

Chapter 2

Safety Rating Systems for Drugs Used in Pregnancy and Lactation

Key Chapter Points

- The most widely used systems for categorizing drug risk during pregnancy in the United States are the Food and Drug Administration (FDA) and Teratogen Information System (TERIS) pregnancy risk classifications.
- Controlled data on using medications during pregnancy and lactation are lacking, making firm recommendations more difficult.
- Only fair agreement on risk category assignment exists when comparing common pregnancy risk classification systems within and between countries.
- Pregnancy risk categories should be used as general guidelines to help choose safer medication alternatives.
- Useful print and Internet resources help guide rational medication selections during pregnancy and lactation.

Keywords FDA · Risk · Teratogen · TERIS

This first-time mom excitedly told her family doctor that she had decided to “get super healthy” during her pregnancy, exercising regularly, eating only organic foods, and avoiding most medications. “I read that the FDA says drugs are safe during pregnancy when they’re drug category A. So what can you prescribe for me that will control my migraines and be safe for the baby?”

Use of medications in pregnant and lactating women can be challenging for the clinician, who must carefully balance effectively treating migraines with limiting exposure to maternal medications by the fetus or breastfeeding infant. Making recommendations is compromised by the paucity of controlled studies directly testing drugs in pregnant and nursing women. Most available safety information is gleaned from animal studies, retrospective analyses, case reports, and epidemiological data, all of which have significant limitations.

Statistics about human pregnancy-related risks with prescription and non-prescription medications are most commonly derived from epidemiological study data obtained through cohort or case-controlled studies. Cohort studies compare adverse pregnancy outcomes between large groups of women exposed

to a potential toxin and women not exposed. Case-controlled studies evaluate maternal factors in children with and without a specific developmental abnormality. Cohort studies generally provide a more representative population sample, although large sample sizes are usually needed to identify an increased frequency of negative pregnancy outcomes. Post-marketing data obtained through pregnancy registries can also provide valuable information about pregnancy-related drug effects, although participation in these registries is voluntary, thus limiting data interpretation. Data are currently available for several migraine therapies using large, European epidemiological surveys and pharmaceutical company-sponsored exposure registries.

Despite the lack of ideal drug toxicology data during pregnancy and lactation, careful interpretation of available animal and human studies has resulted in the development of several widely accepted risk rating systems designed to facilitate safe drug recommendations during pregnancy and while nursing. This chapter will provide information on drug risk determination during pregnancy and nursing, explain commonly used risk classification systems and their shortcomings, and provide resources to assist the clinician when making important decisions about medication selection.

Pearl for the practitioner:

While controlled trials directly testing medications during pregnancy and lactation are lacking, useful resources and rating systems are available to help guide the clinician to make prudent choices when selecting medications.

Pregnancy

Medication Use During Pregnancy

Although women usually tell their doctors that they want to avoid medication during pregnancy, the vast majority of pregnant women consume both prescription and non-prescription medications. In one survey, 578 obstetric patients were interviewed about their medication use [1]. Prescription medications (excluding vitamin, mineral, and iron supplements) were used by 60% of women, over-the-counter medications by 93%, and herbal remedies by 45% (Fig. 2.1). The four most commonly prescribed categories of medications were: antibiotics (used by 35% of patients), respiratory drugs (15%), gastrointestinal products (13%), and opioids (8%). The most commonly used over-the-counter drugs were analgesics: acetaminophen (76%), ibuprofen (15%), and aspirin (2%). Herbal remedies were usually peppermint for nausea (18%) and cranberry for urinary tract symptoms (13%). Clinicians may be unaware that their patients are using over-the-counter therapies or prescriptions from

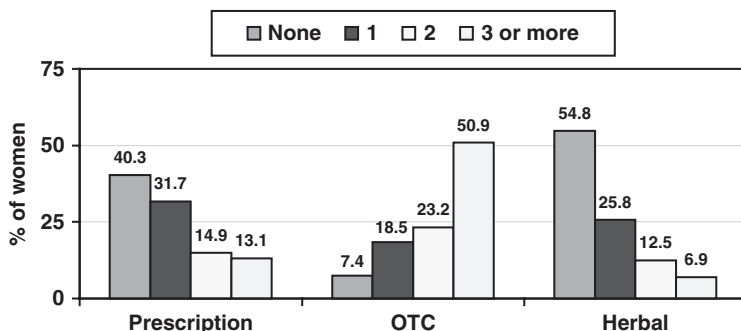


Fig. 2.1 Number of drugs used by pregnant women (Based on [1])
 Prescription medications category excludes vitamin, folate, and iron supplementation.
 OTC = over-the-counter medications.

other providers; consequently, healthcare providers must directly and explicitly ask patients about all prescription and non-prescription medications they are using.

