Continuing Education

Evaluating Medication Use in Pregnancy and Lactation: What Every Pharmacist Should Know

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As a pharmacist, being asked to give advice about medication use during pregnancy or lactation can be daunting. This article reviews the principles of drug transfer across the placenta, into breast milk, and reviews the rating scales and different resources available. The Food and Drug Administration classification scale is reviewed and the upcoming changes are explained, along with recent labeling changes for specific medications or drug classes when appropriate. This article provides the pharmacist with a practical set of tools to review the information available and assess the risks of treating or withholding a medication for mother and infant.

INDEX TERMS adverse drug effect, lactation, medication use, pregnancy, teratogen, teratogenicity

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INTRODUCTION

Most pharmacists will encounter questions regarding the safety of medication use during pregnancy and breastfeeding either from patients, family, or friends. Many may feel that they lack the knowledge to answer these questions confidently. Certainly this topic is rarely addressed in detail as part of pharmacy school curriculum or continuing education programs. This article seeks to provide readers with a foundation for making sound judgments regarding the use of medications during pregnancy and lactation.

PREGNANCY AND MEDICATION RISKS

Thalidomide was used in the late 1950s as a sedative and as an agent to combat "morning sickness." Although it did not cause teratogenic effects in rats or mice, it has developed a reputation as one of the most potent human teratogens known. The thalidomide tragedy highlighted the fact that interspecies variability cannot accurately predict possible risks of medication exposure at different stages of fetal development. Today, we recognize that many medications cross the placenta to enter fetal circulation, and that the timing of that exposure plays a critical role in causing harm.

The damage caused by medications can be classified into 2 broad categories: those that are teratogens and those that cause adverse fetal affects. Teratogens cause alteration of tissue development or organ formation and occur early in pregnancy.[1] The teratogenic period is generally defined as day 31 (from the start of the last menstrual cycle) to 71 assuming a 28-day cycle or approximately 2 to 8 weeks post conception.[1] Therefore, one of the first things a health professional should ascertain when considering medication use in an individual is the stage of their pregnancy. The most common teratogenic effects are neural tube defects, congenital heart abnormalities, cleft lip or palate, and fetal stillbirth.

Conversely, adverse fetal effects result in dysfunction of an organ or tissue after that organ or tissue has been formed.[1] Some examples include difficult postnatal adaptation, withdrawal, electrolyte abnormalities, and altered glucose metabolism. Medications that may cause adverse fetal effects include some antipsychotic, antidepressant, and opioid medications. It is important to note that some maternal diseases predispose an infant to have these same problems, making it difficult to accurately identify the origin of any teratogenicity or adverse fetal effects.

Relatively few medications are known terato-

Table 1. Drugs Identified With Known Risk of Teratogenicity

Human teratogen	Identifiable or Related Outcome
Alcohol	Fetal alcohol syndrome: IUGR and FTT; decreased muscle tone and poor coordination; developmental delay; and craniofacial abnormalities
Angiotensin converting enzyme inhibitors	Oligohydramnios; hypocalvaria; IUGR; renal effects (renal tubular dysplasia, anuria/oliguria, and hyperkalemia, end-stage renal failure); neonatal hypotension; cardiovascular abnormalities (e.g. patent ductus arteriosus, aortic arch obstructive); fetal death
Carbamazepine	10 × increased risk of neural tube defects; fetal anticonvulsant syndrome (IUGR, developmental delay, craniofacial defects, fingernail hypoplasia)
Cocaine	Placental abruption, fetal loss, low birth weight, microcephaly, limb and urinary tract malformations, poor neurodevelopmental performance
Coumarin anticoagulants	Fetal warfarin syndrome (nasal hypoplasia, eye abnormalities [i.e. optic atrophy, microphthalmia, and blindness]); epiphyseal stippling, hypoplasia of the extremities and fingernails; low birth weight; developmental retardation; fetal hemorrhage
Diethylstilbestrol (DES)	Clear cell adenocarcinoma and benign adenosis in exposed offspring
Methotrexate (Folic acid antagonists)	Central nervous system (i.e. anencephaly, neural tube defects); cardiovascular (tetralogy of Fallot); craniofacial (i.e. absence of lambdoid, coronal sutures, and frontal bone, low set ears, depressed/wide nasal bridge); long webbed fingers and absence of digits; growth and mental retardation
Phenytoin	Fetal anticonvulsant syndrome: IUGR; dysmorphic craniofacial features (i.e. microcephaly, low nasal bridge, cleft lip and cleft palate, maxillary hypoplasia); limb defects (i.e. hypoplastic nails and distal phalanges); cardiac defects
Isotretinoin	Spontaneous abortion; craniofacial abnormalities (i.e. microcephalus, hydrocephalus, deformity of ears, face, limbs); thymic hypoplasia; cardiac defects
Lithium	Tricuspid valve malformation (Ebstein's anomaly)
Misoprostol	Association with limb and neural tube defects
Tetracyclines	Weakened fetal bones, tooth enamel dysplasia, permanent tooth discoloration
Thalidomide	Limb, ear, cardiovascular and gastrointestinal anomalies
Valproate	Neural tube defects; fetal valproate syndrome: dysmorphic facial anomalies including microcephaly, hypertelorism, prominent forehead, low flat nasal bridge, low-set or odd-shaped ears

