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Drugs that affect the fetus and newborn infant via the placenta or breast milk

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The fetus is exposed to many xenobiotic agents during pregnancy through placental drug transfer; the infant is exposed through breastfeeding. The effects of the drugs on the fetus or infant depend on several factors, including not only the amount of drugs that cross the placenta and breast milk but also the distribution, metabolism, and excretion of these drugs. This article is devoted mainly to drug transfer across the placenta and breast milk, and the reader is directed to excellent reviews for further information on drug pharmacokinetics in the fetus and newborn [1–3]. This article focuses principally on drugs used during pregnancy, with reported effects on the fetus. The strength of the evidence presented is implied from the study design of the report (eg, case report versus prospective, randomized clinical study). On the other hand, for breast milk, a general overview of drug transfer and potential effect is presented. This article is written principally with the general pediatrician in mind; its scope does not entail an exhaustive review of all classes of drugs, but rather drugs that are commonly encountered in general practice and would be of practical use in such a setting. For more extensive information on the subject matter, the reader is referred to several excellent references [4,5].

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Drug transfer across the placenta

With few exceptions, most of drugs that are ingested by a pregnant woman during pregnancy can cross the placenta and reach the fetus. Whether knowingly or not, a mother is exposed to several drugs during pregnancy; the number can range from one to as many as six to eight drugs [6–8]. The drugs can be prescribed, obtained over the counter, or obtained illicitly (eg, drugs of abuse). In any case, the drugs may pose potential danger to the fetus or newborn infant in view of their pharmacologic effects, side effects, or complications. For example, drug withdrawal has been observed in infants whose mothers used narcotics or hypnosedatives during pregnancy [9]. Pulmonary hypertension has been observed in infants whose mothers antenatally used nonsteroidal anti-inflammatory drugs [10]. Several drugs are also used throughout pregnancy, such as anticonvulsant agents, whereas other drugs are used late in pregnancy or during labor. A common example of the latter are tocolytics or antenatal corticosteroids for fetal lung maturation in preterm ($\leq$34 weeks') gestation [11].

Placental barrier and difference among species

As an organ of drug transfer, the human placenta is unique from other animal species. The maternal blood is separated from the fetal blood in the villus by a barrier that consists of a layer of syncytiotrophoblast, cytotrophoblast, connective tissue, and endothelium (hemochorial placenta). The human placenta differs from the placenta of other animal species, such as the sheep or pig (epitheliochorial) or dogs and cats (endotheliochorial). Studies of placental drug transfer in these animals are difficult to translate into human settings. The thickness of the placental barrier also differs at different stages of gestation in humans. After 16 weeks' gestation, there is a reduction in the thickness of the barrier because of the partial disappearance of the cytotrophoblast layer, which results in higher permeability in the term placenta compared with preterm placenta [12,13].

Mechanism of drug transport

The transfer of drugs across the human placenta is generally governed by several basic mechanisms [14].

Diffusion

Most drugs cross the placenta by simple diffusion. The transfer does not require energy and depends on the concentration gradient between maternal and fetal blood, the surface area, and the thickness of the membrane barrier, as described by Fick's equation:

$$\frac{\Delta \mathrm{q}}{\Delta \mathrm{t}} = \frac{\mathrm{KA}(\mathrm{C}_2 - \mathrm{C}_1)}{\mathrm{d}}$$

where $\Delta q/\Delta t$ represents the rate of transfer of a drug, K is the diffusion constant, A is the surface area of the membrane, C_2 and C_1 are the concentrations

of the drug on each side of the membrane, and $C_2 - C_1$ represents the concentration gradient across the membrane. The diffusion constant (K) is determined by the physicochemical characteristics of the drugs, such as its molecular weight, pKa (the pH at which the drug is 50% ionized), lipid solubility, state of ionization, and protein binding (Aa). Molecules that have low molecular weight (up to 600 d) and are non-ionized and lipid soluble essentially show unimpeded diffusion. The ionization constant is related to lipid solubility. The more ionized the compound, the more water soluble and less lipid soluble it is. Lipid-soluble drugs diffuse across the placenta with greater facility than water-soluble compounds. Conversely, strongly ionized compounds cross the placenta poorly, although there are some exceptions. Highly acidic drugs, such as ampicillin and methicillin, exhibit complete transfer across the placenta despite their highly ionized state [15,16]. For drugs whose pKa is near the pH of the blood, the difference in pH between maternal and fetal blood favors less diffusion of drugs from the fetal to maternal side during equilibrium because of lower pH of fetal blood and more ionized form of the drug.

In terms of surface area, there is a linear relationship between the villous surface area and bodyweight at birth, which suggests that as the fetal weight increases, the exchange surface to supply the required nutrients (and drugs) also increases [17,18].

Facilitated diffusion

The placental transfer of compounds is carrier mediated but does not depend on energy. Transfer occurs down a concentration gradient, is inhibited by competitive analogs, and is saturable. Transport of glucose across the placenta probably occurs through this mechanism. Drugs are not commonly transferred across the placenta by facilitated diffusion, except for drugs that are structurally related to endogenous compounds that are transported via this mechanism. For instance, drug transport of cephalosporin, gancyclovir, and corticosterone occurs by facilitated diffusion, probably because these drugs are transported by systems primarily present for endogenous dipeptides, nucleosides, and hormones [19–22].

Active transport

The active transport process occurs against a concentration gradient and requires energy. The transport is carrier mediated and saturable, exhibits competition among related molecules, and may be inhibited by metabolic poisons [23]. Essential amino acids are generally transported actively across the placenta. Fetal excretion of xenobiotics into the maternal circulation probably occurs through this mechanism.

Phagocytosis or pinocytosis

Phagocytosis and pinocytosis are less important mechanisms of placental drug transfer. In this process, compounds are invaginated into the cell membrane and transferred across the opposite end.

Membrane versus flow-limited drug transport

The rate of transfer of drugs across the placenta is defined not only by factors in the Fick equation but also by factors that regulate maternal and fetal blood flows. Molecules that have low molecular weight and are nonionized and lipid soluble generally show umimpeded diffusion. The rate of transfer of such compounds does not depend on the diffusibility across the membranes but rather on factors that regulate maternal and fetal blood flow (flow limited). As gestation proceeds to term, there is an increase in uterine blood flow, which favors more transfer of nutrients and other xenobiotic agents across the placenta. Conversely, polar, ionized and hydrophilic compounds diffuse across the placenta more slowly than the rate of its delivery by the blood stream. This exemplifies a membrane-limited transfer.

Overall, placental drug transport seems small, which indicates impaired transport based on the physicochemical characteristics of the drug or placental factors, such as drug metabolism or tissue binding. The principal mechanism of placental drug transport is simple diffusion, although several drug transport systems have been found particularly for drugs that are structurally related to endogenous compounds.