Pearl for the practitioner:

Prescription medications (excluding vitamin, mineral, and iron supplements) are used by nearly two in every three women during pregnancy. Herbal remedies are used by nearly half, and almost all women will use over-the-counter medications when pregnant. Clinicians must directly ask patients about the use of both prescription and non-prescription treatments.

Epidemiological studies further disclose that a substantial minority of pregnant women use potentially harmful medications. Prescription records were reviewed for over 200,000 women in the Netherlands from 1995 to 2001 [2]. Among the 7,500 pregnant women included in this analysis, prescription medications were used by 86% of women when considering all prescriptions and 69% if vitamins, folate, and iron were excluded. Although most medications prescribed to pregnant women were considered safe, 21% of pregnant women were prescribed potentially harmful medications and 9% received prescriptions for drugs of unknown risk. As expected, prescription patterns differed between pregnant and non-pregnant women, favoring drugs with known better safety during gestation among pregnant women (Fig. 2.2). Interestingly however, one in five medications prescribed to pregnant women was considered to be potentially harmful or to have unknown risk. A similar cohort study of prescription medication use in 43,470 pregnant Finnish women revealed that one in five

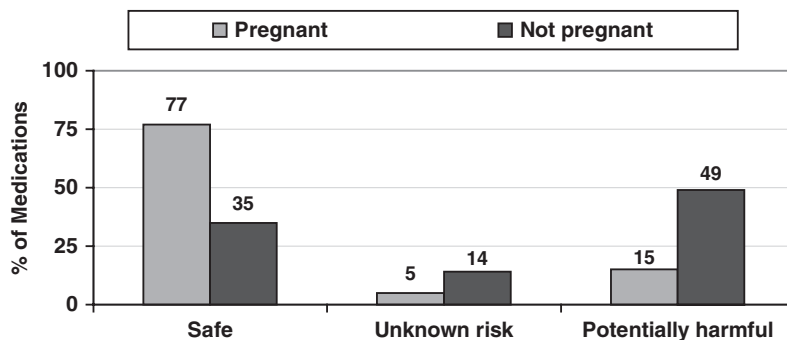


Fig. 2.2 Comparison of prescription risk between pregnant and non-pregnant women (Based on [2])

Pregnancy risk categories were compared for drugs prescribed to pregnant and non-pregnant women. Vitamins, folate, and iron were excluded from this analysis.

similarly purchased at least one drug classified as potentially harmful during pregnancy and 3% purchased at least one drug classified as clearly harmful [3].

Pearl for the practitioner:

In one large survey, one in five pregnant women was prescribed a potentially harmful medication.

Birth defects affect about 4% of deliveries in the United States, with <1% generally considered to be attributable to maternal drug exposure. Women are often very concerned about medication effects on the developing baby, although the risk, as noted above, is quite low. Clinicians must be able to provide patients with credible information about safe migraine treatment, as unfounded patient fears may result in substantial maternal stress and anxiety and even consideration of pregnancy termination. A negative impact on pregnancy by maternal stress has been supported by studies showing that women exposed to high stress during pregnancy have a higher risk of delivering offspring with low birth weight when babies are born prematurely and a higher incidence of cranial-neural crest malformations (especially cleft lip/palate and conotruncal heart defects [e.g., double-outlet ventricle, tetralogy of Fallot, and ventricular septal defects]) [4,5]. Providing accurate information about safe treatment options can alleviate a considerable amount of the pregnant patient's fear and concern. Since migraine predominates during childbearing years, discussions about the treatment of headaches during pregnancy should ideally occur before conception. Effective planning for treatment during pregnancy helps maximize use of safer therapies and minimize maternal anxiety, excessive

headache-related disability, dehydration, and analgesic overuse when standard therapies are excessively restricted.

Pearl for the practitioner:

Less than 1% of birth defects are attributed to maternal drug exposure. Preconception discussion about real risks and safer treatments reduces patient fears and maximizes focus on the safest therapies.

