drug in maternal plasma. Although the M/P can be helpful, this ratio is not clinically relevant unless other factors are considered. For example, a high M/P may not create a problem if the drug poses no harm to the infant. Conversely, a low M/P may be problematic if drug clearance is slow in the neonate or the half-life of the drug is unusually long, exposing the baby to the pharmaceutical over a longer period of time.

In 2001, the American Academy of Pediatrics Committee on Drugs published an evidence-based

listing of drug information for breastfeeding that included approximately 400 primary research references.<sup>85</sup> This group currently uses a list of seven categories to rate the threat posed by licit and illicit drugs. Six of the categories include those drugs that (1) are contraindicated, (2) require temporary cessation, (3) are of possible concern, (4) to be used with caution, or (5) compatible with breastfeeding. The additional category includes food and environmental agents.

Fortunately, most drugs commonly used by lactating women are compatible with breastfeeding. Although more research is needed regarding many agents, drug transfer is rarely a reason to discontinue breastfeeding, and the midwife should be encouraged to seek out the most current and reliable information when counseling a woman about the safety of this practice. **Box 5-5** summarizes guidelines for breastfeeding and the use of medications.

#### Drugs That Stimulate Breast Milk Production: Galactagogues

Breast milk production is controlled by the interplay of two key hormones, oxytocin and prolactin. Nipple stimulation stimulates release of prolactin from the anterior pituitary and release of oxytocin from the posterior pituitary. However, many factors can interfere with successful breastfeeding and

#### BOX 5-5 Guidelines for Breastfeeding and Medication Use

1. Use pharmaceuticals only when necessary.
2. Use the smallest therapeutic dose for the shortest time that is effective.
3. Whenever possible, choose an agent with a short half-life, an agent with a milk plasma ratio of 1 or less, and an agent that is not delivered by sustained release.
4. Arrange the timing of drug dosing so that it is given immediately after nursing or before the infant has a long sleep period.
5. If the drug is contraindicated for infant exposure, pumping and discarding the breast milk may be necessary.
6. Remember, it is rare that a medication is a reason to discontinue breastfeeding.



nipple stimulation. When lactogenesis is not well established, drugs that can stimulate breast milk production are considered. These agents are called galactagogues.

For example, metoclopramide (Reglan) is a dopamine antagonist used for gastrointestinal indications. A side effect of the drug is galactorrhea; thus it is used on an off-label basis to help women increase their milk supply. Metoclopramide tends to have a number of side effects, including fatigue, mental exhaustion, and extrapyramidal effects that produce dystonia, so it is typically used for only a limited duration.<sup>86</sup>

Herbal galactagogues are common. For example, fenugreek (*Trigonella foenum-graecum* L.) has been used for years and is well accepted in many countries, yet data demonstrating its efficacy remain elusive. Studies are ongoing in several areas of the world regarding efficacy of various galactagogues and other herbal remedies. More information about galactagogues can be found in the *Breastfeeding and the Mother–Newborn Dyad* chapter.

## Conclusion

Pharmaceutical agents are part of modern life. Pharmacology is an essential area in women's health care, and it is one that continues to grow and challenge providers and women alike. Like any other intervention in a midwife's repertoire, drugs and herbs should be used appropriately and monitored for therapeutic as well as adverse effects. Various publications, both in print and electronic media, have emerged to help with maintaining pharmacologic information. Prominent among these innovations are applications for smart phones that can download information about all FDA-approved medications, including doses, contraindications, cautions, interactions, adverse reactions, cost, and pregnancy categorization. Of course, such resources are only useful when they are updated and consulted regularly.

A single agent is rarely a magic cure for a woman independent of the larger context of her health, social, educational, economic, and other factors. No professional should simply prescribe or recommend any pharmaceutical product without taking such considerations into account. Viewing the woman and her needs holistically is one of the skills of a great midwife. As an ancient Chinese saying states, "It is easy to get a thousand prescriptions, but hard to get one single remedy."