Models to study placental drug transport

Various models have been used to study drug transfer across the human placenta, including perfusion studies of placental tissues, isolated placental membrane vesicles or trophoblastic cell cultures, and maternal and fetal blood sampling [24]. The perfusion of isolated human placentas allows the study of the direction of drug transport, the influence of metabolic pathways and tissue binding, and the relation of drug transport to membrane or flow-limited reference compounds, such as antipyrine and inulin. Isolated membrane vesicles of human placenta allow the study of basic transport mechanism, the role of inhibitors, and the saturability of carriers systems [24,25]. Comparison of the serum concentrations in the maternal and umbilical cord blood after maternal bolus drug administration is a widely used method to study placental drug transport. Certain limitations must be considered with this method, however. The maternal and fetal serum drug concentrations depend on the time between drug administration and drug sampling. Lack of a proper reference compound and the role of placental drug metabolism are also limiting factors.

Placental transfer of drugs and their adverse effects on the fetus

Various classes of drugs that cross the placenta and their adverse effects on the fetus are shown in Table 1. Only reports in human are included in this table, and animal data are purposely excluded. The strength of the evidence that associates the drug to its adverse effect on the fetus can be determined in the

Table 1
Transfer of drugs across the placenta and their adverse effects on the fetus

Drug	Adverse effects on fetus	Reference
Antiepileptics		
Carbamazepine	Prospective cohort study or meta-analysis: Major congenital malformations; abnormal auditory brain evoked response, strabismus, astigmatism, anisometropia, negative influence on body weight, length, head circumference, mental retardation (carbamazepine syndrome)	[29,33–37]
Clonazepam and carbamazepine	Case report: paralytic ileus	[44]
Lamotrigine and valproic acid	Case report: dysmorphic features, including IUGR, hypertelorism, flattened nasal bridge, low-set malformed auriculas, micrognathia, small, bow-shaped mouth with thin upper lip, cleft palate, arachnodactyly, camptodactyly, secundum atrial septal defect, bilateral hammer toes and decreased creases on the soles; at 6 months old, motor retardation; karyotype 47,XXX	[26]
Phenylhydantoin	Case report: vascular disruption sequence (atypical cleft hand)	[38]
	Retrospective cohort: clotting defects: elevated PT/PTT and decreased factor V, VII, IX	[39]
Phenobarbital + phenytoin	Prospective cohort study: smaller occipitofrontal circumference	[40]
	Case report: neonatal hypocalcemia	[41]
Phenytoin	Case report: atrioventricular septal defect with separate right and left atrioventricular valvar orifices in a patient with fetal hydantoin syndrome	[42]
Phenobarbitone	Case report (high-dose exposure): facial dysmorphism, developmental delay	[43]
Trimethadione	Retrospective cohort: "trimethadione syndrome"—fetal loss, congenital malformation—malformed ears, cleft palate, cardiac defects, urogenital malformation, skeletal abnormalities	[45]
Valproate	Retrospective case control study and meta-analysis: major congenital malformations; valproate embryopathy (myopia, strabismus, astigmatism, anisometropia), cardiac malformation, raniosynostosis, autism	[27–33]
Anxiolytics		
Benzodiazepine	Case report: aplasia cutis congenita of the scalp; floppy infant syndrome	[46,47]
Benzodiazepine + selective serotonin reuptake inhibitors	Retrospective cohort: alters neonatal acute pain response	[49]

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Table 1 (*continued*)

Drug	Adverse effects on fetus	Reference
Paroxetine	Prospective cohort: neonatal complications; Respiratory distress, hypoglycemia, jaundice	[48]
Antidepressants		
Fluoxetine	Prospective cohort: no increased risk of fetal malformations	[51]
Selective serotonin uptake inhibitors	Retrospective cohort: low Apgar score, low Bayley psychomotor development index and motor quality factor of Bayley behavioral rating scale	[52]
Venlafaxine	Multicenter, prospective control: no increase in the rate of major congenital malformations	[50]
Antipsychotic		
Lithium	Case report: neonatal goiter and hypothyroidism; neonatal lithium toxicity—lethargy, poor suck-swallow coordination	[53,54]
Neuroleptics		
Phenothiazines	Review: congenital malformations	[55]
Chemotherapeutics		
Cyclophosphamide	Case report: cytoxan embryopathy	[59]
Azathioprine or cyclophosphamide	Nested case control: increased fetal losses in women with systemic lupus erythematosus (SLE)	[60]
Gancyclovir	Case report: mild anemia in infant	[61]
Idarubicin and cytosine arabinoside	Case report: prematurity, growth retardation, mildly abnormal transaminases and erythroblastosis	[56,57]
Methotrexate	Case report: craniofacial and digital anomalies; IUGR	[62]
Mitomycin C	Case report: severe IUGR; chromosome breakage syndrome	[58]
Immunosuppressives		
Immunosuppressive drugs	Review: increased prematurity, IUGR, adrenal insufficiency, with steroids, immunologic disturbances with azathioprine and cyclosporine	[63]
Antiretroviral		
Antiretroviral combination	Retrospective cohort: no risk to premature delivery or low Apgar score or stillbirth	[65]
Protease inhibitor	Retrospective cohort: low concentration; no teratogenic effect	[64]
Steroids		
Betamethasone	Retrospective cohort: steroids may influence cholesterol and lipoprotein synthesis in the fetus	[66]
Betamethasone, dexamethasone, hydrocortisone	Review: fetal lung maturity	[67]

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Table 1 (*continued*)

Drug	Adverse effects on fetus	Reference
Dexamethasone	Retrospective cohort: steroids decrease cortisol secretion in preterm infants	[68]
Glucocorticoids	Retrospective cohort: steroids modulate the amplitude of pulsatile cortisol secretion in premature neonates	[69,70]
Nonsteroidal anti-inflammatory drugs		
5-acetylsalicylic acid	Retrospective cohort: increased risk to stillbirth and preterm birth	[71]
Aspirin	Prospective cohort: congenital heart defect and septation of truncus arteriosus	[72]
Nimesulide, naproxen, ibuprofen diclofenac	Case report: neonatal chronic failure, oligohydramnios Retrospective cohort/case report: persistent pulmonary hypertension of the newborn Retrospective cohort: reduction in amniotic fluid index, fetal urine production and ductal pulsatility index	[10,73–78]
Tocolytics		
Beta sympathomimetic	Prospective cohort: neonatal hypoglycemia	[80]
Ritodrine, isoxsusprine	Prospective cohort: electrocardiographic evidence of myocardial ischemia	[79]
Antibiotics		
Beta lactams, macrolides	Review: no deleterious effect	[90]
Chloramphenicol	Case control: teratogenic effect	[89]
Gentamicin	Case report: renal dysplasia Prospective cohort: fetal kidney defect Review: retarded nephron growth, oligonephronia	[84–86]
Phenoxymethyl penicillin	Prospective cohort: no risk	[81]
Streptomycin	Case cohort: hearing loss	[87,88]
Tetracyclines	Review: injurious to fetal bone and teeth Case control: teratogenic	[82,83]
Antifungals		
Griseofulvin	Meta-analysis: abnormal germ cell maturation, embryotoxicity, aneuploidy, abnormal microtubule formation, hepatocarcinogenic	[91]
Itraconazole	Prospective cohort: no effect on fetus	[92]
Sulfa antimicrobials		
Cotrimoxazole	Case report: spinal malformation Case control: no teratogenic effect	[93,94]
Amoebicide		
Metronidazole	Meta-analysis: no congenital malformation	[95]
Quinolones		
Fluoroquinolone	Clinical trials: no increased risk for malformation and musculoskeletal problems; no fetal risk	[96,97]