Understanding Reproductive Risk

Drugs that may result in the development of congenital malformations or other negative fetal outcomes are called teratogens. Negative outcomes may include:

- Altered growth or development;
- Structural malformations;
- Physiological malformations;
- Mortality.

Although teratogen exposure increases the risk of negative fetal outcomes, it does not guarantee the occurrence of any fetal effects. The probability that exposure to a teratogen will result in a negative outcome depends on several factors:

- Drug dosage and duration of exposure;
- Gestational age during exposure;
- Individual susceptibility to exposure;
- Cumulative teratogenic exposures.

Risk of a negative outcome is greater with higher drug dosages and longer duration of exposure, especially when additional use of other teratogenic agents has occurred or the mother or baby are genetically more susceptible to development of a specific malformation or other negative outcome.

Tools for Assessing Reproductive Risk

The most widely used tool for evaluating drug safety during pregnancy in the United States is the Food and Drug Administration (FDA) safety rating system. The FDA system rates medication risk using categories A, B, C, D, and X, based on the available data in human and animal studies (Table 2.1). A survey of FDA pregnancy risk category assignment of drugs in the 2001 and 2002 Physicians' Desk References revealed that >60% of drugs assigned a pregnancy risk category are risk category C (Table 2.2) [6]. While clinicians generally agree that drugs in categories A and B are relatively safe and those in categories D and X should be limited, the majority of medications are classified as the more nebulous category C, reflecting the lack of available risk data for

Table 2.1 FDA risk classification system**Category A: safety established**

Controlled studies in women fail to demonstrate a risk to the fetus in the first trimester, there is no evidence of a risk in later trimesters, **AND** the possibility of fetal harm appears remote.

Category B: safety likely

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.

Category C: teratogenicity possible

Either studies in animals have revealed adverse effects on the fetus (teratogenic, embryocidal, or other) and there are no controlled studies in women **OR** studies in women and animals are not available. These drugs should be given only if the potential benefit justifies the potential risk to the fetus.

Category D: teratogenicity probable

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).

Category X: teratogenicity likely – contraindicated in pregnancy

Studies in animals and humans have demonstrated fetal abnormalities **AND/OR** there is evidence of fetal risk based on human experience **AND** the risk of the use of the drug in pregnant women clearly outweighs any possible benefit. These drugs are contraindicated in women who are or may become pregnant.

Table 2.2 FDA pregnancy risk categories of drugs in the United States, N (%) (Based on [6])

FDA risk category	2001 PDR N = 2,249 drugs	2002 PDR N = 2,150 drugs
A	5 (0.2)	7 (0.3)
B	291 (12.9)	296 (13.8)
C	821 (36.5)	802 (37.3)
D	99 (4.4)	81 (3.8)
X	117 (5.2)	124 (5.8)
None listed	916 (40.7)	840 (39.1)

most medications. While FDA pregnancy-risk categories have been a standard for many years, the FDA is currently proposing to eliminate this rating system in favor of providing more detailed sections on pregnancy safety for each drug. Descriptive passages might include more extensive information about what data are available for each drug, detailing whether data are from animal or human studies and contrasting pros and cons of drug exposure. Drug labels will also include a discussion of background risk of specific birth defects to help put warnings into context.

Another source of information is the Teratogen Information System (TERIS), which catalogs risk of teratogenic effects for the offspring of exposed women as none, minimal, small, moderate, or high. When no or limited human data are available, a drug is classified as having an undetermined risk in the TERIS system. An unlikely rating is given when risk is considered to probably be very low, but supportive data are limited.

A comparison of FDA and TERIS risk classifications is shown in Table 2.3. Researchers in the Department of Medical Genetics at the University of British Columbia evaluated drugs approved by the FDA from 1980 to 2000, excluding radioactive agents and drugs subsequently withdrawn from the market [7]. Of the 468 drugs evaluated, a comparison of assigned TERIS ratings to FDA risk category showed a poor correlation. For example, of the 30 drugs identified as having a TERIS risk of none, minimal, or unlikely, 10 received a comparable FDA classification of A or B, while 17 were classified as C and 3 as D or X. This study further highlighted the long period of time that a drug needs to be available on the market before adequate safety data permit determination of risk category. At the time of the study in 2002, 91% of the assessed drugs were still considered to have undetermined pregnancy risk. Two percent of drugs were assigned a TERIS risk designation of small, moderate, or high, with an average time required to identify this risk of 6 years and a range of 3–12 years. Six percent of drugs were assigned a none, minimal, or unlikely TERIS rating, which was determined after an average of 9 years on the market (range of 2–19 years).

