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Minimizing Infant Exposure to and Risks from Medications while Breastfeeding

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Minimizing Infant Exposure to and Risks from Medications while Breastfeeding

The advantages of breastfeeding to the mother and newborn are many. Lactating mothers frequently ask about the safety of taking medications and the risk to their newborn. It is well established that all drugs are excreted into breast milk. However, most medications appear in only small amounts within the breast milk. With the availability of numerous resources on drug use while breastfeeding, a medication can be identified as contraindicated or compatible with breastfeeding. By understanding the anatomy of the breast, principles of lactation, and drug passage into breast milk, an approach to minimize the transfer of the medications in the breast milk to the newborn can be developed. The plan should usually support and encourage the mother to continue to breastfeed her infant. Key words: *breastfeeding, breast milk, drugs, lactation, medications*

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NO MATTER whether the agent is an over-the-counter medication or one prescribed by a health care provider, most medications are detected in breast milk. The presence of a medication in breast milk may be inferred as a potential hazard to the infant, although only 1% to 2% of total maternal intake is likely to be found.[1] Therefore the primary consideration in maternal drug therapy is the risk to the nursing infant, rather than the mere presence of the medication in the breast milk. Based on the many advantages of breastfeeding, the benefit of this physiologic process in the majority of cases far exceeds the potential risk. Few medications are truly contraindicated for the breastfeeding mother. While maternal medication therapy may be viewed as a reason for stopping breastfeeding, it usually should not be.

PHYSIOLOGY OF LACTATION

Understanding breast anatomy and the physiology of lactation is essential to com-

prehending the complex interaction occurring with maternal medication use during breastfeeding.

Breast anatomy

The basic structure of the breast is the alveolus, or acinus, which is composed of secretory cells where the terminal ductules end. Each cluster of secretory cells of the alveolus is surrounded by a contractile unit of myoepithelial cells responsible for ejecting milk into the ductules (Fig 1). Each terminal ductule then merges into the larger, lactiferous, or mammary, duct. Lactiferous ducts widen into the ampullae or lactiferous sinuses located behind the nipple and the areola. The lactiferous sinus opens at the nipple (Fig 2). It is the compression on the lactiferous sinuses by the newborn's suck that causes breast milk to be expressed.

Except for a small segment at the nipple opening where squamous epithelium lines the duct, the entire duct system is lined by a two-cell layer. The inner epithelial cell layer along the luminal side is surrounded by a spindled, interrupted layer of myoepithelial cells. The two-cell layer is surrounded by a layer of basal lamina and delimiting fibroblast.[2]

Initiation and maintenance of lactation

During pregnancy, maternal prolactin, progesterone, and estrogen levels increase. Prolactin is the major hormone responsible for lactation initiation and causes an increase in the number of secretory cells and prolactin receptors. During pregnancy, high levels of progesterone inhibit prolactin action. After birth the delivery of the placenta triggers a prolactin surge while progesterone and estrogen levels fall. The prolactin activates the secretory cells of the alveolus to manufacture breast milk. This initial milk production occurs whether a newborn breastfeeds or not. Afterward the nursing newborn's suckling stimulates the afferent nerves to release prolactin which causes milk synthesis (Fig 3). Prolactin levels remain elevated as long as breastfeeding occurs. With each breastfeeding episode there is a prolactin burst. The prolactin burst is vital in maintaining milk volume, rather than a constantly elevated prolactin

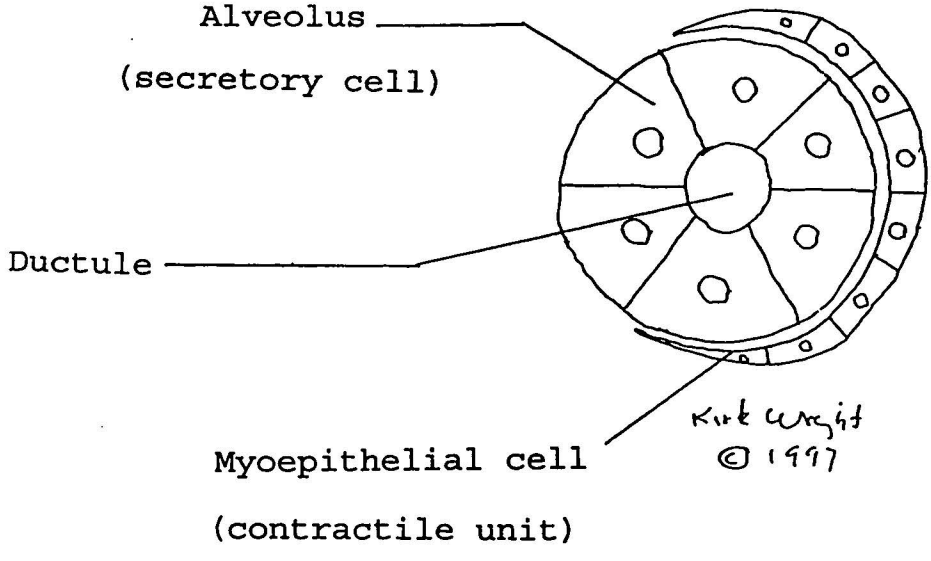

Fig 1. Schematic diagram of the myoepithelial cells around the ductule opening into alveolus.