## References

1. Osborne K. Regulation of prescriptive authority for certified nurse-midwives and certified midwives: a national overview. *J Midwifery Women's Health*. 2011;56(6):543-557.
2. Institute of Health Care Informatics. The use of medicines in the United States: review of 2010. Available at: [http://www.imshealth.com/imshealth/Global/Content/IMS%20Institute/Documents/IHII\\_UseOfMed\\_report%20.pdf](http://www.imshealth.com/imshealth/Global/Content/IMS%20Institute/Documents/IHII_UseOfMed_report%20.pdf). Accessed September 8, 2012.
3. Dieringer NJ, Kukkamma L, Somes GW, Shorr RI. Self-reported responsiveness to direct-to-consumer advertising and medication use: results of a national survey. *BMC Health Serv Res*. 2001;11(1):232.
4. Quackenbush R, Hackley B, Dixon J. Screening for pesticide exposure: a case study. *J Midwifery Women's Health*. 2006;51(1):3-11.
5. Title 21 Food and Drug Regulations enforcement policy. Available at: <http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=7.3>. Accessed September 8, 2012.
6. Brucker MC. Modern pharmacology. In: King TL, Brucker MC, eds. *Pharmacology for Women's Health*. Sudbury, MA: Jones and Bartlett; 2011:3-23.
7. Parekh A, Fadiran EO, Uhl K, Throckmorton DC. Adverse effects in women: implications for drug development and regulatory policies. *Expert Rev Clin Pharmacol*. 2011;4(4):453-466.
8. Frederickson M. The drug development process and the pregnant woman. *J Midwifery Women's Health*. 2002;47(6):422-425.
9. Chong YY, Arulkumaran K. Misoprostol: a quarter century of use, abuse and creative misuse. *Obstet Gynecol Surv*. 2004;59(2):128-140.
10. U.S. Department of Justice, Drug and Enforcement Administration, Office of Diversion Control. Mid-level practitioners authorization by state. Available at: <http://www.deadiversion.usdoj.gov/drugreg/practioners/index.html>. Accessed January 10, 2012.
11. Tharpe N. Adverse drug reactions in women's health care. *J Midwifery Women's Health*. 2011;56(3):205-214.
12. Tache SV, Sonnichsen A, Ashcroft DM. Prevalence of adverse drug events in ambulatory care: a systematic review. *Ann Pharmacother*. 2011;45(7-8):977-989.
13. Bruggemann RJM, Alffenaar JW, Blijlevens NMA, et al. Clinical relevance of the pharmacokinetic interactions with azol antifungal drugs and other coadministered agents. *Rev Anti-infect Agents*. 2009;48:1441-1446.