Unfortunately, clinicians utilizing several different risk classification systems will soon discover that drugs are not necessarily categorized in comparable risk categories among different systems. For example, pregnancy risk category assignment was compared for drugs common to three different classification systems: the United States FDA, the Australian Drug Evaluation Committee (ADEC), and the Swedish Catalogue of Approved Drugs (FASS) [8]. Only one in four of the drugs common to all three systems received the same risk factor category (Table 2.4). Differences were attributed to disparity in definitions among the three systems, as well as dissimilarities in the way accessible literature was used to determine risk category.

Pearl for the practitioner:

Individual risk classification systems often categorize the safety of drugs differently. Selecting drugs with better safety ratings in several systems can maximize the safety of recommendations.

Table 2.3 Comparison of FDA and TERIS classifications

FDA	TERIS
A, B	None, minimal, or unlikely
C	Undetermined risk
D, X	Small, moderate, or high risk

Table 2.4 Pregnancy risk category assignment for 236 drugs common to three international systems, N (%) (Based on [8])

Risk category	FDA	ADEC	FASS
A	6 (2.5)	50 (21.2)	59 (25.0)
B	62 (26.3)	71 (30.1)	65 (27.2)
C	115 (48.7)	84 (35.6)	85 (36.0)
D	45 (19.1)	29 (12.3)	27 (11.4)
X	8 (3.4)	2 (0.8)	Not used

So what is a clinician to do? While these rating systems certainly have shortcomings, the data provided can be used as guides to recommend safer versus less safe alternatives.

Many excellent resources are available that summarize the safety ratings of various drugs to allow the clinician to make more informed recommendations. Patients need to be educated about safety classification options to help determine which specific therapies they will be able to use comfortably. FDA risk categories for specific acute and preventive migraine therapies will be described in detail in Chapters 4 and 6.

Pearl for the practitioner:

Several safety rating systems are available, but they don't always agree on individual drug safety classifications. Clinicians need to consider inconsistency in rating systems when synthesizing available information to develop relatively safe treatment option recommendations.

Lactation

The American Academy of Pediatrics recommends breastfeeding exclusively during the first 6 months of a baby's life, with additional nursing recommended for at least the baby's first year of life. Breastfeeding has numerous health benefits for the baby (Fig. 2.3):

- Optimizes nutrition;
- Limits exposure to foreign proteins;
- Provides necessary hormones, growth factors, and immune complexes;
- Provides important fatty acids to facilitate good brain development;
- Reduces infant infections and mortality;
- Promotes maternal-baby bonding.

Breastfeeding also benefits the nursing mother [9–11]:

- Assists with return to normal weight;
- Reduces risk for breast cancer;
- Reduces risk for ovarian cancer;

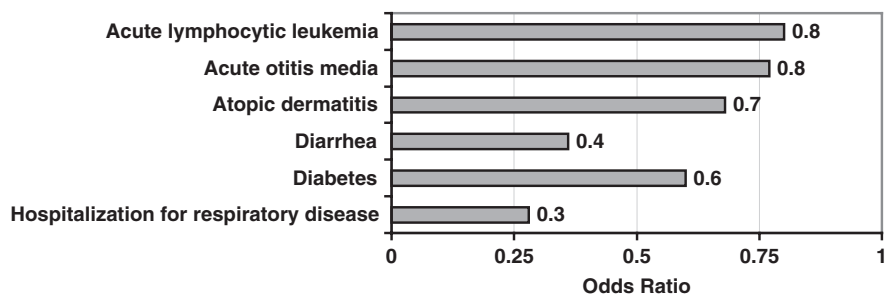


Fig. 2.3 Benefits to developing baby from breastfeeding (Based on [9])

Odds ratios are shown for risk of conditions in term babies who were breast fed compared with those who were bottle fed. Odds ratio for each condition among bottle fed infants was set at 1.0. Data are based on a comprehensive literature review and meta-analyses.

- Reduces risk for rheumatoid arthritis;
- Is cost-effective method of supplying baby's nutrition;
- Improves maternal-baby bonding;
- Delays migraine recurrence during the first postpartum month.