FTT, failure to thrive; IUGR, intrauterine growth retardation

gens (Tables 1 and 2). It is estimated that only 2% to 3% of birth defects are related to medications, leaving 97% to 98% to other causes. Although the number of mediations associated with teratogenicity is small, it is important because many of the underlying causes of congenital anomalies cannot be affected or changed, whereas drug exposure can be controlled.

It is often difficult to link a medication to a congenital anomaly because the incidence of that anomaly occurs infrequently. Further, randomized, controlled trials in pregnant individuals are ethically, monetarily, and legally daunting. The majority of the information available is in the form of case reports, case series, drug registry data, and/or retrospective cohort trials. It is that data, clinical reasoning, historic use, and risk/benefit data that lead to the different ratings and assessment of safety for medications used during pregnancy.

THE CURRENT CLASSIFICATION SYSTEM

The current US Food and Drug Administration (FDA) drug classification system was established in 1979 and places drugs into 5 categories: A, B, C, D, and X (Table 3). Unfortunately, these drug classifications can be confusing and misleading.

Table 2. Drugs Identified With Possible Teratogenic Risk

Medication	Possible Risk
D-penicillamine	Administration of large doses has been associated with connective tissue disorders of the skin, bone, and aorta
Methimazole	Scalp defects (aplasia cutis congenital)
Diazepam	Cleft lip and palate

Table 3. Current FDA Pregnancy Risk Categories*

Category	Definition
A	AWC studies in pregnant women have failed to demonstrate a risk to the fetus in the first trimester of pregnancy (and there is no evidence of a risk in later trimesters).
B	Animal reproduction studies have failed to demonstrate a risk to the fetus, and there are no AWC studies in humans, AND the benefits from the use of the drug in pregnant women may be acceptable despite its potential risks. OR animal studies have not been conducted, and there are no AWC studies in humans.
C	Animal reproduction studies have shown an adverse effect on the fetus, there are no AWC studies in humans, AND the benefits from the use of the drug in pregnant women may be acceptable despite its potential risks. OR animal studies have not been conducted, and there are no AWC in humans.
D	There is positive evidence of human fetal risk based on adverse reaction data from investigational or marketing experience or studies in humans, BUT the potential benefits from the use of the drug in pregnant women may be acceptable despite its potential risks (for example, if the drug is needed in a life-threatening situation or serious disease for which safer drugs cannot be used or are ineffective).
X	Studies in animals or humans have demonstrated fetal abnormalities OR there is positive evidence of fetal risk based on adverse reaction reports from investigational or marketing experience, or both, AND the risk of the use of the drug in a pregnant woman clearly outweighs any possible benefit (for example, safer drugs or other forms of therapy are available).

AWC, adequate and well-controlled
**Adapted from fda.gov/drugs/drugsafety*

The original intent was to describe the risk of teratogenicity after first trimester exposure and not all adverse fetal effects. However, health care providers often assume that something classified as a category B is safer than a category C, which may not be true. The system describes the type of available information, as well as the amount data that are available in animals and humans. Unfortunately, the classification is frequently based on few data. Another system used to describe the risk of teratogenicity associated with a medication-exposure during pregnancy is the Teratogen Information System (TERIS), which is an online database (www.http://depts.washington.edu/terisweb/teris/). This system uses general labels such as "unlikely, none or minimal risk," "small to moderate," "moderate to high risk," or "risk undetermined."