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Table 1 (*continued*)

Drug	Adverse effects on fetus	Reference
Hypoglycemics		
Insulin lispro	Review: no increase in congenital malformations	[98]
Oral hypoglycemics	Case report: severe hypoglycemia	[99]
	Prospective cohort: congenital malformation; ear malformation	[100]
Drugs of abuse		
Alcohol	Review: fetal alcohol syndrome, decreased birth weight, adverse cognitive outcomes, and poorer linguistic abilities and deficits in attention and memory	[101–105]
Cocaine	Review: decreased neonatal head circumference, birth weight, prematurity, growth retardation, fetal loss, decreased adaptability to stress, including a disruption in the habituation response in infants, and impaired attention In vitro study: fetal myocardial depression	
Marijuana	Review: decreased birth weight and length and deleterious cognitive and attention effects in some preschool and early school-age samples	
Nicotine	Review: physical, cognitive, and behavioral effects in offspring	
Heroin, morphine	Review: neonatal abstinence syndrome Review: intrathecal morphine associated with fetal bradycardia	[106–109]
Caffeine	Prospective cohort: low birth weight, small head circumference	[110,111]
Estrogens		
Diethylstilbestrol	Retrospective cohort: irregular menstruation, primary infertility, premature birth, nonviable pregnancy outcomes (stillbirth, ectopic pregnancy, neonatal death, miscarriage); in males: epididymal cyst, hypoplastic testis, cryptorchidism, semen abnormalities	[112,113]
Norethindrone	Case control: high abortion rate, high prenatal mortality rate	[114]
Progestins		
Epostane	Double blind, placebo controlled trial: lowers maternal and fetal progesterone levels	[116]
Progestogen	Case control/ cohort: congenital heart lesions, neural tube defects Meta-analysis: prematurity, stillbirth, neonatal death	[114,115]
17-α-OH-progesterone caproate	Randomized clinical trial: effect on fetal outcome is not clear	[117]
Antithyroids		
Carbimazole	Retrospective cohort: no effect; elevation of thyroid-stimulating hormone Case report: choanal atresia	[127,128]

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Table 1 (*continued*)

Drug	Adverse effects on fetus	Reference
Iodide	Case report: congenital goiter	[118]
Methimazole	Review: aplasia cutis	[119–125]
	Case report: esophageal atresia, tracheoesophageal fistula	
	Case report: hypothelia, athelia, developmental delay, choanal atresia	
Methimazole and propylthiouracil (PTU)	Prospective cohort: neonatal thyotoxicosis, congenital defects	[126]
Matimazole and carbimazole	Case report: congenital skin defects	[129]
ACE inhibitors		
ACE inhibitor (general)	Meta-analysis: oligohydramnios, IUGR, prematurity, fetal and neonatal renal failure, bony malformations, limb contractures, persistent patent ductus arteriosus (PDA), pulmonary hypoplasia, respiratory distress syndrome, prolonged hypotension, neonatal death	[130,131]
Enlapril	Case report: oligohydramnios, impaired renal functions, unilateral kidney hypoplasia	[132]
Beta blockers		
Acebutalol	Retrospective cohort: low blood pressure and heart rate in infant	[142]
Atenolol	Prospective, randomized clinical trials: direct effects on fetal hemodynamics and cardiac function, increase in utero- or umbilicoplacental vascular impedance, increase in pulsatility index, decrease in pulsatility indices in the fetal renal artery, decrease in peak systolic velocity in the pulmonary trunk.	[133,134]
	Retrospective cohort: low birth weight, fetal growth retardation, prematurity	[135,136]
Labetalol	Randomized control trial: fetal beta-blockade, vasoconstriction in the fetoplacental circulation, fetal loss	[140,141]
	Retrospective cohort: hypoglycemia	
Methyldopa	Prospective, randomized clinical trial: perinatal death, low birth weight, increased fetal loss	[138,139]
Propranolol	Prospective, randomized clinical trial: low birth weight, low blood glucose	[137]
Diuretics		
Acetazolamide	Case report: renal tubular acidosis	[143,144]
	Retrospective cohort: increased risk of schizophrenia; interferes with fetal neurodevelopment	
Benzothiadiazide	Case report: neonatal hypoglycemia	[145]
Class III antiarrhythmics		
Almokalant, dofetilide, butelide	Review: embryonic death, decreased fetal weight, malformation—distal digital reduction, orofacial clefts, and cardiovascular defects	[146]
Amiodarone	Case report: neonatal hypothyroidism	[147]

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Table 1 (*continued*)

Drug	Adverse effects on fetus	Reference
Anesthetics		
Sulfentanil (intrathecal)	Prospective, randomized clinical trial: fetal distress (intrapartum fetal heart tones [FHT] abnormalities)	[148]
Anticoagulants		
Aspirin	Prospective, randomized control trial: increased prematurity rate	[149]
Coumarin	Retrospective cohort: decreased cognitive functioning	[150]
Warfarin	Review: embryopathy, fetal intraventricular hemorrhage, cerebral microbleeding, microencephaly, mental retardation Case report: optic atrophy, blindness, dilated cerebral ventricles Case report: nasal hypoplasia, abnormal facial cartilages, brachydactyly Case report: chondrodysplasia punctata, telebrachydactyly, facial dysmorphism, nasal hypoplasia, cataract, pyeloureteral junction syndrome Retrospective cohort: low birth weight, embryopathy, neonatal death	[151–155]
Opioids		
Alphaprodine	Prospective analysis: sinusoidal fetal heart rate pattern	[180]
Co-proxamol	Case report: arthrogryposis multiplex congenital, bilateral midbrain infarction	[173]
Fentanyl	Randomized clinical trial: fetal bradycardia, nonreassuring fetal heart tracings. depressant on many fetal biophysical parameters	[161–169]
Meperidine	Prospective cohort: depressed fetal activity Case report: sinusoidal fetal heart rate pattern	[174,175]
Meperidine + promethazine	Prospective cohort: fetal heart rate deceleration	[176,177]
Methadone	Retrospective cohort/review: narcotic withdrawal, small for gestational age, small head circumference, sudden infant death syndrome Case control: neonatal thrombocytosis, abnormal nonstress test and modified biophysical profile	[156–159]
Nalbuphine	Randomized clinical trial: effect on fetal heart rate tracing Case report: resolution of marked intrapartum fetal tachycardia; sinusoidal fetal heart rate pattern	[170–172]
Paroxetine hydrochloride	Prospective cohort: neonatal withdrawal, respiratory distress, hypoglycemia, jaundice; discontinuance syndrome	[160]
Pentazocine, nalbuphine, butrophanol	Prospective cohort: fetal acidosis of varying degrees, highest with pentazocine and lowest with butrophanol	[178]
Propoxyphene + acetaminophen	Case report: teratogenic in combination	[179]

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Table 1 (*continued*)

Drug	Adverse effects on fetus	Reference
Others		
All transretinoic acid	Case report: transient dilated cardiomyopathy	[184]
Cafergot	Case report: jejunal atresia and IUGR	[189]
Castor oil	Case report: "ricin syndrome"—moderate growth retardation, craniofacial dysmorphia, absence deformity of limb, vertebral segmentation defect	[188]
Isotretinoin	Review: craniofacial and cardiac malformations	[181,182]
Misoprostol	Randomized clinical trial: stillbirth	[186]
Radioiodine	Case report: congenital neonatal hypothyroidism	[190]
Synthetic retinoids	Review: teratogenicity	[183]
Thalidomide	Clinical trial, historical article: phocomelia	[187]
Vaginal douche of povidone-iodine	Prospective cohort: increased fetal iodide content	[185]

table from the study design of the report (eg, retrospective cohort study versus case report).