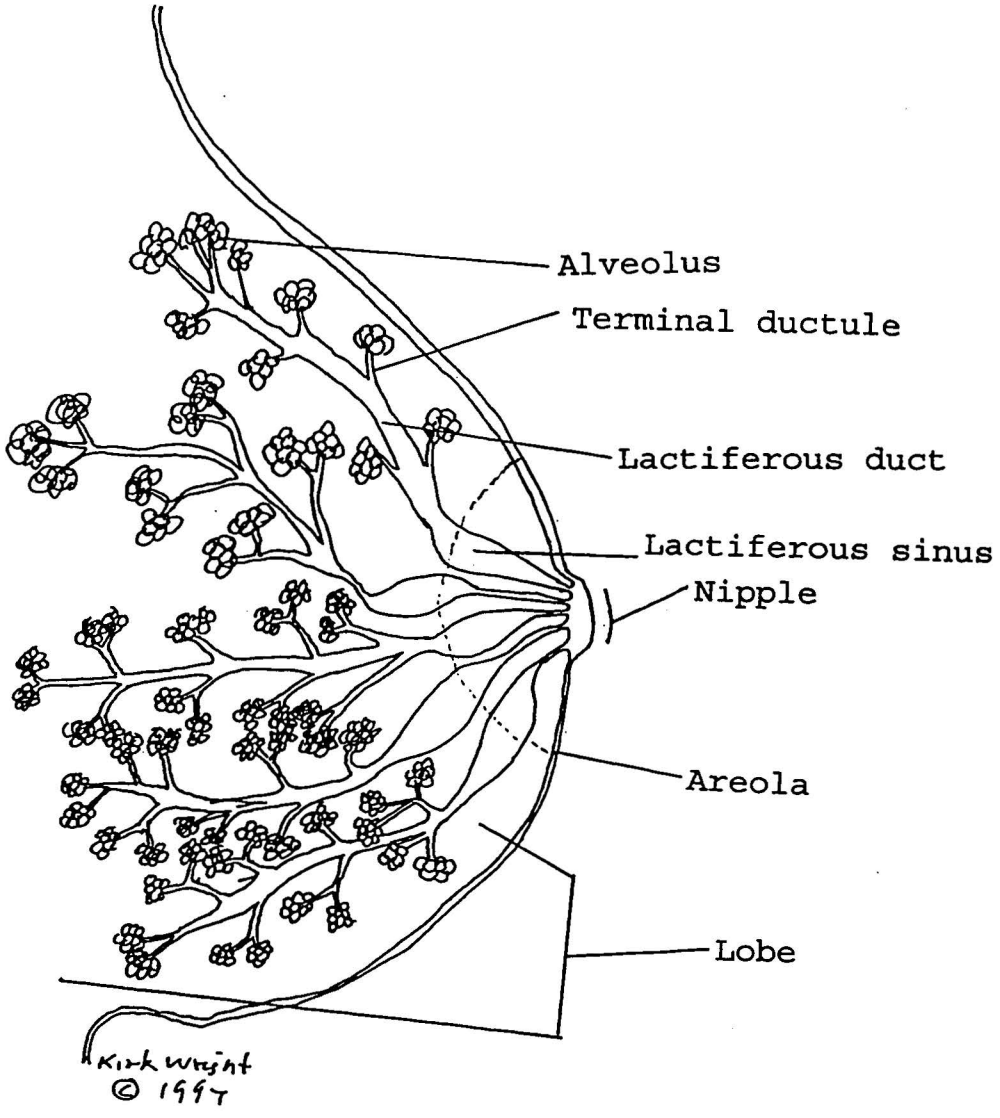

Fig 2. Schematic diagram of the breast.

level. At the same time, the posterior pituitary gland releases oxytocin, which mediates the contraction of myoepithelial cells around the alveolus, causing milk ejection into the larger terminal ductule (Fig 4). Milk is moved along to the lactiferous sinuses, becoming available to the newborn via the openings in the nipple.

Breast milk composition

At the time of delivery, colostrum is present within the maternal breast. Colostrum is high in proteins and low in sugar and fat. As a result, colostrum is easy for the newborn to digest. Within 2 to 3 days after delivery, the secretion of milk be-