14. Zhou SF. Polymorphism of human cytochrome P450 2D6 and its clinical significance. *Clin Pharmacokinetics*. 2009;48(11):689-723.
15. Zhou SF, Liu JP, Chowbay B. Polymorphism of human cytochrome P450 enzymes and its clinical import. *Drug Metabol Rev*. 2009;41(2):89-295.
16. Enright MC, Robinson DA, Randle G, et al. The evolutionary history of methicillin resistant *Staphylococcus aureus* (MRSA). *Proc Natl Acad Sci USA*. 2002;99(11):7687-7692.
17. Drawz SM, Bonomo RA. Three decades of beta-lactamase inhibitors. *Clin Microbiol Rev*. 2010;23(1):160-201.
18. King TL, Mitchell AM, Lannen BJ, Daly M. Anti-infectives. In: King TL, Brucker MC. *Pharmacology for Women's Health*. Sudbury, MA: Jones and Bartlett; 2011:284-286.
19. Hooper D. Emerging mechanisms of fluoroquinolone resistance. *Emerging Infect Dis*. 2001;7(2):337-341.
20. Roe V. Antibiotic resistance: a guide for effective prescribing in women's health. *J Midwifery Women's Health*. 2008;53:216-226.
21. Hoffman FA. Regulation of dietary supplements in the United States: understanding the Dietary Supplement Health and Education Act. *Clin Obstet Gynecol*. 2001;44(4):780-788.
22. Marty AT. The complete German Commission E Monographs. *JAMA*. 1999;281(19):1952.
23. Blumenthal M, Busse W, Goldberg A, et al., eds.; Klein S, Rister R, trans. *Complete German Commission E Monographs: Therapeutic Guide to Herbal Medicines*. Newton, MA: Integrative Medicine Communications; 1998.
24. Munir M, Enany N, Zhang JM. Nonopioid analgesics. *Med Clin North Am*. 2007;91:97-111.
25. Khan MI, Walsh D, Brito-Dellan N. Opioid and adjuvant analgesics: compared and contrasted. *Am J Hosp Palliat Care*. 2011;28(5):378-383.
26. Lowe N, King TL. Labor. In: King TL, Brucker MC, eds. *Pharmacology for Women's Health*. Sudbury, MA: Jones and Bartlett; 2011:1109.
27. van der Bijl P, van der Bijl P Jr. Efficacy, safety and potential clinical roles of the COX-2-specific inhibitors. *Int J Immunopathol Pharmacol*. 2003;16(2 suppl):17-22.
28. Wolfe MM, Lichtenstein DR, Singh G. Gastrointestinal toxicity of nonsteroidal antiinflammatory drugs. *N Engl J Med*. 1999;340:1888-1900.
29. Manns-James L. Pregnancy. In: King TL, Brucker MC, eds. *Pharmacology for Women's Health*. Sudbury, MA: Jones and Bartlett; 2011:1050.
30. Anderson D. A review of systemic opioids commonly used for labor pain relief. *J Midwifery Women's Health*. 2011;56(3):222-239.
31. Craft RM. Sex differences in opioid analgesia: "from mouse to man." *Clin J Pain*. 2003;19:175-186.
32. Sandner-Kiesling A, Eisenach JC. Estrogen reduces efficacy of mu but not kappa-opioid agonist inhibition in response to uterine cervical distention. *Anesthesiology*. 2000;96:375-380.
33. Arnold SR, Straus SE. Interventions to improve antibiotic prescribing practices in ambulatory care. *Cochrane Database System Rev*. 2005;4:CD003539. doi: 10.1002/14651858.CD003539.pub2.
34. Waller DG. Rational prescribing: the principles of drug selection and assessment of efficacy. *Clin Med*. 2005;1(5):26-28.
35. Simons FE, Simons KJ. Histamine and H(1)-antihistamines: celebrating a century of progress. *J Allergy Clin Immunol*. 2011;128(6):1139-1150.
36. Briggs GG. Drug effects on the fetus and breast-fed infant. *Clin Obstet Gynecol*. 2002;45(1):6-21.
37. Syme MR, Paxton JW, Keelan JA. Drug transfer and metabolism by the human placenta. *Clin Pharmacokin*. 2004;43(8):487-514.
38. Wen SW, Yang T, Krewski D, et al. Patterns of pregnancy exposure to prescription FDA C, D and X drugs in a Canadian population. *J Perinatol*. 2008;28:324-329.
39. Hansen WF, Yankowitz J. Pharmacologic therapy for medical disorders during pregnancy. *Clin Obstet Gynecol*. 2002;45(1):13-52.
40. Buhimschi CS, Weiner CP. Medications in pregnancy and lactation: part 1. Teratology. *Obstet Gynecol*. 2009;113(1):166-188. Review. Erratum in: *Obstet Gynecol*. 2009;113(6):1377.
41. Koren G. Fetal risks of maternal pharmacotherapy: identifying signals. *Handb Exp Pharmacol*. 2011;205:285-294.
42. Pregnancy labeling. *FDA Drug Bull*. 1979;9:23-24.
43. Law R. FDA pregnancy risk categories and the CPS: mother risk update. *Can Fam Phys*. 2010;56:239-241.
45. Hansen W, Peacock A, Yankowitz J. Treatment of illnesses in pregnancy and lactation. *J Midwifery Women's Health*. 2002;47(6):409-421.
46. Content and format of labeling for human prescription drug and biological products: requirements for pregnancy and lactation labeling. *Federal Register*. 2008;73(104):30831-30832.
47. Lee E, Maneno MK, Smith L, et al. National patterns of medication use during pregnancy. *Pharmacoepidemiol Drug Safety*. 2006;15:537-545.
48. Skerret PJ, Willett WC. Essentials of health eating: a guide. *J Midwifery Women's Health*. 2010;55(6):492-501.
49. Czeizel AE, Banhidy F. Vitamin supply in pregnancy for prevention of congenital birth defects. *Curr Opin Clin Nutrition Metabolic Care*. 2011;14:291-296.