Breastfeeding and drug transfer in breast milk

After birth, an infant may be exposed, through breastfeeding, to drugs that are taken by the mother. Breastfeeding has increased considerably since the past decades. In a 1994 to 1995 survey, the national breastfeeding initiation rate was 73% in Canada and 60% in the United States [191,192]. The use of medication among nursing women is high, however. Approximately 90% of women take some form of medication during the first week postpartum [193,194]. In a study of 14,000 pregnant or breastfeeding women, 79% used medication while breastfeeding, for an average drug intake of approximately 3.9 drugs. Studies also have shown that there is a decrease in breastfeeding initiative or duration when women require medications after birth [195]. The general fear in the mother is that the drugs will get into her breast milk and adversely affect her infant. This is a sad situation because many of the drugs taken by the mother are found at low concentrations in her breast milk and have little or no untoward effect on her infant. If the breastfeeding mother requires medication, her compliance with drug intake can be erratic because of her effort to minimize the exposure of her infant to drugs through breastfeeding. In a study of breastfeeding women who were on prescribed antibiotics, 22% either stopped breastfeeding or did not begin therapy [195]. Appropriate advice to the mother regarding the risk of drug therapy and breastfeeding is necessary.

Drug transfer into the breast milk

As a rule, although most drugs that are taken by the mother are transferred into her breast milk, the amount and concentration that are transferred are low

and relatively safe for the infant. Several maternal and infant factors influence the amount of drug transferred into breast milk [196].

Maternal factors

Dose and duration of therapy

Low dose, infrequent dosing, and short duration of therapy are likely to be safe for breastfeeding because of the low dose of drug in the breast milk and short exposure of the infant to the drugs. For drugs that are contraindicated in breastfeeding, breastfeeding may be interrupted temporarily until the period of therapy is over.

Route of administration

The bioavailability and serum concentration of drugs are different if the drugs are taken orally versus parenterally. Drugs that are administered parenterally because of poor oral bioavailability may be poorly absorbed by the infant through the breast milk.

Drug pharmacokinetics

The serum concentration of drugs in the mother depends on the distribution, metabolism, and excretion of the drugs in the mother. Drugs with a long half-life may result in cumulative exposure in the breastfed infant.

Infant factors

The drug concentration in breast milk and the volume of milk ingested per day determines the daily, total amount of drug that is taken by the infant. The serum concentration of the drug in the infant depends on several factors, including the infant's ability to absorb, metabolize, and excrete the drugs. These factors are influenced further by the gestational age of the infant and its postnatal age. Because of less mature liver and kidney functions, the preterm infant is less able to metabolize and excrete drugs compared with term or older infants. Compared with drugs in term infants, drugs in preterm infants have a more prolonged half-life and may reaccumulate with repeated dosing.

Determinants of infant drug exposure through breast milk

Estimates of the potential amount of drug that an infant obtains through breastfeeding are expressed in several ways: (1) milk-to-plasma ratio, (2) exposure index, and (3) relative infant dose [196–198].

Milk-to-plasma ratio

The milk-to-plasma ratio is an estimate of the amount of drug in breast milk and is calculated from the ratio of the drug concentration in the milk and in ma-

ternal plasma at steady state. In general, a low ratio indicates less drug in milk for a given maternal serum drug concentration. Sometimes, a milk-to-plasma point ratio is used. This ratio refers to the ratio of the milk to maternal plasma drug concentration at a given point in time. It is less useful because it refers to the concentration ratio at a specific point in time, which may vary throughout the day depending on the factors that determine drug transfer into breast milk and serum concentration in the nursing mother. A time-integrated ratio of the area under the curve of the milk and maternal serum concentrations also has been used and is probably a more reliable index because the concentrations in the milk and maternal serum are taken for an extended period rather than a single time point.

Infant dose

The infant dose is calculated from the drug concentration in the breast milk and multiplied by the total volume of milk that is ingested by the infant:

$$\text{Dinf} = \text{Drug concentration in milk} \times \text{volume of milk ingested}$$

Unfortunately, the accurate volume of milk taken by the infant is difficult to determine. Estimates of milk intake are made based on average milk consumption by the infant (0.15 L/kg/d). The safety of the estimated infant dose is determined by relating it to the dose that is commonly used if the drug were given orally to the infant.

Relative infant dose

One of the most useful methods of estimating drug exposure in the breastfeeding infant involves calculating the relative infant dose, which shows the relationship of the infant dose obtained through the breast milk to the maternal oral dose. The relative infant dose is calculated as follows:

$$\text{Relative infant dose} = \text{infant dose (mg/kg/d)/maternal dose (mg/kg/d)} \times 100$$

The relative infant dose is expressed as a percentage. The general recommendation is that the relative infant dose value should not be more than 10% of the maternal dose [197]. In preterm infants, however, the relative infant dose should be less than 10% because of lower drug clearance capacity compared with term infants.

Ways to minimize infant drug exposure

The ideal situation is not to expose the infant to any drugs while breastfeeding. This may not always be possible, however. The risk versus benefit of breastfeeding in an infant when the mother is on any medication drug therapy must be assessed. Because breastfeeding offers many advantages to the mother and infant, the use of drugs by the mother normally should not be a deterrent to breastfeed-

ing. In most instances, the amount of drug that is transferred into the breast milk is small and relatively safe for the infant. Safety may not be absolute, however, because drugs, even at low concentrations, can elicit other problems in the infant, such as allergic reaction to drugs (eg, antibiotics). The safety of drug therapy in the breastfeeding infant is relative and must be individualized.