While migraine often disappears or significantly decreases in the second and third trimesters in most pregnant migraineurs, the majority of women will unfortunately experience an unwelcome recurrence of their headaches during the postpartum period. Fortunately, as described in Chapter 1, breastfeeding offers a protective effect against migraine recurrence [11]. Some migraine sufferers may fear unnecessarily that they must either expose their baby to harmful medications to achieve headache control or suffer from untreated, disabling headaches that will negatively impact their ability to care for their new baby. Migraine sufferers may opt to forego breastfeeding due to the fear that nursing will excessively limit their access to effective migraine therapy. Due to the numerous and substantial health benefits for both mother and baby from breastfeeding and the availability of relatively safe therapies, clinicians should encourage women to breastfeed and reassure mothers about the availability of safer, effective treatment options when nursing.

Pearl for the practitioner:

Breastfeeding provides important physical and emotional health benefits for both baby and mother. Safer and effective headache treatment options are available for breastfeeding mothers.

Trends in Breastfeeding

National surveys show that 50–90% of women in industrialized countries and >90% in developing countries begin infant nutrition with breastfeeding [12].

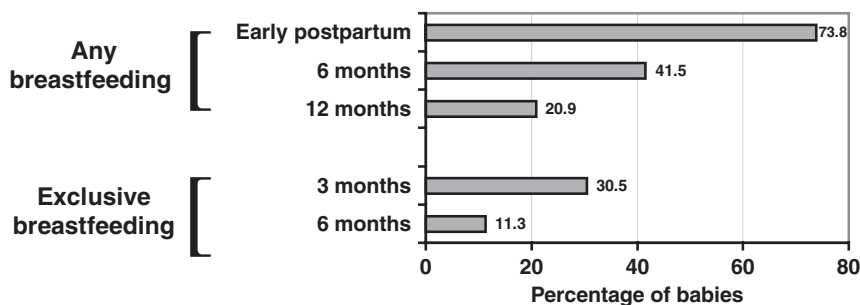


Fig. 2.4 Prevalence of breastfeeding in the United States (Based on [13])

Data are based on a survey of babies born during 2004. Early postpartum refers to the days immediately following delivery and before hospital discharge.

Only about one in three babies worldwide are still breast fed when they are 4 months old. In the United States, most mothers nurse during the first few days of a baby's life, with 2 of every 5 mothers still breastfeeding when the baby is 6 months old and 1 of every 5 mothers breastfeeding when the baby turns 1 year old (Fig. 2.4) [13]. Only one in three mothers exclusively breastfeeds for 3 months. While there may be many reasons women choose not to breastfeed or to discontinue nursing early, safety concerns about headache medications and breastfeeding should be carefully reviewed to ensure the decision to nurse or not is based on sound information.

Pearl for the practitioner:

Although over half of women breastfeed after delivery, only one in three babies worldwide are still breastfed when they are 4 months old. The decision to not begin or stop breastfeeding early should not be based on the fear that postpartum headaches will go untreated. There are safer, effective treatment options available for women with headaches who choose to breastfeed their infants.

Maternal Drug Effects on the Baby

A variety of factors influence the likelihood that a maternal drug will affect the breastfed baby:

- Timing of drug administration;
- Time to peak drug concentration;
- Drug half-life in both the mother and the baby;
- Drug bioavailability (the amount of medication that enters the blood);
- Factors that influence how much drug appears in breast milk (e.g., molecular weight, as very large drugs are less likely to enter the breast milk).

Formulae exist that can estimate the baby's exposure to drugs in the breast milk [14]. These formulae must consider a wide range of variables:

- Characteristics of the ingested drug, including medication pH and presence of active metabolites;
- Route of administration in the mother;
- Variability in maternal milk composition between and during feedings;
- Variability in infant milk consumption and clearance;
- Age of the baby.

Formula calculations, however, are limited in accurately estimating drug exposure. For example, the initial 10 mL of expressed milk during a feeding has about half of the fat content that will be seen with milk consumed later in the feeding [14]. Consequently, a lower concentration of fat-soluble drugs will be present in the first milk of each feeding. In addition, glomerular filtration and drug metabolism are less robust in younger babies, resulting in lower drug clearance in babies until they are 6–12 months old.

Because of the wide range of patient and pharmacokinetic variables required to accurately measure a baby's true exposure, it is not feasible to calculate risk in most clinical settings individually. In general, risk can be minimized by:

- Selecting drugs with poor transfer into breast milk (e.g., large molecular weight compounds);
- Selecting drugs that are safe in babies;
- Timing maternal drug dosing to minimize exposure in the baby.