In order to assess the risk of teratogenicity, a study evaluated a total of 468 new medications that were approved by the FDA from 1980 to 2000.[2] It was found that 91.2% of medications did not have sufficient evidence available for health care professionals to determine if the risk of teratogenicity outweighed the benefit of the therapy. The authors also compared the FDA letter classification to TERIS and found very little correlation between the 2. Interestingly, the medications that were the oldest (15-20 years from approval) had the highest percentage of "undetermined risk." Further, the article noted that frequently used medications such as albuterol (category C), azithromycin (category B), loratadine (category B), and zolpidem (category C) were classified as having unknown risk (Table 4). This reinforces the fact that many medications, whether they are new or old, common or uncommon, have insufficient data available to make a fully informed decision. Finally, the article quantified the average time to identify medications that did confer some risk to the fetus. For the 11 drugs on the list, the average time was 6 years. Although some were known to have risk at the time of FDA approval, the range of discovery went up to 12 years.[2]

Table 4. Additional Medications With Risk Identified in a 20-year New Medication Review*

"New" Medication	Risk Identified	FDA Category	TERIS Category
Amiodarone	Fetal goiter	D	Small-moderate
Cyclosporine	IUGR	C	Small-moderate
Fosphenytoin	Not described	D	Small-moderate
Lamotrigine	Not described	C	Minimal-small
Nifedipine	Not described	C	None-minimal

FDA, US Food and Drug Administration; IUGR, intrauterine growth retardation; TERIS, Teratogen Information System
*Only medications not included in Tables 1 and 2 were summarized above

Medications With Updated Warnings

In early 2012, the FDA strengthened cautionary labeling for several mediations (Table 5). Topiramate (Topamax, Janssen Pharmaceuticals, Titusville, NJ) was known to be teratogenic in animals prior to approval. It was reclassified as category D after a pregnancy registry reported an oral cleft prevalence of 1.4%. The risk of this malformation is 0.07% in nonexposed infants and 0.38% to 0.55% of infants exposed to other antiepileptic medications. Opioid analgesics, including hydrocodone, oxycodone, and codeine, have been associated with a higher risk of heart defects when taken early in pregnancy. The typical and atypical antipsychotics were more clearly linked to difficult adaptation in newborn infants, including breathing difficulties, poor feeding ability, jitteriness, and irritability. Finally, the use of terbutaline, a drug primarily used to stop preterm labor, was relabeled with much stricter guidelines for use, including limits for duration of therapy (maximum of 48-72 hours.). This updated warning is primarily related to adverse cardiac events in the mother; however, this can result in poor neonatal outcomes.

WHAT'S TO COME

In May of 2008, the FDA proposed a new, comprehensive classification system to address the deficiencies and confusion that arises currently. The new labeling will do away with the typical letter classifications and require manufacturers to add more detail. It should address not only first-trimester exposure risk, but use throughout the entire pregnancy (including labor and delivery) and during lactation as well. The new labeling will contain 2 sections: pregnancy and lactation. Both parts contain 3 subsections including a risk summary, clinical considerations, and a data section. Background risk is also a new inclusion that will provide professionals and consumers information about the baseline risk of an event and compare that to the risk when a medication is taken.

The fetal risk summary will describe what is known about the effect of the drug on the fetus and whether this risk is based on data from humans, animals, or both. The risk conclusion requires use of a standardized statement. There can be more than 1 risk conclusion to highlight the different risks based on the dose, duration, or gestational age at the time of exposure. When available, the fetal risk summary would also include information about the specific abnormality (such as neural tube defects), the frequency, seriousness, and reversibility or correctability.

The clinical consideration subheading would include information about the potential effects of the medicine if used before a woman knows that she is pregnant. It also includes any available information about risk to the mother and infant if a disease is left untreated. Dosing information and anticipated complications in a pregnant patient would be discussed in this section. For those needing a more in-depth review, the data section would supply all available human and animal data. The implications of this data would be discussed here.

Background risk inclusion is important to illustrate absolute risk. The retrospective trial that led paroxetine to be reclassified from category C to D contributed more evidence associating the risk of specific congenital heart defects. The new labeling would give the background risk of a congenital cardiac anomaly in the general population and show the absolute risk in plain numbers. This trial found no greater statistically significant risk for all combined congenital anomalies in the nonexposed general population versus those exposed to any selective serotonin reuptake inhibitor; 315 cases in 10,000 versus

Table 5. Medications With New Concerns*

Medication	FDA Category	Risk Identified
Topiramate	D	Increased cleft lip and/or palate
Opioid analgesics	B/C	Heart defects, opioid withdrawal in newborn
Atypical and typical antipsychotics	C	Withdrawal syndromes, with difficult breathing and feeding, irritability
Terbutaline	C	Arrhythmias, tachycardia, hyperglycemia, myocardial ischemia, pulmonary edema in mother. Tachycardia in fetus, transient hypoglycemia in infant.

* *as* of 2012

392 in 10,000. The background risk of congenital anomaly was just over 3 per 100 births. The specific defect associated with paroxetine (right ventricular outflow defects) was statistically significant but only occurred in 3 cases in the entire cohort.[3] This can help put the risk of medication use into context when considering pharmacotherapy in a pregnant patient who has significant psychological problems.