There are also many ways to minimize the exposure of the breastfed infant to drugs taken by the mother. (1) Avoid feeding the infant at the time of peak concentration of the drug in milk. Usually, peak concentration occurs 1 to 2 hours after an oral dose. Feeding should occur at the end of the dose interval and after prior emptying of the breast of milk that contains the maximum amount of drug. This procedure may be useful only for drugs with short half-life, and it is practical only if the infant is not fed frequently (every 2 hours). (2) Withhold

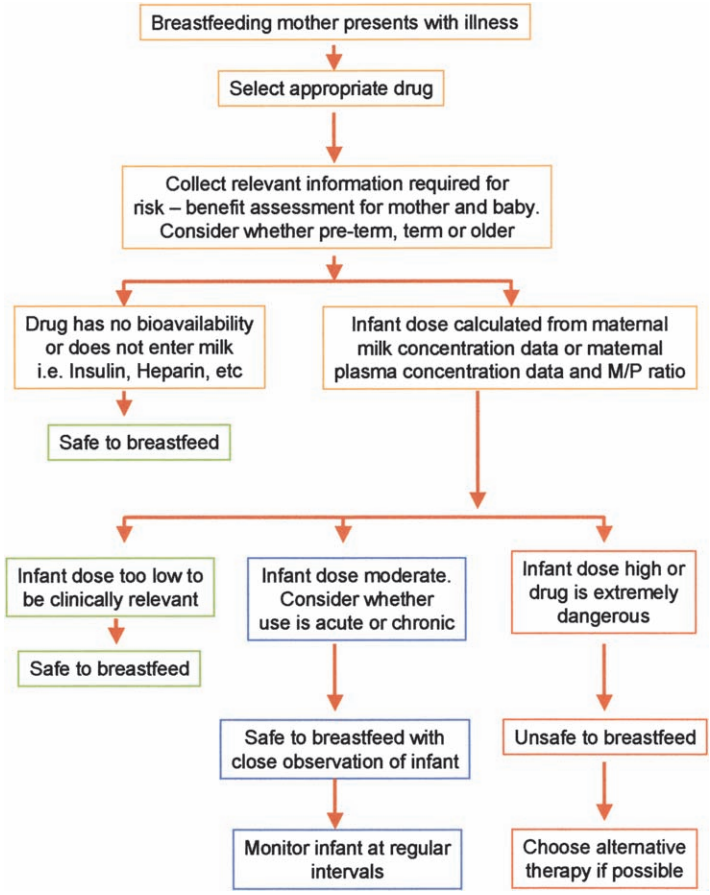

Fig. 1. Algorithm to assess risk-benefit of drug therapy and breastfeeding. (*Adapted from* Hale TW, Ilett KF. Drug therapy and breastfeeding: from theory to clinical practice. New York: Parthenon Publishing; 2002; with permission.)

breastfeeding temporarily if the drug is only used for a short duration. This is particularly true for drugs that are contraindicated in breastfeeding. (3) Choose drugs for the mother that have known and established information about their pharmacokinetics and toxicity and have low concentrations in breast milk and low relative infant dose. (4) Choose drugs that can be locally rather than systemically administered. (5) In case of long-acting drugs, time the drug administration to a once-a-day dose just before the infant's longest sleep period to lessen exposure.

For these measures, it is important that the mother empty her breast of milk at the appropriate time before she breastfeeds so that the drug content of her milk is low. An algorithm to assess risk benefit of breastfeeding in the mother who is taking medications is shown in Fig. 1.

Commonly used medications

The transfer of drugs into breast milk and their reported effects on the breastfed infant are presented in Table 2. Most drugs are transferred into breast milk at low concentrations (low milk-to-plasma ratio and low relative infant dose) and are relatively safe for the nursing infant. No drug, however small its concentration in breast milk, is absolutely safe, however, because of idiosyncratic reactions in the infant, allergic sensitization (eg, antibiotics), or unknown potential long-term sequelae of the drug, particularly on the neurobehavioral development of the infant. Likewise, variations in an infant's ability to metabolize, excrete, and respond to the medications also may account for the adverse problems reported in infants for drugs that have been determined to be compatible with breastfeeding. Maternal use of drugs while breastfeeding should be reserved only for specific indications that are necessary for a mother's continued health and well-being. In instances in which maternal drug use is necessary, measures to minimize exposure of the infant should be taken (see previous discussion). While breastfeeding, the infant always should be monitored for any adverse drug effect so that further adjustment in drug therapy or breastfeeding schedules can be implemented. Because of the multiple advantages of breastfeeding, discontinuance of breastfeeding should not be the initial consideration for the mother who is on medication. A balance usually can be achieved so that the benefits of breastfeeding can outweigh its disadvantages in this situation.

Herbal drugs

The growing and widespread use of herbal medications has been of concern for breastfed infants. Most of the herbal medications contain multiple ingredients and have ill-defined pharmacologic action even for the principal agent. There is inconsistency in the drug concentration of many of their elements, which makes it difficult to determine the specific risk on breastfed infants. It is advisable for mothers to refrain from using any herbal medication while breastfeeding [196].

Table 2
Drugs transferred into breast milk and their effects on the infant

Drugs	Reported findings in infant	Reference
Opioids analgesics		
Codeine	7% protein bound; milk-to-plasma (M:P) ratio is 1.3:2.5; relative infant dose is 7% of maternal dose; no reported adverse effects in infant	[199,200]
Fentanyl	Transfer into maternal milk is low; relative infant dose is <3%; milk levels too low for detection; safe	[201]
Hydromorphone	Distributes rapidly from plasma to breast milk but does partition into fat; protein binding minimal in milk and plasma; M:P ratio = 2.57 ± 0.47; infant receives approximately 0.67% of maternal dose; dose well below that used to treat neonates; unlikely to have deleterious effect	[202]
Morphine	M:P ratio always <1 for morphine; small morphine and metabolites (morphine 6-gucuronide) concentrations in colostrum during pain controlled analgesia (PCA) with morphine; oral bioavailability low; amounts of drug likely to be transferred to breastfed neonate negligible thus supporting safety of breastfeeding in mothers on IV PCA with morphine	[203]
Meperidine	Randomized clinical trial of meperidine versus morphine; on third and fourth day of life, infants in morphine group significantly more alert and oriented compared to meperidine group; in meperidine group, neurobehavioral delay and sedation noted from half-life of metabolites (normeperidine); 54% oral bioavailability; M:P ratio is 1:1.4; relative infant dose is 1	[204]
Methadone	Relative infant dose is 0.24–0.83; M:P ratio is 1:5.6; breastfeeding is safe but does not deliver enough drug to prevent withdrawal	[205,206]
Nonsteroidal antiinflammatory drugs		
Aspirin	49%–70% protein bound; M:P ratio of 0.03–1; reported one case of metabolic acidosis; give with caution	[207,208]
5-ASA and metabolite Ac-5-ASA	Study of 13 lactating women; low concentration in milk; infant receives <15 mg Ac-5-ASA daily by breastfeeding; no risk to newborn	[209]
Acetaminophen	0–25% protein bound; M:P ratio is 0.2–1.9; safe for breastfeeding	[210]
Ibuprofen	Relative infant dose is 0.6; no detected adverse effects in infant; more than 80% oral bioavailability; 99% protein bound; M:P ratio is 0.01; no detected adverse effect in infant; safe during breastfeeding	[211]
Indomethacin	Cohort study of 16 mothers and 7 infants; M:P ratio of 0.37; relative infant dose of 0.07% to 0.98% of maternal dose; no adverse effects reported in infants	[212]
Ketorolac	M:P ratio from 0.015–0.037; on a weight-adjusted basis, infant dose equivalent to approximately 0.16%–0.40% of total daily maternal dose and dose too low to affect infant	[213]