Most drugs enter the breast milk through passive diffusion, with transfer highest for fat-soluble drugs. Because milk is slightly more acidic than plasma, basic drugs are more likely to transfer into the breast milk. The milk-to-plasma ratio is a ratio of the level of drug in milk divided by the level of drug in maternal plasma. For example, some migraine medications, such as non-steroidal anti-inflammatory drugs and sumatriptan have a low milk-to-plasma ratio, resulting in minimal effects on the nursing baby. Similarly, the milk-to-plasma ratio is high with topiramate (1.2), while acceptably low with valproic acid (0.42) [15]. The milk-to-plasma ratio is limited, however, by not providing an indication of the absolute drug dose provided by breast milk.

Another method for quantifying the infant exposure through breast milk is the relative infant dose, which is calculated as a percentage of the infant dose to maternal dose [16]. The relative infant dose is calculated by dividing the dose of the drug in milk (mg/kg/day) by the dose administered to the mother each day (mg/kg/day). In term infants, a relative infant dose <10% is generally considered to be safe with short-term use. A lower percentage is preferred for premature babies. A listing of relative infant doses for some medications used in headache treatment is provided in Box 2.1. Consistent with the low milk-to-plasma ratio with non-steroidal anti-inflammatory drugs, naproxen similarly has a low relative infant dose [17]. Among anti-epileptics, topiramate has free passage of drug into breast milk, with high drug

Box 2.1 Relative infant dose (generally <10% is recommended as relatively safe) (Based on [17–20])

- Codeine – 7%
- Gabapentin – 1–4%
- Ibuprofen – 0.6%
- Naproxen – 2–3%
- Propranolol – 0.2%
- Sumatriptan – 3–7%
- Valproic acid – 2%
- Topiramate – up to 23%

concentrations [18], while relative infant doses are acceptably low with valproic acid (2%) and gabapentin (1–4%) [19,20]. Selecting drugs with lower relative infant doses may also help maximize safety. Recently published data show a lower relative infant dose with sertraline (0.3–0.5%) [21] compared with venlafaxine (6.4%) [19], supporting a preference for sertraline in patients requiring newer antidepressants [22]. Both print and online resources, described below, can help provide extensive information about milk-to-plasma ratios and relative infant doses for a wide variety of medications.

Pearl for the practitioner:

Safety of exposure to maternal medications used when nursing can be minimized by selecting drugs with limited concentration in breast milk, drugs that are themselves safe to use in babies, and timing maternal exposure to reduce concentration in milk used for feedings.

Drugs that might affect the baby may still be used by the nursing mother if she and her doctor can identify how long a harmful concentration will be present in her milk following drug ingestion. In general, it is recommended that milk be pumped and dumped for approximately 4 half-lives of the ingested drug to reduce the concentration to safer levels for the baby [23]. For example, if the half-life of a drug is 2 hours, then the mother should pump and discard her milk for 8 hours after medication ingestion. The mother can then supplement the baby with bottle feeding with either stored breast milk or formula during that time. Holding a maternal medication until immediately after nursing may also limit effects on the baby, especially with short-acting acute migraine medications. Furthermore, when baby is sleeping through the night, mother might take her once daily medication immediately after his last feeding before bedtime and possibly dump her first supply of breast milk in the morning.

Published guidance during breastfeeding is available from the American Academy of Pediatrics (AAP), noting drugs that are compatible with breastfeeding and providing citations for reported possible symptoms of concern that require greater caution with use [24]. A brief summary of these guidelines is also available [25]. Several books are regularly updated detailing the latest information on drug safety during nursing, including *Medications and mothers' milk: a manual of lactational pharmacology (medications and mother's milk)* by Thomas W. Hale; and *Drugs in pregnancy and lactation: a reference guide to fetal and neonatal risk (8th edition)* by Gerald G. Briggs, Roger K. Freeman, and Sumner J. Yaffe. Specific recommendations for the use of acute and preventive migraine medications while nursing are provided in Chapters 5 and 7.