The lactation section follows a similar format including the same 3 sections. The risk summary describes to what extent the medication crosses into breast milk, the effects of the drug on milk production, and the possible effects in the breastfed infant. The clinical implications will describe how to minimize infant exposure to the medication, appropriate monitoring in the exposed infant, and dosing adjustments if needed. The data section includes more in-depth information as available from the first 2 sections. There is also language emphasizing the benefits of breast milk in relation to the possible risk of infant exposure to the medication. The links below provide mock-ups from the FDA for both pregnancy and lactation sections:

Pregnancy: http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/DevelopmentResources/Labeling/UCM093313.pdf

Lactation: http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/DevelopmentResources/Labeling/UCM093316.pdf

As of November 2012, the rule had not yet been finalized by the FDA and there was no date available for when it may take effect; however, the FDA stated that the final rule writing and clearance phase was begun (February 2011).[4] Once approved, these labeling changes will apply immediately for all new medication labels and be phased in as old labels require updates. However, new medications often have a small amount of available data for pregnancy and lactation, so while the new labeling may apply, very little detail may be included.

THE PLACENTAL "BARRIER"?

The placenta is the lifeline of the developing fetus (Figure 1). It is a semipermeable barrier through which all nutrients and waste products must pass. Several factors affect a medication's ability to cross the placenta, although the majority of drugs are transported by passive diffusion based on the concentration gradient. Medications most likely to cross are lipophilic, un-ionized in maternal blood, have a low molecular weight (< 600 Daltons), and are not highly protein bound (Table 6). Conversely, if a medication is hydrophilic, ionized in maternal serum and highly protein bound, little to no medication will cross. If there is little to no published safety data for a medication, the pharmacist can evaluate these details of a medication to predict the possibility of fetal exposure.

Maternal and fetal factors play a role as well, including maternal blood flow to the placenta and hydrostatic pressures and osmotic pressure differences between the maternal and fetal sides of circulation. Placental properties that influence drug transfer are the exchange membrane surface area, thickness, and blood pressure in fetal capillaries.

So how should a pharmacist evaluate a medication for use during pregnancy? First, consider the stage of pregnancy. Second, review the information available regarding exposure of the fetus during that time. Do not rely on the pregnancy risk category to make your decision, but read the narration in the drug information resources. It is optimal to read multiple references to get a broader picture of all the data available. Counsel-

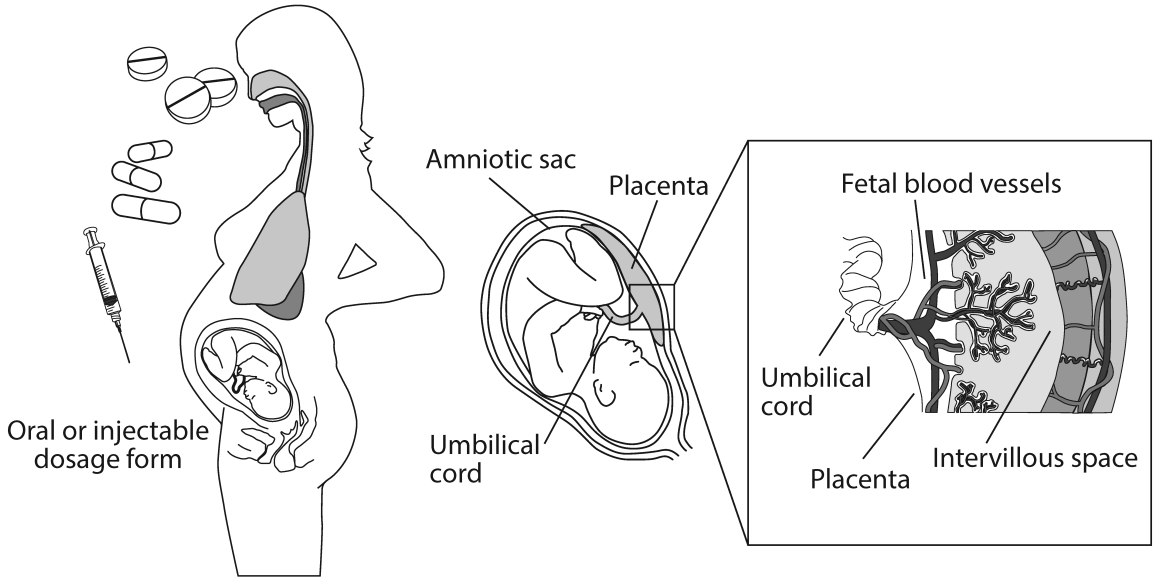

Figure 1. Medication delivery to infant during gestation.

ing a patient may be easier with the new labeling if it is for a medication for which a good amount of information is available. However, recently approved medications generally have less than ideal amounts of information; an average of 6 years was needed after FDA approval to identify drugs with risk. Finally, consider the risk to the mother and infant if the disease state is left untreated. When appropriate, consult the prescribing or obstetric physician to get background and make a final recommendation.