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Table 2 (*continued*)

Drugs	Reported findings in infant	Reference
Naproxen	Relative infant dose is 3%; low potential toxicity in infant; drug has long half-life and may accumulate in infant; bleeding, diarrhea reported in one infant; short-term use acceptable; avoid chronic use	[214]
Sumatriptan	Used for migraine headache; M:P ratio from area under the curve = 4.9 (95% CI 4.1–5.7); relative infant dose is 3%–6.7% of maternal dose; because sumatriptan is usually administered as a single dose at infrequent intervals, low level of excretion in breast milk suggests that continued breastfeeding after its use will not pose a significant risk to the suckling infant	[215]
Propoxyphene and norpropoxyphene	M:P ratio of 0.417 for propoxyphene and 0.382 for norpropoxyphene; estimated amount consumed by newborn not likely to reach toxic plasma level	[216]
Antibiotics		
Ampicillin	Relative infant dose is 0.24%; 22% protein bound; M:P ratio of 0.01–0.58; safe; observed for changes in intestinal flora	[196,217]
Azithromycin	Relative infant dose of 5.8%; safe; observe for change in intestinal flora	[218]
Aztreonam	Distribution into milk to concentration between 0.4 and 1 μg/mL by 6 h after administration; no side effect observed	[219]
Cefpirome	Consistently <5% in breast milk; safe	[220]
Cefprozil	M:P ratio is 0.05–5.67; 90% oral bioavailability; single dose pharmacokinetics studied in nine infants; at highest concentration of 3.36 μg/mL in milk, infant exposure is 3 mg/d; safe	[221]
Ceftibuten	Single and multiple dose pharmacokinetic study shows negligible levels in breast milk; safe	[222]
Ceftriaxone	M:P ratio is 0.03–0.04; acidic and highly protein bound (60%–95%); relative infant dose is 0.9%; safe	[223]
Chloramphenicol	53% protein bound; M:P ratio is 0.05–0.73; best avoided in breastfeeding because of potential for idiosyncratic reaction	[224]
Ciprofloxacin	Relative infant dose is 2.6%; oral dose concentrated in breast milk at levels higher than serum; possibly safe but one case of pseudomembranous enterocolitis reported; American Academy of Pediatrics considers ciprofloxacin usually compatible with breastfeeding, but little is known about long-term use; mothers should consider expressing and discarding breast milk so that breastfeeding can be resumed when antimicrobial prophylaxis is completed	[225–228]
Ciprofloxacin, ofloxacin, pefloxacin	Relative infant dose of ofloxacin is 3.2; two pharmacokinetic studies of cipro, oflo, or pefloxacin after termination of pregnancy; quinolones penetrate placenta and found in amniotic fluid at low concentrations and at much higher levels in breast milk; because of potential for	[229]

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Table 2 (*continued*)

Drugs	Reported findings in infant	Reference
Ciprofloxacin, ofloxacin, pefloxacin	quinolones to cause arthropathy in juvenile animals, use should be avoided in pregnant and lactating women	
Clindamycin	Relative infant dose is 1.4%; 93.6% protein bound; M:P ratio is 0.1–3; probably safe but observe changes in intestinal flora; pseudomembranous colitis reported in one infant	[230,231]
Cloxacillin	Relative infant dose is 0.8%; safe; observe for changes in intestinal flora	[232]
Erythromycin	Relative infant dose is 1.4%; 66% protein bound; M:P ratio is 0.02–1.6; safe; observe for change in intestinal flora; hypertonic pylorus reported in one case	[233]
Fleroxacin	Single dose pharmacokinetic study (n = 7); in breast milk, mean of 3.5 mg/L reached 2.6 h after drug administration; cumulative excretion in milk only 0.219 mg within 48 h	[234]
Gentamicin	Multiple dose cohort; protein binding is 0–30%; M:P ratio of 0.4–2.1; relative infant dose is 2.1%; multiple dose cohort study (n = 10) showed drug transferred into breast milk and detectable in half of nursing newborns; poor oral bioavailability; no adverse effect reported	[235]
Isoniazid	Relative infant dose is 13.5% of maternal dose; caution and monitor infant for liver toxicity; no report of hepatotoxicity in infants	[236]
Metronidazole	Relative infant dose is 9.9% to 29% of maternal dose; M:P ratio is 0.4–1.8; in vitro mutagen; American Academy of Pediatrics recommends temporary discontinuance of breastfeeding during treatment	[237]
Minocycline	Case report: discoloration of breast milk 3 wk after start of oral treatment for acne vulgaris; histochemical analysis revealed pigment particles within macrophages with iron staining characteristics; pigment ? iron chelate of minocycline or one of its derivatives	[238]
Nitrofurantoin	Case report: four lactating women; single-dose pharmacokinetic study; relative infant dose is 6% of maternal dose; milk:serum ratio of 6.21:2.71; actively transported into human milk, with concentrations in milk exceeding those in serum; concerns for suckling infants or infants with G6PD deficiency or sensitivity to nitrofurantoin	[239,240]
Phenoxymethylpenicillin (PMP)	Case control: higher rates of appearance and disappearance of PMP in breast milk of mastitis patients versus healthy controls	[241]
Penicillin	Relative infant dose is 0.24%; 60% protein bound; M:P ratio is 0.016–0.37; weak acid and excreted into breast milk in small amounts; allergic sensitization or reaction in previously sensitized infants; disruption of gastrointestinal flora	[196]
Sulbactam	Multiple intravenous doses pharmacokinetic study; concentration in breast milk averaged 0.5 μg/mL, similar to several beta-lactam antibiotics; no adverse effects noted in infant	[242]

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Table 2 (*continued*)

Drugs	Reported findings in infant	Reference
Sulfisoxazole	88% protein bound; M:P ratio is 0.06–1; caution in G6PD deficient and jaundiced infants	[243]
Vancomycin	Relative infant dose is 6.6% of maternal dose; M:P ratio is approximately 1.0; 10%–55% is protein bound; oral bioavailability is low; safe in breastfeeding	[244]
Tetracycline	Relative infant dose is 1.35%; M:P ratio is 0.2–1.5; low bioavailability in milk; American Academy of Pediatrics reports negligible absorption by infant and no untoward effect	[245]
Antifungals		
Ketoconazole	Case report: infant exposure in human milk approximately 0.4%–1.4% of dose expected from therapeutic doses given directly to infants; potential risk of adverse reactions from low exposure level is outweighed by benefits of breastfeeding; caution in young infants with poor renal function or on cisapride because of potential drug interaction	[246]
Fluconazole	Relative infant dose is 17%; no untoward effects report in breastfed infants; if dose is high, caution in young infants with poor renal function	[247,248]
Antivirals		
Acyclovir	Low concentrations in milk (4.16–5.81 μg/mL); M:P ratio is 3.24; relative infant dose is 1.1% of maternal dose; no adverse effects; safe	[249–251]
Interferon-alpha	Case report: one case report of mother on massive intravenous dose for malignant melanoma (30 million IU); concentration in human milk only slightly elevated (1551 IU/mL) when compared to control milk (1249 IU/mL); data suggest that even with high doses, interferon is probably too large in molecular weight to transfer into human milk in clinically relevant amounts	[252]
Anthelminthics		
Praziquantel	Currently listed as pregnancy category B by Food and Drug Administration (ie, drug presumed safe based on animal studies); however, interpreted by national programs and WHO to exclude lactating and pregnant women from treatment; some experts advocate excluding adolescent girls from mass treatment campaigns over this issue; requires further study because of high risk of untreated schistosomiasis	[253]
Anti-leprosy		
Clofazimine	Pharmacokinetic study: eight leprosy patients (50 mg daily or 100 mg on alternate days) for 1–18 mo in early lactating phase; amount of drug ingested by infants 0.199 + 0.013 mg/kg/day or 22.1 + 1.9% of maternal dose	[254]