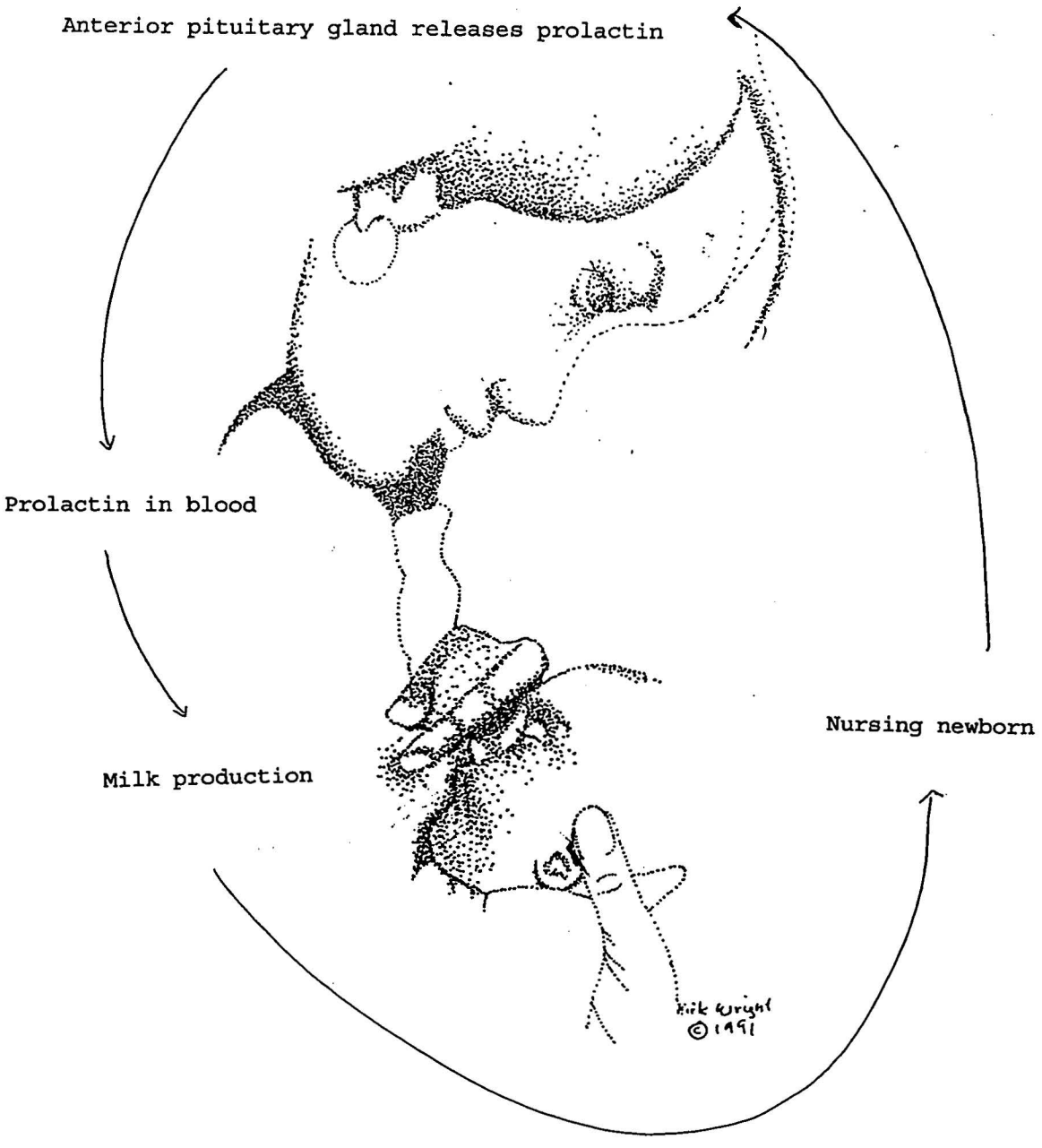

Fig 3. Release and effect of prolactin.

gins. The changes in milk composition continue for 10 days, when "mature milk" is established. Mature milk is higher in proteins and fat, thus higher in caloric content.

PASSAGE OF DRUGS INTO BREAST MILK

A medication given to a lactating mother follows an intricate route to the infant. The