HUMAN MILK AND LACTATION

Milk produced by mammals to feed their young is species-specific in composition. The major proteins in human milk are whey (60%-80%) and casein (20%-40%). Human milk also contains growth factors, immune factors, cytokines, and other substances shown to be beneficial to the newborn infant that cannot be replicated in artificial feedings.

Lactation is established during the first hours to weeks following birth of the infant and follows the law of supply and demand. The more the infant eats or the mother pumps, the more milk the body will produce in response. Suckling by the infant or use of a mechanical pump stimulates the release of the hormone prolactin, which stimulates milk production and the release of a second hormone, oxytocin. Oxytocin stimulates contraction of the milk glands, also referred to as the "let-down reflex."

Breastfeeding has many proven benefits for both the mother and the infant. Mothers who breastfeed experience less postpartum bleeding and return to pre-pregnancy weight more rapidly. They also have a lower risk for postpartum depression, type 2 diabetes, and breast and ovarian cancer.[5] Infants who are breastfed have fewer infections, most notably otitis media, as well as a lower incidence of sudden infant death syndrome, necrotizing enterocolitis, childhood leukemia, diabetes, asthma, and obesity. One study published in July 2010 found that exclusive breastfeeding until the age of 4 months and partially thereafter was associated with a significant reduction in respiratory and gastrointestinal morbidity in infants.[6] The American Academy of Pediatrics recommends breastfeeding for the first year of life, including breast milk exclusively for the first 6 months.[6] As health care professionals, pharmacists can act as advocates for breastfeeding since many women stop breastfeeding unnecessarily when a medication is prescribed.

Contraindications to breastfeeding do exist; however, they are rare. In industrialized nations such as the United States, human immunodeficiency virus infection is a contraindication to breastfeeding.[5] Other absolute contraindications to breastfeeding include: illicit drug use, galactosemia in the infant, herpes simplex virus

Table 6. Properties That Influence Medications Crossing the Placenta

- pH of maternal blood influences the degree of ionization
- Placental blood flow
- Fetal to maternal concentration gradient
- Placental phase I and II drug-metabolizing enzymes (e.g. CYP1A1, 2E1, 3A4, 3A5, 3A7, and 4B1 have been detected in the term placenta)
- Molecular weight (> 600 Da have an incomplete transfer across the human placenta)
- Degree of ionization (pKa)
- Only the nonionized fraction can diffuse. Strongly dissociated acid drug molecules generally have an incomplete transfer
- Lipid solubility (lipophilic moieties readily diffuse)
- Degree of protein binding (Unbound drug diffuses. Acidosis reduced the unbound fraction)

lesion on the breast, active tuberculosis or human T-cell lymphocytic virus infection, radioactive isotopes/radioactive material exposure, and antimetabolite or other chemotherapy use. Conditions that are not prohibitive of breastfeeding include: herpes simplex virus infection that does not include a lesion on the breast, hepatitis B infection, cytomegalovirus infection, and methadone maintenance therapy (although the mother must be counseled against use of her milk if she uses any illicit substance in addition to the methadone).

Some physicians may advise against the use of mother's milk in the case of methadone maintenance therapy for opiate withdrawal due to concerns over associated illicit drug use. Methadone itself is not a contraindication and can actually be advantageous to the infant in preventing withdrawal. A retrospective chart review published in 2006 examined the effects of breast milk versus formula in infants of drug-dependent mothers.[7] The review found that infants who received breast milk experienced lower severity of neonatal abstinence syndrome, including a decreased need for pharmacologic treatment. One caveat to this approach would include counseling the mother against abrupt cessation of breastfeeding as that could potentially precipitate withdrawal in the infant.

The use of medications, either prescription or over-the-counter, is seldom a contraindication to breastfeeding. Short courses of a medication may require that a mother use a pump to collect her milk to continue to stimulate the milk production, alleviate symptoms of engorgement, and then discard it rather than feed it to the infant. The common vernacular for this process is to "pump and dump." Some pharmacists may feel that they are erring on the side of caution to advise this strategy for all short-term medication use, but that is not necessary in most cases.