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Table 2 (*continued*)

Drugs	Reported findings in infant	Reference
Antimalarials		
Chloroquine, hydroxychloroquine	Six subjects who were administered chloroquine phosphate (5 mg/kg) postpartum had chloroquine milk levels of 0.192–0.319 μg/mL; milk:blood ratio ranged from 0.268–0.462; data on secretion of hydroxychloroquine in breast milk of patients on steady-state therapy are minimal, and further studies are required	[255]
Chloroquine, dapsone, and pyrimethamine	Single dose pharmacokinetic study: M:P ratio from 1.96–4.26 for chloroquine, 0.22–0.45 for dapsone, and 0.46–0.66 for pyrimethamine; relative infant dose is 4.2% for chloroquine, 14.3% for dapsone, and 45.6% for pyrimethamine over a 9-day period	[256]
Anticoagulants		
Dalteparin	Clinical trial: 15 lactating mothers on routine subcutaneous (SQ) injection of 2500 IU; anti-Xa activity (as an index of low molecular weight heparin or LMWH activity) of 0.074 to 0.308 IU/mL in plasma and <0.005–0.037 IU/mL in breast milk; equivalent to a M:P ratio of <0.025:0.224; unlikely that thromboprophylaxis with LMWH has effect on nursing infant	[257]
Danapiroid	Case report: patient with deep vein thrombosis treated with SQ twice-daily danaparoid; no anti-Xa activity in breast milk noted	[258]
Dicumarol	Review: no demonstrable alterations in coagulation profiles or adverse clinical effects in 125 breastfed infants	[259–261]
Enoxaparin	Breastfeeding safe in case of maternal treatment with enoxaparin	[262,263]
Pheninedione	Case report: increased prothrombin and thromboplastin time in one infant	[264]
Anticonvulsants		
Carbamazepine	Relative infant dose is 2.3% of maternal dose; M:P ratio of 0.6; no effect of medication on breastfed infants	[265–267]
Lamotrigine	Cohort study: nine mothers with epilepsy (10 newborns); excreted in considerable amount in breast milk (estimated dose >0.2–1 mg/kg/d), which in combination with a slow elimination may result in plasma concentrations comparable to what is reported during active therapy; no adverse effects observed in infants, however	[268,269]
Phenobarbital	Relative infant dose is 24% of maternal dose; milk concentration may be significant; observe for sedation; infantile spasms after weaning from milk containing phenobarbital	[270]
Phenytoin	Relative infant dose of 7.7%; M:P ratio of 0.13; average milk concentrations are low; dose obtained in breast milk is less than 5% of infant dose; report of methemogloginemia in one infant	[271]

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Table 2 (*continued*)

Drugs	Reported findings in infant	Reference
Primidone	Sedation, feeding problems	[272,273]
Topiramate (TPM)	Cohort study: five mothers with epilepsy; free passage of drug into breast milk; breastfed infants had low TPM concentrations, and no adverse effects observed	[274]
Valproic acid	Relative infant dose is 1.6% of maternal dose; milk concentrations low (0.4–3.9 μg/mL) compared to maternal dose; no untoward effect	[275,276]
Antidepressants/anxiolytics		
Alprazolam	Cohort study: eight lactating mothers; observed M:P ratio of 0.36 + 0.11	[277]
Citalopram	Clinical trial: case (n = 11)-control (n = 10) study; concentrations in milk two to three times more than with maternal plasma, but infant plasma concentration low or undetectable; delivery outcome and neurodevelopment of all infants up to 1 y normal; need to monitor infant	[278]
Citalopram, demethylcitalopram	Clinical trial (n = 7): plasma concentration of both drugs low or absent; no adverse effects; mean combined dose of citalopram and demethylcitalopram transmitted to infants < 10% notional level of concern; however, one case report of sleep problem in infant that normalized when dose was halved or replaced with formula	[279–281]
Fluoxetine, norfluoxetine	Clinical trial: pharmacokinetic study; relative infant dose to fluoretine and norfluretine was 2.4% and 3.8% of maternal weight-adjusted daily dose, respectively; pregnancy outcome, growth and development of all infants to 1 y normal; reported cohort study of reduced growth curves for first 6 months in infants; colic, irritability, feeding and sleep disorder reported	[282–284]
Moclobemide	Single-dose pharmacokinetic study: six lactating white women; active metabolite only detected in plasma; concentrations of drug in milk highest at 3 h after drug administration and not detectable after 12 h; metabolite not detected in any milk sample; relative infant dose is 1% of maternal dose; low excretion into breast milk; unlikely to be hazardous to breastfeeding infants	[285]
Nefazodone	Case report: drowsiness, lethargy, poor feeding in infant; resolved after breastfeeding discontinued	[286]
Paroxetine	Multiple-dose pharmacokinetic study: breast milk concentrations highly variable (2–101 ng/mL) and present in all breast milk samples (n = 108); greater concentration in hindmilk than in foremilk; M:P ratio of 0.39–1.11; relative infant dose of 0.7%–2.9%; none to low detectable drug in serum of nursing infants; no observable adverse effects	[287,288]
Sertraline	Multiple dose pharmacokinetic study (n = 26); M:P ratio is 0.42–4.81; high concentration in hindmilk 8–9 h after maternal ingestion; discarding breast milk after maternal dose decreased infant daily dose by a mean of 17.1% (1.8%); no observed adverse effect in infant	[289]

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Table 2 (*continued*)