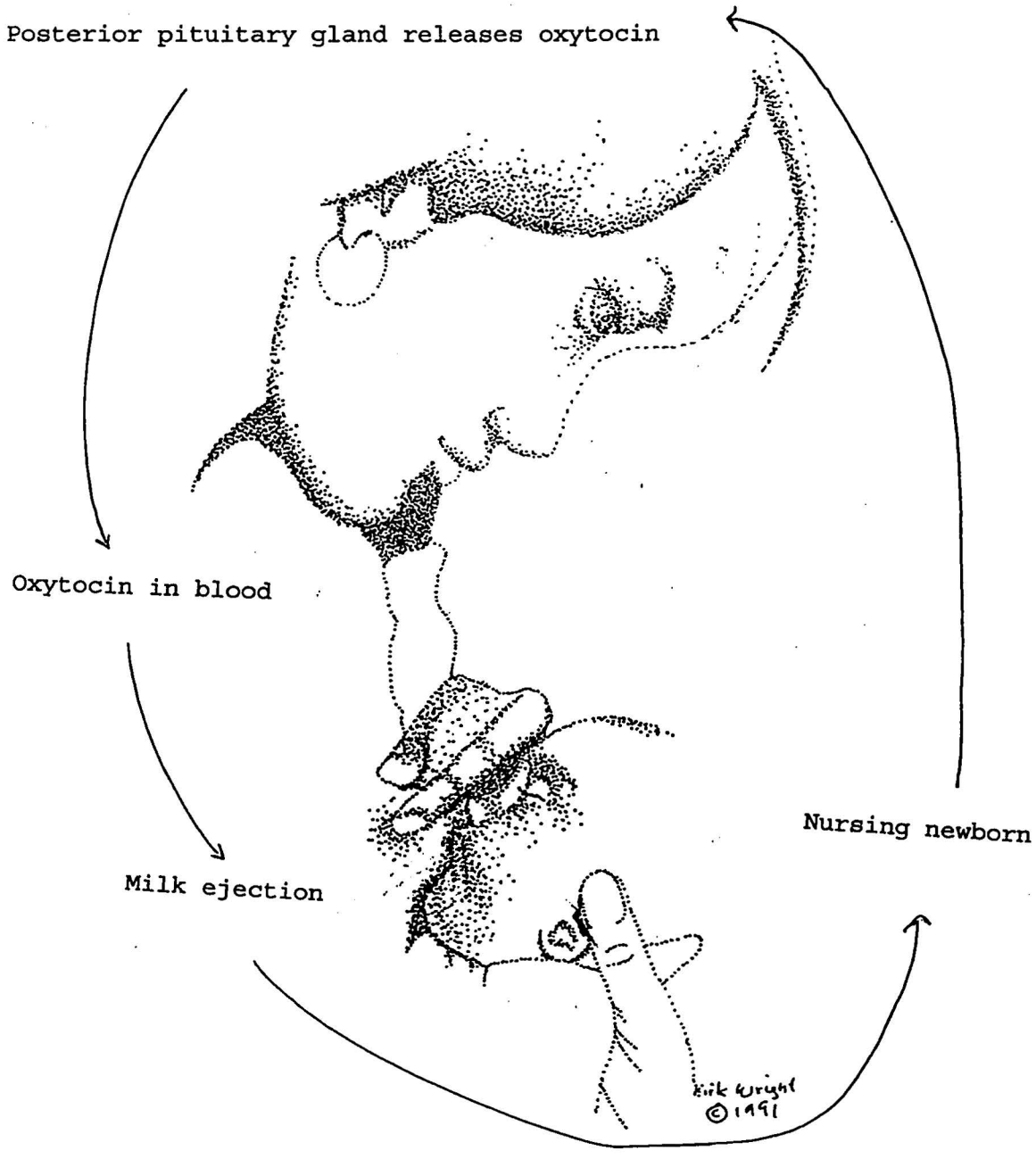

Fig 4. Release and effect of oxytocin.

drug may be partially inactivated in the mother's liver, excreted in her urine, or distributed and protein bound. As a result, the free serum concentration in the mother is frequently low. When the medication is absorbed by the infant, it continues to undergo metabolism, renal excretion, protein binding, and tissue distribution. In addition, the

amount and frequency of breastfeeding will affect the concentration of the drug. Thus there are many factors that influence the passage of drugs into breast milk. These factors include the drug itself, maternal factors, infant factors, and the blood–milk barrier.

Drug factors

The drug's characteristics determine the amount of it that will be transferred into the breast milk. These characteristics include the molecular weight of the drug, the proportion of the drug that is bound to plasma and milk proteins, the solubility of the drug in lipids and in water, the proportion of the drug that is ionized or nonionized, the pH of the drug, and the half-life of the drug.

Molecular weight

The mammary epithelium membrane acts as a semipermeable lipid barrier. Small pores permit drugs with a low molecular weight to pass through. The lower the molecular weight of the drug, the easier the drug passes through to the milk. Drugs with a molecular weight of more than 200 kilodaltons, such as heparin and insulin, are unable to cross the alveolar membrane.[3]

Protein binding

Only the fraction of the medication in the maternal plasma that is not protein bound can leave the maternal circulation, diffuse across the alveolar membrane, and accumulate in the breast milk. Casein, alpha-lactalbumin, lactoferrin, and immunoglobulinA (IgA), the main milk proteins in breast milk, do not bind drugs well.[4] More than half of the plasma protein in the maternal circulation is albumin, a major drug-binding protein. The high protein binding in the maternal plasma effectively restricts many drugs to the plasma compartment and are not transferred into the breast milk. Thus highly protein-bound medications, such as phenytoin (Dilantin), are excreted into the breast milk in small amounts.

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Lipid solubility

The more lipid soluble the drug, the greater the quantity and the faster the transfer into breast milk. Lipid-soluble drugs cross cell membranes more rapidly by dissolving in the lipid bilayer. In contrast, a water-soluble drug must cross the cell membranes through the pores. Thus drugs with a low lipid solubility diffuse slower into the breast milk.[5] For example, diazepam (Valium), which is very lipid soluble, rapidly accumulates in the breast milk.[6]

Drug pH ionization

While average plasma pH is 7.4, the mean pH of breast milk is 7.2, which is significantly lower.[7] Weak acids are ionized in the maternal plasma, decreasing their passage into the breast milk. Weak bases are nonionized in the maternal plasma, increasing their lipid solubility and transfer into breast milk. At the lower pH of breast milk some weak bases will become ionized, preventing diffusion back across the membrane. As a result, the drug molecule becomes trapped in the breast milk and may achieve a higher concentration than otherwise predicted. Conversely, drugs that are more acidic tend to concentrate in the maternal plasma and do not readily transfer into breast milk. For example, erythromycin and antihistamines, drugs that are weak bases, would be more likely to cross the membranes from plasma into breast milk than barbiturates and penicillins, drugs that are weak acids.[8]

Half-life of the drug

The half-life of a drug is determined by the drug's volume of distribution and clearance. Half-life varies greatly from one drug to another. For example, the half-life of ampicillin is 1 hour, Coumadin about 36 hours, and digoxin approximately 1 week.[9] A drug with a short half-life will have plasma concentrations that fluctuate the most and must be taken more frequently than a drug with a longer half-life to maintain therapeutic levels. Thus the longer the half-life of the drug over time, the greater the accumulation will be in the mother, in the breast milk, and in the infant.