DRUG TRANSFER INTO MILK

The transfer of medication into human milk shares some of the same principles as crossing the placenta, with most by passive diffusion. A medication may cross through the placenta into fetal circulation and back on the concentration gradient, just as a drug may pass into milk and diffuse back into the bloodstream as serum concentrations decrease. Certain properties of some medications may cause them to be sequestered into or actively excreted into breast milk.[8] By better understanding the pharmacokinetics and pharmacodynamics of medications during lactation, pharmacists can assist mothers in making well-informed decisions about medication use during lactation.

The most important factor in infant exposure through breast milk is the amount of medication in the mother's serum. Next, the properties that affect the transfer of medication from serum into milk should be considered. These include: bioavailability, molecular weight, protein binding, pKa, and lipid solubility.[8] Although all of these properties may not be listed in standard drug information sources, when available, they are included in lactation references. Time to maximum concentration and drug half-life may play a role in how much medication is in the milk at the time of a feeding. Milk to plasma ratio is a useful description of how much medication passes into milk and may be available as part of

Table 7. Examples for Evaluation

Example 1. Evaluating an L3 Medication	Medications classified as an L3 (Moderately Safe) may seem to be open to interpretation with regards to safety in breastfeeding. Some pharmacists may feel that the more conservative approach would be to advise against breastfeeding while using these medications. One example of using the pharmacokinetic properties of a medication to assess safety in breastfeeding for an L3 medication is enoxaparin. Some physicians and/or pharmacists may be skeptical about using a medication such as this in a breastfeeding mother. Although specific information is not documented on passage into milk, consideration should be given to the fact that enoxaparin is a large molecule that would be unlikely to pass into breast milk. Furthermore, if any enoxaparin did pass into milk, oral absorption by the infant would not be likely since enoxaparin is a protein that would be degraded in the GI tract. When taking these principles into consideration, pharmacists may be able to confidently recommend breastfeeding while using enoxaparin.
Example 2. Theoretic Infant Dose as an Evaluation Tool	In a published case report of severe apnea following exposure to lamotrigine in breast milk, the authors calculated the theoretical infant dose by multiplying the milk concentration (7.68 µg/mL) times the daily milk intake of the infant (150 mL/kg/day) to determine a value of 1.15 mg/kg/day. This theoretic infant dose can be compared to the usual maintenance pediatric dose that is 1 to 5 mg/kg/day. This tells us that exposure through breast milk can potentially provide the infant with a therapeutic amount of lamotrigine.[3]
Example 3. Drug Contraindicated in Lactation	A 28-year-old delivered a 31-week-old 1800-g infant who was admitted to the NICU. The mother was interested in breastfeeding and pharmacy was consulted for evaluation of safety of her medications in breastfeeding. Among other medications, the mother was taking nefazodone, an L4 (Possibly Hazardous) medication. Alternative medications such as sertraline and trazodone were discussed. This mother had previously failed treatment with both alternative medications, and it was determined that she should continue nefazodone for her well-being, as well as the infant's. She was advised not to breastfeed. In this instance, the mother requested that donor breast milk be used for her infant. The infant was transitioned to formula prior to discharge from the NICU.

GI, gastrointestinal; NICU, neonatal intensive care unit

the drug monograph.

Bioavailability is an important consideration in determining breastfeeding compatibility. Even medications that pass freely into breast milk may be considered compatible with breastfeeding if the medication has poor oral bioavailability (Table 7: Example 1). This results in a drug that cannot be absorbed by the gastrointestinal tract of the infant or undergoes significant first-pass effect and therefore poses little risk. Medications that are not absorbed from the gastrointestinal tract will not reach infant plasma, but can cause side effects including diarrhea or constipation and rarely pseudomembranous colitis.[8]

Similar to crossing the placenta, molecular weight and protein binding can predict a medication's likelihood to cross into breast milk. Medications with small molecular weights (< 200 Da) are more likely to pass,[8] and those that have a large molecular weight exhibit reduced entry into breast milk. Drugs that are highly protein bound pass into milk to a lesser degree (Table 7: Example 1).

The pKa of a medication does not have a direct effect on diffusion of a medication from maternal serum into breast milk. However, medications with a high pKa (i.e., > 7.2) may be sequestered in breast milk due to "ion trapping." Weakly basic drugs such as barbiturates do not diffuse back across even when maternal blood levels drop due to the ionization that occurs in the lower pKa of breast milk.[8]

In general, the properties necessary for a medication to cross into the central nervous system (CNS) also predict diffusion into breast milk. Medications that are highly lipid soluble easily pass into breast milk and cross the blood-brain barrier. If a medication is a centrally active medication, advising the mother to watch for CNS side effects in the infant is important. Two other tools are available for many medications to quantify the amount of medications an infant might be

exposed to through breast milk:

The milk:plasma (M:P) ratio is the concentration of drug in the mother's milk divided by the amount in the mother's plasma. An M:P ratio of less than 1 indicates minimal levels of a medication are transferred into milk, while a ratio in the range of 1 to 5 indicates that a medication may be sequestered in milk. Although based solely on animal data, doxazosin has a M:P ratio of 20 indicating it is concentrated in milk, which leads to the human recommendation to use extreme caution if breastfeeding.[8]

The theoretical infant dose is an estimate of the maximum likely dose in milligrams per kilogram per day that an infant would ingest via mother's milk.[8] The theoretical dose can be used to calculate the relative infant dose by dividing it by the maternal dose in milligram per kilogram per day. The relative infant dose is a weight normalizing process that can be used to estimate how much of the maternal dose the infant receives. Many authors are now using this method to better quantify medication transfer into milk (Table 7: Example 2).

TOBACCO USE

Ideally, mothers should be advised to avoid tobacco use all together; however, pharmacists may still get questions regarding the safety of breastfeeding while smoking. Tobacco use in the form of smoking contributes to exposures beyond what passes into the breast milk. A study conducted in the 1990s found that infants born to mothers who smoked had less acute respiratory illness when breastfed as compared to bottle-fed, demonstrating that any risk from nicotine in the breast milk as well as exposure to secondhand smoke was potentially outweighed by the positive effects of the immune properties of breast milk.[9]

ALCOHOL

Mothers may be counseled to avoid breastfeeding for 2 hours after consuming alcohol. Avoiding alcohol in general is preferred as alcohol can concentrate in breast milk as well as decrease milk production.[5] Mothers may inquire about the benefits of drinking beer to assist with breast milk production since this is a widespread myth. The origin of this fable may be related to a polysaccharide found in barley that has been linked to increases in prolactin secretion. A study conducted in 2010 examined the relationship between breastfeeding and prolactin levels in lactating women with a family history of alcoholism.[10] This study found that alcohol did not enhance lactation performance. Furthermore, it demonstrated that although alcohol stimulates prolactin release, it interferes with both milk production and ejection.

GALACTOGOGUES

The development of a consistent, sufficient milk supply can be challenging for breastfeeding mothers. These women frequently seek assistance from chemical substances, known as galactogogues, to aid in breast milk production. Fenugreek is commonly used and thought to increase breast milk production, although formal studies demonstrating safety or efficacy have not been conducted. Fenugreek is included on the US government's list of herbal products that are "Generally Recognized as Safe."[11] Mammary glands are modified sweat glands and fenugreek is theorized to work by increasing sweat production. A dose of 2 to 3 capsules three times daily is most common.[8] The hallmark side effect associated with the use of fenugreek is a maple syrup odor in the urine and sweat of the mother. Transfer into human milk is unknown but untoward effects have been rarely reported. The most significant of these is suspected gastrointestinal bleeding in a premature infant.

A common agent available in the United States to augment lactation is metoclopramide. The mechanism of increasing milk is related to the side effect of increasing prolactin levels in the mother. The usual dose is 10 mg orally three times a day for 7 to 14 days.[8] In addition to questions about efficacy, reports of side effects have limited metoclopramide's utility. Tardive dyskinesia is a serious complication; it is rare but has not been reported in neonates. Lastly, concerns of increasing depression or dysthymia in the mother further limit its routine use.

Domperidone is a medication that is not available commercially in the United States. It was removed from the market based on safety reasons when it was used in much higher doses for a different indication. It is the drug of choice as a galactogogue in other countries where it is

Table 8. Resources for Pregnancy and Lactation Questions

Reference	Comments
Drugs in Pregnancy and Lactation by Briggs, Freeman, Yaffe[14]	Published approximately every 3 yr Provides information on medications in both pregnancy and lactation
LactMed http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?LACT[15]	Free and available anywhere you have access to the internet (Recommend bookmarking this page on your desktop) Compiled by experts and peer reviewed Updated regularly Provides information on medications in lactation only
Lexi-Drugs	Updated regularly Online and book form available Requires a subscription Has in-depth pregnancy information for many drugs in addition to standard information
Medications and Mother's Milk by Thomas W. Hale[8]	Published every 2 yr. Classifies medications based on risk with L1 being the safest and L5 being contraindicated. Provides information on medications in lactation only
Micromedex[16]	Updated regularly Requires a subscription Contains TERIS and Shepard's Catalog of Teratogenic Agents Provides US and Australian pregnancy drug risk classification along with additional detailed information when available Provides the AAP and Thomson Lactation classification
TERIS	Available online Requires subscription Also available with online subscription to Micromedex[16]