50. Gill SK, Maltepe C, Koren G. The effectiveness of discontinuing iron-containing prenatal multivitamins on reducing the severity of nausea and vomiting of pregnancy. *J Obstet Gynaecol.* 2009;29(1):13-16.
51. Barger MA. Maternal nutrition and perinatal outcomes. *J Midwifery Women's Health.* 2010;55(6):502-511.
52. Kaludjerovic J, Veith R. Relationship between vitamin D during perinatal development and health. *J Midwifery Women's Health.* 2010;55(6):550-560
53. Jordan RG. Prenatal omega-3 fatty acids: review and recommendations. *J Midwifery Women's Health.* 2010;55(6):520-528.
54. Haider BA, Bhutta ZA. Multiple-micronutrient supplementation for women during pregnancy. *Cochrane Database System Rev.* 2006;4:CD004905. doi: 10.1002/14651858.CD004905.pub2.
55. *Standing Committee on the Scientific Evaluation of Dietary Reference Intakes, Food and Nutrition Board, Institute of Medicine. Dietary Reference Intakes: Folate, Other B Vitamins, and Choline.* Washington, DC: National Academy Press; April 17, 1998. Available at: [http://www.nap.edu/openbook.php?record\\_id=6015&page=196](http://www.nap.edu/openbook.php?record_id=6015&page=196). Accessed January 1, 2010.
56. Wolff T, Witkop CT, Miller T, Syed SB. *Folic Acid Supplementation for the Prevention of Neural Tube Defects: An Update of the Evidence for the U.S. Preventive Services Task Force.* Evidence Synthesis No. 70. AHRQ Publication No. 09-051132-EF-1. Rockville, MD: Agency for Healthcare Research and Quality; May 2009.
57. Centers for Disease Control and Prevention. Recommendations to prevent and control iron deficiency in the United States. *MMWR.* 1998;47:1-29.
58. Pena-Rosas JP, Viteri FE. Effects of routine oral iron supplementation with or without folic acid for women during pregnancy. *Cochrane Database System Rev.* 2006;3:CD004736. doi: 10.1002/14651858.CD004736.pub2.
59. Graves BW, Barger MK. A "conservative" approach to iron supplementation during pregnancy. *J Midwifery Women's Health.* 2001;46:159-166.
60. Public Health Committee of the American Thyroid Association; Becker DV, Braverman LE, Delange F, et al. Iodine supplementation for pregnancy and lactation-United States and Canada: recommendations of the American Thyroid Association. *Thyroid.* 2006;16(10):949-951.
61. Leung AM, Pearce EN, Braverman LE. Iodine nutrition in pregnancy and lactation. *Endocrin Metabol Clin.* 2011;40(4):765-777.
62. Rothman K, More L, Singer J, et al. Teratogenicity of high vitamin A intake. *N Engl J Med.* 1995;333(21):1369-1373.
63. Piper JM, Mitchel EF, Ray WA. Prenatal use of metronidazole and birth defects: no association. *Obstet Gynecol.* 1993;82(3):348-352.
64. Buhimschi CS, Weiner CP. Medications in pregnancy and lactation: part 2. Drugs with minimal or unknown human teratogenic effect. *Obstet Gynecol.* 2009;113(2 Pt 1):417-432.
65. Ozyuncu O, Beksac MH, Nemutlu E, et al. Maternal blood and amniotic fluid levels of moxifloxacin, levofloxacin, and cefixime. *J Obstet Gynecol Res.* 2010;36(3):484-487.