Maternal factors

Several maternal factors influence the plasma level of a drug in the breast milk. These factors include the dose, frequency, timing and route of administration, the mother's health, breast milk composition, and breast anatomy.

Dose

The dose of the medication is one factor that determines how much of the drug will enter the maternal circulation and the breast milk. The higher the dose, the more drug passes into breast milk. Thus the recommendation to use the lowest dose needed decreases the amount of a drug that will pass into the breast milk.

Route of administration

The route of administration determines how much of the medication will enter the maternal circulation and, therefore, the breast milk. The medication may be administered through one of several routes, such as intravenously, intramuscularly, orally, topically, or by inhalation. The intravenous (IV) route allows a drug to transfer into the breast milk without consideration of an absorption factor. The amount of a drug that enters the plasma following all other routes of administration is decreased compared with IV dosing. Thus breast milk levels will be highest following IV dosing compared with other routes.

Timing of medication

Breast milk is manufactured while the infant is suckling. The breast stores only a small amount of breast milk between feedings. Thus the timing of a drug dose in relation to breastfeeding influences how much of the drug will appear in the breast milk. For example, if the infant is breastfeeding when the maternal serum drug level is peaking, the amount of a drug that transfers to the breast milk is higher than if her serum level is at a trough. In addition, the blood flow to the breast increases when the breasts begin to lactate. A peaking drug-serum level combined with an increase in mammary blood flow will deliver a higher amount of the drug to the milk. Conversely a drug taken immediately after breastfeeding has the maximum time to clear the maternal blood. However, with a newborn who is breastfeeding more than eight times a day, trying to time the dose is nearly impossible.

Maternal health

The mother's health is another factor of drug transfer into the breast milk. If the mother's ability to clear the medication is impaired, such as by poor liver or kidney function, a greater quantity can accumulate in the breast milk and be ingested by the infant.

Composition of breast milk

The composition of the maternal breast milk also affects the ability of the drug to cross the plasma into the milk. Colostrum is high in proteins and low in lactose and fat. As mature milk develops, this ratio is

reversed. As the protein, fat, water, and sugar content changes, the drug transfer mechanisms change. Lipid-soluble drugs may concentrate in the breast milk fat. The usual amount of fat in breast milk is low when compared with the total milk volume. As a result, the amount of a drug that reaches the infant is probably small with mature milk.

Breast anatomy

Immediately after birth, the spaces between the myoepithelial cells of the alveolus are large and allow the passage of larger plasma proteins like IgA. However, these spaces close to become small pores within a week. As a result, the passage is restricted to lower molecular weight, water-soluble, nonelectrolytes.

Blood–milk barrier

A drug in the mother's blood stream must first pass out of the blood capillary into the connective tissue surrounding the secretory lobes. To pass through the alveolar lumen, the drug must penetrate the membranes of myoepithelial cells and walls of the secretory cells lining the alveolus (Fig 5). This penetration is accomplished by either diffusion through the lipid portion of the membranes or through protein channels in the membranes. Passive diffusion of drugs is most common. A secondary route is to pass through the alveolar lumen via small intercellular clefts, bypassing the secretory and myoepithelial cells.

Infant factors

Infants are continually growing and maturing, especially the premature infant. Thus what adversely affects the newborn at one point in time may not be an issue a week or a month later. There are several infant factors that influence the plasma drug level in the infant acquired from the breast milk. These factors include absorption, protein binding, hepatic metabolism, renal excretion, and frequency and volume of feedings.

Absorption

In infants, gastric emptying time is delayed and intestinal absorption is irregular, resulting in delayed absorption of some drugs. In addition, the infant has a higher gastric pH during the first few days of life, probably allowing gastric absorption of weak bases that would not occur later.[10] Other factors that can influence drug absorption are the infant's gastrointestinal flora and reduced amounts of bile salts and pancreatic enzymes.

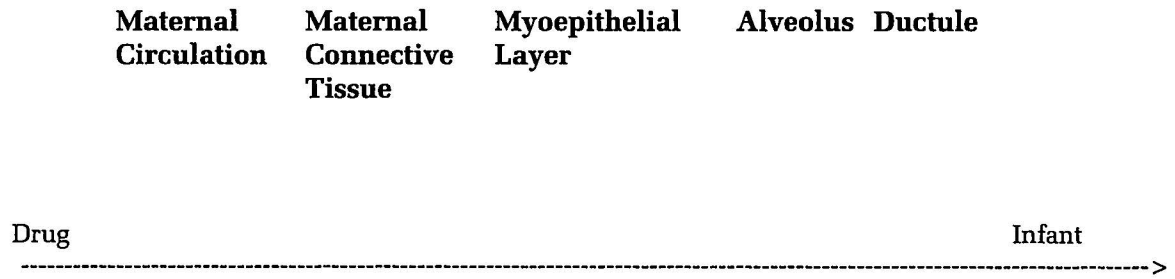

Fig 5. Simplistic diagram of the blood–milk pathway.