AAP, American Academy of Pediatrics; TERIS, Teratogen Information System

available.[12] Like metoclopramide, domperidone increases milk production by increasing prolactin. However, domperidone does not cross the blood brain barrier and therefore it does not cause tardive dyskinesia. Domperidone has been described as the safest product for stimulating milk production. Although doses as large as 20 mg four times daily have been documented in literature, experts recommend lower doses that have been demonstrated to be effective such as 10 mg three times daily for 7 to 10 days.[8]

INFORMATION RESOURCES

As with pregnancy, there are several sources of information available for pharmacists to refer to when confronted about the safety of a given medication in mother's milk (Table 8). In general, one should not refer to the manufacturer's package insert for information regarding compatibility with breastfeeding. These inserts tend to advise against the use of most products during breastfeeding. When the new FDA rules take effect and the medication labels are updated, this will no longer be true. The American Academy of Pediatrics "The Transfer of Drugs and Other Chemicals Into Human Milk"[13] was quite frequently utilized to guide clinicians with breastfeeding patients. This reference has fallen out of favor due to the long gap between publications. An update is expected from the American Academy of Pediatrics this year.

Drugs in Pregnancy and Lactation is a reference with which most pharmacists are familiar.[14] Although this reference may be preferred when determining safety of a medication during pregnancy, it is not the most comprehensive reference for evaluating the use of medications in lactation. The World Health Organization and the United Nations Children's Fund have a list of recommendations that can be referenced online; however, it is also quite dated. The National Institutes of Health supports a site, Lactmed (http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?LACT) that may be helpful for pharmacists confronted with questions about medications during nursing.[15]

This site is peer reviewed, frequently updated, and is free and available to anyone with Internet access. For subscribers, Micromedex has acceptable information for medication use during breastfeeding.[16]

Medications and Mother's Milk by Thomas Hale is a comprehensive and user-friendly reference that is published every 2 years.[8] Each drug included in this reference is assigned a category from the following: L1- Safest; L2- Safer; L3- Moderately Safe; L4- Possibly Hazardous; and L5- Contraindicated (Table 7: Examples 1 and 3). Drug monographs summarize specific findings related to that medication and breast milk. Relative infant dose is included if known. Drug monographs frequently include alternate medications within the same class that are preferred in breastfeeding. For example, if a patient is prescribed atenolol, which should be used with caution in breastfeeding mothers, this reference recommends propranolol or metoprolol as safer alternatives for breastfeeding in that same class of medication. Many of these references have recently become available as smartphone apps.

Surprisingly, recommendations from each of these references are not always equivalent.[17] It may be prudent to refer to more than one resource when determining safety of medication use during breastfeeding. The potential safety of the medication exposure must be weighed carefully against the known benefits of breast milk. The pharmacist's role in this decision-making process is to provide recommendations based on the best, scientific evidence available.

So how should a pharmacist evaluate a medication for use during lactation? First, consider the age of the child; could we give this medication to them? How frequently are they drinking breast milk? If the infant is closer to 1 year, he or she may only be drinking milk every 6 to 8 hours versus a newborn infant who may breastfeed as frequently as every 1 to 4 hours. Could the mother take a once-daily dose after the last feeding of the day to minimize exposure? Then the peak of the dose occurs overnight when the infant is not feeding. Second, consult as many references as are available and consider the properties of the drug, including bioavailability. Third, assess the mother's milk supply and if this medication might adversely affect it. If significant risk exists and a better option is not identified, consulting the pediatrician and/or the prescribing physician may be reasonable. After a careful review, the recommendation for a mother to pump and discard her milk should be fairly rare.

CONCLUSION

Many resources are available for pharmacists to help guide patients in their quest to find the safest and most effective medical management of chronic and acute disease states during pregnancy and thereafter. Although evaluating the information available may be challenging, it is important to be aware of the resources available and utilize the most up-to-date information to optimize outcomes for both infant and mother. Pharmacists can support better outcomes for pregnant women and encourage continued breastfeeding in situations where patients may have otherwise chosen to not take a medication or stop providing breast milk for their infant(s).

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CONTINUING PHARMACY EDUCATION CREDIT Course title: Evaluating Medication Use in Pregnancy and Lactation: What Every Pharmacist Should Know; course number: 0180-0000-13-007-H04-P; credit hours: 1.5. To receive credit for this article, you are required to take a post-test. For continuing education information, learning objectives, and the post-test, please go to http://www.ppag.org/en/courses/view.asp?courseid=43. The Pediatric Pharmacy Advocacy Group is accredited by the Accreditation Council for Pharmacy Education as a provider of continuing pharmacy education.

ABBREVIATIONS AWC, adequate and well-controlled; FDA, US Food and Drug Administration; FTT, failure to thrive; IUGR, intrauterine growth retardation

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