66. Lowe SA. Anticonvulsants and drugs for neurological disease. *Best Pract Res Clin Obstet Gynecol.* 2001;15(6):863-876.
67. Banach R, Boskovic R, Einarson T, Koren G. Long-term developmental outcome of children of women with epilepsy, unexposed or exposed prenatally to antiepileptic drugs: a meta-analysis of cohort studies. *Drug Safety.* 2010;33(1):73-79.
68. Molgaard-Nielsen D, Hviid A. Newer-generation antiepileptic drugs and the risk of major birth defects. *JAMA.* 2011;305(19):1996-2002.
69. Hernandez-Diaz S, Werler M, Walker A, Mitchell A. Folic acid antagonists during pregnancy and risk of birth defects. *N Engl J Med.* 2000;343(22):1608-1614.
70. Hackley B, Sharma C, Kedzior A, Sreenivasan S. Managing mental health conditions in primary care. *J Midwifery Women's Health.* 2010;55(1):9-19.
71. Hackley B. Antidepressant medication use in pregnancy. *J Midwifery Women's Health.* 2010;55:90-100.
72. 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. *J Obstet Gynecol.* 2009;114(3):703-713.
73. American College of Obstetricians and Gynecologists. Thyroid disease in pregnancy. ACOG Practice Bulletin. No. 37. *Obstet Gynecol.* 2002;100:387-396.
74. Negro R, Mestman JH. Thyroid disease in pregnancy. *Best Pract Res Clin Endocrinol Metabol.* 2011;25(6):927-943.
75. Seely EW, Ecker J. Chronic hypertension in pregnancy. *N Engl J Med.* 2011;365:439-446.
76. American College of Obstetricians and Gynecologists. Inherited thrombophilias in pregnancy. Practice Bulletin No. 124. *Obstet Gynecol.* 2011;118:730-740.
77. Reedy NJ. Addressing the epidemic: pharmacotherapeutic management of diabetes in women. *J Midwifery Women's Health.* 2002;47(6):471-486.
78. Langer O. Management of gestational diabetes: pharmacologic treatment options and glycemic control. *Enocrin Metabol Clin North Am.* 2006;35:53-78.

79. Refuerzo JS. Oral hypoglycemic agents in pregnancy. *Obstet Clin North Am.* 2011;38:227-234.
80. Langer O, Conway D, Berkus M, et al. A comparison of glyburide and insulin in women with gestation diabetes mellitus. *N Engl J Med.* 2000;343(16):1134-1138.
81. American College of Obstetricians and Gynecologists. Pregestational diabetes mellitus. ACOG Practice Bulletin No. 60. *Obstet Gynecol.* 2005;105:675-685.
82. Ito S. Drug therapy for breast-feeding women. *N Engl J Med.* 2000;343(2):118-121.
83. Hale TW. Breastfeeding mothers. In: King TL, Brucker MC, eds. *Pharmacology for Women's Health.* Sudbury, MA: Jones and Bartlett; 2011:1146.
84. Berlin CM, Briggs GG. Drugs and chemicals in human milk. *Semin Fetal Neonatal Med.* 2005;10:149-159.
85. American Academy of Pediatrics Committee on Drugs. The transfer of drugs and other chemicals into human milk: policy statement. *Pediatrics.* 2001;108(3):776-789.
86. Gabay MP. Galactogogues: medications that induce lactation. *J Hum Lact.* 2002;18:274-210.