Protein binding

Less protein and less binding per unit protein in the infant compared with the adult results in increased clearance of highly protein-bound drugs by glomerular filtration. This appears to compensate for the decrease in clearance observed due to immature glomerular function. The infant approaches adult values for protein binding by 10 to 12 months of age.[11]

Renal excretion

Glomerular filtration and tubular secretions are both underdeveloped in the neonate at birth. Immediately following delivery there is a rapid maturation of the kidneys. By 2 to 3 days postdelivery, the glomerular filtration rate (GFR) values are three times those of the first day of delivery.[12] As a result, a term newborn will have a GFR of one third of adult values. In contrast, a preterm newborn born at 28 weeks will have only a GFR of 10% of adult values.[13] The GFR approximately doubles during the first 2 weeks after delivery, reaching adult GFR values between 2 to 5 months of age.[14]

Tubular development lags behind glomerular development. Functional tubular maturation is not reached until 7 to 9 months of age.[15]

Metabolism

Hepatic enzymes responsible for the metabolism of exogenous and endogenous compounds mature at varying rates. For example, phenytoin (Dilantin) is metabolized at adult rates within 1 to 2 weeks of delivery. However, theophylline metabolism in the infant does not reach adult capacity until 1 year of age.[16]

Conjugation capacity of the newborn is poor and frequently variable. The impaired conjugation of bilirubin is one factor contributing to high unconjugated bilirubin concentrations in the newborn.[17] A healthy, term newborn will not need to have close monitoring of bilirubin levels if the mother is taking sulfamethoxazole-trimethoprim (Bactrim) and is breastfeeding. However, if the newborn is ill, stressed, premature, or has hyperbilirubinemia, an alternative medication for the mother should be recommended as it competes with bilirubin for albumin-binding sites. As a result, there is an increase in free bilirubin in the plasma.

Other metabolic reactions are also reduced. For example, esterase activity is approximately 25% of an adult level in newborns born 4 to 7 weeks early. This increases to 33% at term, but does not approach adult capacity until after 1 year.[18]

Frequency and volume of feedings

The frequency of breastfeeding and volume of breast milk must be considered. The infant that is breastfeeding only once or twice a day and taking solids and juices consumes much less than the neonate who is breastfeeding eight times or more a day and not taking any solids.

STRATEGIES TO MINIMIZE INFANT EXPOSURE AND RISK TO DRUGS WHILE BREASTFEEDING

Often a mother will be instructed to stop breastfeeding when a drug is prescribed or recommended. This recommendation is usually unjustified and reflects a lack of knowledge regarding drugs and breast feeding. The following strategies were developed from the WellStart/The San Diego Lactation Program.[19] The goal is to minimize the infant's exposure to drugs in the breast milk. These strategies should be used with available information on the specific drug or drugs being considered for the lactating mother, such as the American Academy of Pediatrics (AAP) Committee on Drugs statement on *The Transfer of Drugs and Other Chemicals into Human Milk.*[20]

Essential medication

Often the medication is nonessential. Thus the nurse should question the mother's need for the drug. For example, recommend a single-cold product to treat only one or two symptoms, rather than a multicold product.

Delayed therapy

An elective surgery may be postponed until after the mother has stopped breastfeeding.

Established history

Little or no information on a newer drug on the market may be available regarding the safety or pharmacokinetics for the breastfeeding mother. An older drug may provide more reassurance as to the risks to the infant.

Poor passage into milk

Within a class of drugs, there may be a wide amount in the degree of drug that passes into breast milk. Reviewing the list of available drugs to identify one that is poorly transferred into breast milk and has minimal activity would greatly reduce the infant's exposure. If the mother needs a mild analgesic, the list includes acetaminophen, aspirin, and ibuprofen. Of these three, acetaminophen and ibuprofen are preferred to aspirin. Acetaminophen rapidly enters the maternal circulation. The amount of acetaminophen in the breast milk, however, is very small. Ibuprofen does not cross into breast milk. In contrast, aspirin crosses into breast milk and is slower to be eliminated from the milk than the plasma. A cumulative effect from aspirin could have consequences for the nursing infant.

Alternative routes of administration

Attempting to decrease the maternal blood–drug concentration will lower the amount of a drug in the breast milk that is passed on to the infant. For example, an inhaled bronchodilator will minimize the amount of drug passed into breast milk compared to an oral agent for asthma.

Milk production

Certain drugs decrease prolactin levels and thereby decrease milk production (Table 1). As a result, the mother is forced to stop breastfeeding earlier than planned or the need for supplementation with formula results or both. If the mother has resumed taking oral contraception, she should take an oral contraception that contains only progestin without estrogen. Estrogen decreases prolactin levels, thus decreasing breast milk volume and duration of lactation. In contrast, progestin has no effect on breast milk production or duration of lactation. However, most recommend that progestin-only oral contraception therapy be started only after breastfeeding is well established, usually after 6 weeks.

Peak drug concentrations

When possible, coordinate drug-dosing times with nursing times to avoid breastfeeding when peak drug concentrations are present in the maternal serum. This works best with drugs that have a short half-life, such as ampicillin. Peak drug concentration of oral medications occurs 1 to 3 hours after the dose. If the mother can nurse just before the dose, this will reduce the amount that the infant will receive. This plan does not work for the newborn who is nursing frequently or is on an irregular sched-

Coordinate drug-dosing times with nursing times to avoid breastfeeding when peak drug concentrations are present in the maternal serum.