Helpful Online and Print Resources

A variety of Internet resources exist that offer information about possible effects of maternal drug exposures, including over-the-counter and prescription medications, herbal products, and illicit drugs (Table 2.5). Reliable books may also be used to help assess the safety of maternal drug use during pregnancy and lactation (Box 2.2). In general, both online and print media utilize widely accepted safety rating systems, such as the FDA, TERIS, and AAP classification systems, supplemented by additional reviews of available literature and results of clinical practice experiences.

Box 2.2 Print resources

- *Drugs during pregnancy and lactation*, by Christ of Schaefer, Paul W. Peters, and Richard K Miller, published by Academic Press, 2007
- *Medications and mothers' milk: a manual of lactational pharmacology (medications and mother's milk)*, by Thomas W. Hale, published by Pharmasoft Medical Publishing, 2008
- *Drugs in pregnancy and lactation: a reference guide to fetal and neonatal risk (8th edition)*, by Gerald G. Briggs, Roger K Freeman, and Sumner J Yaffe, published by Lippincott Williams & Wilkins, 2008
- *Medication safety in pregnancy and breastfeeding*, by Gideon Koren, published by McGraw-Hill, 2007
- *Textbook of human lactation*, by Thomas W. Hale and Peter E. Hartmann, published by Hale Hartmann's, 2007.

Table 2.5 Internet resources for medication use during pregnancy and lactation

Website	Site Sponsor	Information Available
<i>Pregnancy information</i>		
http://otispregnancy.org/	Organization of Teratology Information Services	Free fact sheets available for a range of treatments. Available migraine drugs include: acetaminophen, antidepressants, caffeine, & St. John's wort
http://www.reprotox.org/	Reproductive Toxicology Center	Membership provides access to information for a wide range of therapies, with detailed references provided for each compound.
http://depts.washington.edu/terisweb/teris/	Teratogen Information System (TERIS)	Subscription provides TERIS summaries of drugs, including quantification of both level of risk and quality of data analyzed. Online version of <i>Shepard's Catalog of Teratogenic Agents</i> is also available.
http://www.safefetus.com/	King's College London	Provides FDA recommendations for the use of medications during pregnancy and breastfeeding (when available).
http://www.motherisk.com	The Hospital for Sick Children of the University of Toronto	Evidence-based information on drug safety during pregnancy and breastfeeding

Table 2.5 (continued)

Website	Site Sponsor	Information Available
<i>Lactation information</i>		
http://www.babycenter.com/0_drug-safety-during-breastfeeding_8790.bc?Ad=com.bc.common.AdInfo_401a60ca44	Recommendations developed by pharmacist and director of Drug Information Service at University of California, San Diego	Wide assortment of commonly used prescription and non-prescription medications divided into 4 categories: safe, probably safe, potentially hazardous, and not safe
http://neonatal.ttuhschool.edu/lact/	Thomas W. Hale, RPh, PhD, Professor of Pediatrics at Texas Tech University	In addition to a huge listing of therapies for which safety information is provided, healthcare providers can post questions directly to Dr. Hale.
http://www.breastfeedingbasics.com/html/drugs_and_bf.shtml	Anne Smith, BA, an international board-certified lactation consultant	Comprehensive overview of drug use with breastfeeding with information appropriate for both clinician and patient
http://www.motherisk.com	The Hospital for Sick Children of the University of Toronto	Evidence-based information on drug safety during pregnancy and breastfeeding

Summary

Information on the safety of medications during pregnancy and lactation is generally derived from cohort and case-controlled studies. Despite limitations in available safety data, widely accepted drug safety rating systems, like the FDA risk classification and TERIS systems, provide a synthesis of available data to help develop rational therapeutic recommendations. Fortunately, medication-related birth defects are very rare and selecting drugs generally considered to be safe or relatively safe can minimize risks. The baby's safety from exposure to medications used by the nursing mother can be estimated by understanding the characteristics of the drug and the timing of exposure. Using information from available rating systems and other resources allows the clinician to offer knowledgeable recommendations for safer treatments during pregnancy and lactation.

Practical pointers:

- Although women often state a desire to avoid medications during pregnancy, almost all women will use over-the-counter drugs. Nearly 2/3 will use prescriptions and almost half will take herbal remedies.
- Medication-related birth defects occur rarely.
- Several, well-accepted systems are available to categorize drug safety, although disagreement on individual drug safety ratings often occurs when comparing ratings for the same drug in various systems.
- Many factors affect the safety for the baby from medication ingested by the breastfeeding mother. Published guidelines account for these factors when making recommendations.

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