Table 1. Medications that decrease breast milk volume

Generic name	Trade name
Alcohol (excessive)	
Androgens	(Numerous)
Antihistamines	(Numerous)
Apomorphine	Apomorphine
Barbiturates	(Numerous)
Bromocriptine	Parlodel
Erocryptine	Ergocryptine
Estrogens	(Numerous)
Levodopa	Dopar, Larodopa
Phenelzine	Nardil
Prostaglandin E_2	
Pyridoxine	Vitamin B_6
Tranylcypromine	Parnate

Source: Adapted from Riordan J. Drugs and breastfeeding. In: Riordan J, Auerbach KG. *Breastfeeding and Human Lactation.* Copyright © 1993 Jones and Bartlett.

ule. In addition, encourage the mother to take a nonextended- rather than an extended-release form of the medication.

Infant sleep period

With long-acting drugs that can be given once a day, maternal administration just before the infant's longest period of sleep may help to reduce the amount of drug transferred into the breast milk. For example, warfarin (Coumadin) should be given after the last feeding of the day.

Temporary withholding of breastfeeding

Sometimes taking a drug that would be harmful to the infant is necessary for the mother. If known in advance to drug therapy, the mother may decide to pump extra breast milk that can be frozen for later use or temporarily to substitute formula or both. While the mother is on this medication, she will need to use a piston electrical breast pump to maintain lactation and must then discard the expressed milk. If the mother is given metronidazole (Flagyl) to treat trichomoniasis, breastfeeding should be interrupted for 24 hours and an alternative feeding method should be used.[21]

If the mother needs radioactive pharmaceutical, she must temporarily stop breastfeeding. The mother should be encouraged to inform the nuclear medicine physician before the diagnostic study that she is breastfeeding and of her desire that a radionuclide with the shortest half-life in breast milk be used. The mother will need to use the piston electrical breast pump to maintain her milk supply, but should discard all her expressed milk for the required time that the radioactivity is present in the breast milk. This may vary from 1 day to 2 weeks.[22]

Discontinuation of nursing

Usually it is not necessary to stop nursing completely when taking a drug. However, a

Table 2. Drugs that are contraindicated during breastfeeding

Generic name	Reported sign or symptom in infant or effect on lactation
Bromocriptine	Suppresses lactation
Cyclophosphamide	Possible immune suppression. Unknown effect on growth or association with carcinogenesis. Neutropenia.
Cyclosporine	Possible immune suppression. Unknown effect on growth or association with carcinogenesis.
Doxorubicin	Possible immune suppression. Unknown effect on growth or association with carcinogenesis.
Ergotamine	Vomiting, diarrhea, convulsions.
Lithium	1/3 to 1/2 therapeutic blood concentrations in infants.
Methotrexate	Possible immune suppression. Unknown effect on growth or association with carcinogenesis. Neutropenia.
Phenindione	Anticoagulant. Increased prothrombin and partial thromboplastin time in one infant (not used in United States).

Source: Committee on Drugs, American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics.* 1994;93:137–150.

few drugs require that the mother stop breastfeeding due to the toxicity for the infant. (See Table 2).

SOURCES OF INFORMATION

Several reviews on drug use during breastfeeding have been published. However, the AAP Committee on Drugs has a statement that is of particular importance.[23] This statement is invaluable, as the AAP is considered an authority on the transfer of drugs into breast milk. A health care provider may be persuaded to continue to allow a mother to breastfeed when the drug is listed as safe by the AAP. However, the list is not without problems. The list lacks differentiation of whether the newborn is premature, full term, or an infant; data on the effect of the drug on lactation; and data on comparisons within drug classes.

Drugs in Pregnancy and Lactation is a detailed reference book that compiles the research literature and the AAP recommendations.[24] This book is available for less than $100. The most detailed source is *Drugs and Human Lactation*, compiled by the World Health Organization.[25] The summarized qualitative and quantitative aspects are based upon scientific published data. Unfortunately the cost may be prohibitive at more than $250.

Many communities have drug information centers with hotlines that disseminate information on issues related to drug therapy. The goal of the drug information centers is to present accurate and unbiased information on patient-related problems with drug therapy. There are three different types of drug information centers: university affiliated, usually with a college of pharmacy; hospital affiliated, usually with a department of pharmacy; and pharmaceutical-industry affiliated. For inquiries specific to drug use in lactation, the drug, dose, and duration of therapy for the mother are needed. In addition,

specific information regarding the infant is needed, such as the age and well-being of the infant. The caller should have as much information as possible when calling the drug information center. Many drug information requests require time to investigate.

Some drug information centers restrict their services to health care professionals, a specific health care facility, or even a geographic area. Thus not all drug information centers are able or have the capacity to handle requests from outside their institutions. One should identify the closest drug information center available that will provide the needed service. A comprehensive list of drug information centers is available in an annual pharmacists' reference known as the *Drug Topics Red Book*.[26]

A "fax-on-demand" service for information on drugs in breast milk is available for a fee. *Lactation Fax Hotline* is a service that originated from a computerized database on information on drugs in breast milk.[27] After punching the drug selection number(s) from *Medications in Mother's Milk* into a push button telephone, the documents are received within minutes from the fax machine 24 hours a day, 7 days a week. The business number for the service is 1-800-378-1317.

The drug profile includes the generic and brand name(s), pharmacologic category, AAP compatibility assessment, a summary of the drug's normal indication(s), propensity to distribute in breast milk, references, and pharmacokinetic parameters. This information is usually summarized as a one-page document. The documents can be faxed directly to the subscriber of the serv-ice or to someone else, such as a lactation consultant or pharmacist, anywhere in the world as long as the subscriber is within the United States. This easy-to-use service is affordably priced: $10 registration fee for the first 10 faxes, then $1 per selection.

There are, however, a few shortcomings to the service. At the bottom of each page, six pharmacokinetic parameters (adult half-life, pediatric half-life, oral bioavailability, time-to-peak, milk: plasma ratio, and protein binding) are listed. These are useful if one is familiar with the terms. However, no explanation comes with the terms to assist in determining what each term means or how it plays a significant role in the breast-fed infant. On some medications, the pharmacokinetic parameter section is empty. One must assume that there are no data available. In addition, one must have the book, *Medications in Mother's Milk*, to identify what drug information is desired.

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Breastfeeding has many well-established benefits for the mother and infant. Nursing mothers frequently ask questions regarding the safety of a medication. Basically most drugs do pass into breast milk, most appearing only in small amounts. Very few drugs, however, are truly contraindicated for the nursing mother. The mother's need for a medication is not a reason to stop breastfeeding. There are many ways to obtain information on drug use during lactation. After obtaining information on the specific drug(s), the mother should be assisted to use strategies to minimize her infant's exposure and risk to the medication while breastfeeding. By understanding the principles of drug passage into breast milk and evaluating the mother's needs, a plan can usually be developed that allows the benefits of breastfeeding.

REFERENCES

1. Wilson JT, Brown RD, Smith IJ, Hinson JL. Potentially toxic effects of drug and toxins in human breast milk. In: Goldman AS, Atkinson SA, Hanson LA, eds. *Human Lactation,* New York: Plenum Publishing; 1987;3.
2. Tavassoli FA. Normal development and anomalies. In: *Pathology of the Breast.* New York: Elsevier; 192.
3. Rasmussen F. Excretion of drugs in milk. In: Brodie BB, Gillett JR, eds. *Concepts in Biochemical Pharmacology,* Part 1. New York: Springer-Verlag; 1971.
4. Atkinson HC, Begg EJ. Prediction of drug concentrations in human skim milk from plasma protein binding and acid–base characteristics. *Br J Clin Parmacol.* 1988;25:495–503.
5. Ferris AM, Jensen RG. Lipids in human milk: a review. 1. Sampling, determination, and content. *J Pediatr Gastroenterol Nutr.* 1984;3:108–122.
6. Syverson GM, Ratjke SK. Drug distribution within human milk phases. *J Pharm Sci.* 1985;74:1,071–1,074.
7. Ansell C, Moore A, Barrie H. Electrolyte and pH changes in human milk. *Pediatr Res.* 1977;11:1,177–1,179.
8. Rivera-Calimlim L. The significance of drugs in breast milk. *Clin Perinatol.* 1987;14:619–652.
9. Lawrence RA. Drugs in breast milk and the effect on the infant. In: Lawrence RA, ed. Breastfeeding: A Guide for the Medical Profession. 3rd ed. St. Louis, MO: Mosby; 1989.
10. Green TP, Mirkin BL. Clinical pharmacokinetics: pediatric considerations. In: Benet et al, eds. *Pharmacokinetic Basis for Drug Treatment.* New York: Raven; 1984.
11. Morselli PL. Clinical pharmacokinetics in neonates. *Clin Pharm.* 1976;1:81–98.
12. Leake RD, Trygstad CW, Oh W. Insulin clearance in the newborn infant: relationship to gestational postnatal age. *Pediatr Res.* 1976;10:759–762.
13. Guignard JP, Torrade A, Da Cunha O, Gautier E. Glomerular filtration rate in the first three weeks of life. *Pediatr.* 1975;87:268–272.
14. Rane A, Wilson JT. Clinical pharmacokinetics in infants and children. *Clin Pharmacokinetics.* 1976;1:2–24.
15. Morselli PL, Franco-Morselli R, Bossi L. Clinical pharmacokinetics in newborns and infants: age related differences and therapeutic implications. *Clin Pharm.* 1980;5:485–527.
16. Mannering GJ. Drug metabolism in the newborn. *Fed Proc.* 1985;44:2302–2308.
17. Fichter EG, Curtis JA. Sulphonamide administration in newborn and premature infants. *Am J Dis Child.* 1955;90:596–597.
18. Woodward-Lopez G, Creer AE, eds. *Lactational Management Curriculum : A Faculty Guide for Schools of Medicine, Nursing and Nutrition.* San Diego, CA: Wellstart International; 1994.
19. Committee on Drugs, American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics.* 1994;93:137–150.
20. Erickson SH, Oppenheim GL, Smith GH. Metronidazole in breast milk. *Obstet Gynecol.* 1981;57:48–50.
21. Briggs GG, Freeman RK, Yaffe SJ. *Drugs in Pregnancy and Lactation.* 4th ed. Baltimore: Williams & Wilkins; 1994.
22. Bennett PN, Matheson I, Dukes NMG, et al. *Drugs and Human Lactation.* Amsterdam: Elsevier; 1988.
23. Cardinale VA. *Drug Topics Red Book.* Montvale, NJ: Medical Economics Company; 1996.
24. Ziska D. Lactation Fax Hotline a.k.a.LactFax. *J Hum Lact.* 1997;13:82.