Drugs	Reported findings in infant	Reference
Venlafaxine	Multiple-dose pharmacokinetic study: nine women; concentrations of venlafaxine in breast milk 2.5 times those in maternal plasma; relative infant dose is 6.4%; no adverse effect in infants	[290]
Zopiclone (Cyclopyrrolone)	Single-dose pharmacokinetic study: 12 lactating women; relative infant dose approximately 1.4% of maternal dose	[291]
Vigabatrin	M:P ratio <1; relative infant dose of 3.6%	[292]
Antipsychotics		
Lithium	Relative infant dose is 56% of maternal dose; M:P ratio is 0.24–0.66; severe sedation in some infants; mandatory monitoring of milk and infant serum concentration; plasma levels from 0.5–0.3 of maternal levels	[293,294]
Benzodiazepines		
Diazepam	Relative infant dose of 3%–4.7% of maternal dose; M:P ratio of 0.2; sedation in infant has been reported; avoid prolonged exposure; in one study, diazepam could not be detected in the infant's plasma, but low levels of N-desmethyldiazepam (20 and 21 μg l-1), temazepam (7 μg l-1) and oxazepam (7.5 and 9.6 μg micrograms l-1) were present	[295–297]
Lorazepam	Relative infant dose is 2.8% of maternal dose; no untoward effect in infant; full-term neonates whose mothers had received oral lorazepam had no complications apart from slight delay in establishing feeding	[298]
Midazolam	Relative infant dose is 0.% of maternal dose; M:P ratio is 0.6; low milk concentration; no untoward effect in breastfeeding	[299]
Antidiabetics		
Oral antihyperglycemic agents	Review: use of four group derivatives of sulfonylyrea, biguanides, glucosidase inhibitors, and thiazolidinediones; little clinical data on exposure to oral antihyperglycemic agents via breast milk and potentially serious effect of neonatal hypoglycemia; safest recommendation is not to breastfeed while taking oral antihyperglycemic agents	[300]
Metformin	Cohort study: seven lactating mothers; median dose 1500 mg orally daily; relative infant dose in milk only 0.28% of maternal dose; drug present in low or undetectable concentrations in plasma of infants; safe; no adverse effects	[301,302]
Antihypertensives and other cardiovascular drugs		
Atenolol (beta-blocker)	90% protein bound; M:P ratio is 1.3–6.8; relative infant dose is 6.6%–18.9%; in one case report, infant developed cyanosis, hypothermia, and bradycardia; caution recommended with use in breastfeeding	[303–306]
Methyldopa	1%–16% protein bound; M:P is 0.19–0.34; relative infant dose is 1.4%; safe; observe for hypotension, gynecomastia	[307,308]

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Table 2 (*continued*)

Drugs	Reported findings in infant	Reference
Digoxin	M:P ratio of 0.6–0.7; only approximately 3% of therapeutic drug levels reached in baby; digoxin accumulation in toxic concentrations should not occur in infant	[309]
Nifedipine	90%–98% protein bound; excretion into human milk insignificant (<5% of a therapeutic dose); relative infant dose of 1%–2%, 4%; safe; infant dose low	[310,311]
Nitrendipine	Case series study: three lactating women; M:P ratio of 0.2–0.5; low concentrations in breast milk; relative infant dose of 0.09%; Safe in breastfeeding	[312]
Quinapril	Controlled clinical trial; single-dose pharmacokinetic study of six lactating women; M:P ratio for quinapril 0.12; relative infant dose is 1.6% of maternal dose; safe for breastfeeding	[313]
Labetolol	45%–55% protein bound; M:P ratio is 0.4–2; relative infant dose of 0.6%; safe; observe for hypotension, bradycardia	[196,314]
Propranolol	87% protein bound; M:P ratio of 0.05–2; relative infant dose of 0.2; safe; observe for hypotension and bradycardia	[196,315,316]
Captopril	30% protein bound; M:P ratio of 0.006–0.6; relative infant dose of 0.01; safe; caution early postpartum; otherwise safe	[317]
Chlorthiazide	75% protein bound; M:P ratio of 0.03–0.05; safe	[318]
Flecainide	Antiarrhythmic drug; M:P ratio of 2.3±1.0 at 24 h after dose; newborn infant consuming all daily milk production of its mother is not expected to exceed approximately 62 ng/mL; risk to suckling infant low	[319]
Antirheumatics		
Celecoxib	Case report: breast milk concentration of 133 ng/mL at 5 h after a 100-mg dose; elimination half-life of 4–6.5 h	[320]
Indomethacin	Cohort study: 16 mothers and 7 infants; M:P ratio of 0.37; relative infant dose of 0.07% to 0.98% of maternal dose; no adverse effects reported in infants	[212]
Gastrointestinal drugs		
Cimetidine	Single-dose pharmacokinetic study: 12 healthy volunteers; relative infant dose was 6.7% of maternal dose; seems to be safe under normal conditions	[321]
Nizatidine (H_2 receptor antagonist)	Single and multiple dose pharmacokinetic studies: five nonlactating and five lactating women; breast milk concentration proportional to maternal serum concentration; on average < 0.1% of maternal dose, secreted into milk during a 12-hour interval after either single or multiple doses	[322]
Omeprazole	Case report: no apparent adverse fetal effects and patient continued 20 mg/d while breastfeeding; peak concentration in breast milk of 58 nM, 3 h after ingestion, which was <7% of peak serum concentration (950 nM at 4 h), indicating minimal secretion	[323]

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Table 2 (*continued*)

Drugs	Reported findings in infant	Reference
Hormones and contraceptives		
Depo-Provera	Children exposed to injectable contraceptive Depo-Provera during pregnancy (n = 1207), or breastfeeding (n = 1215); weights and heights for all children and information on signs of puberty obtained for children aged 10 and older; cross-sectional weight and height by age of Depo-Provera-exposed children similar to those for controls; children with Depo-Provera exposure showed an increased risk of suboptimal growth in height, defined as <2 Z scores on NCHS standards (RR = 1.4, 95% CI 1.2–1.8); however, after adjustment for socioeconomic factors, no increased risk of impaired growth among Depo-Provera-exposed children (RR = 1.1, 95% CI 0.8–1.6); with exception of a delay in onset of reported pubic hair growth among Depo-Provera-exposed girls, no significant effects on attainment of puberty; use of Depo-Provera during pregnancy or breastfeeding does not adversely affect long-term growth and development of children	[324]
Desogestrel	Controlled clinical trial, nonrandomized; desogestrel 75 μg/d group (n = 42) versus copper-bearing intrauterine device group (n = 41); transfer of etonogestrel to breast milk studied in a subgroup of desogestrel users; no significant differences between desogestrel and intrauterine device groups in composition and quantity of breast milk or in growth and development of children to age 2.5 y; desogestrel group with slightly higher incidence of mild adverse experiences of a hormonal nature reported among mothers and infants; seems to be a safe and effective contraceptive method for lactating women	[325]
Drospirenone	Single-dose (93 mg Drospirenone + 30 μg ethynylestradiol) pharmacokinetic study in nine lactating women; maximum Drospirenone concentrations in serum and breast milk amounted to 30.8 + 14.4 and 13.5 + 11.7 ng Drospirenone/mL in serum and breast milk; M:P ratio of Drospirenone increased from 0.16–0.57 within 2 h after dosing and decreased to 0.16 after 24 h; average M:P ratio at 48 h of 0.23 + 0.09; relative infant dose of 0.02% of maternal dose; no adverse events reported	[326]
Elcometrine	Controlled clinical trial: 66 lactating mothers versus 69 women using intrauterine device; no significant differences in growth and development among infants in two groups; no significant differences between concentration of elcometrine in mother's blood and milk; blood levels of elcometrine in infants nearly undetectable and significantly lower than levels in maternal blood or milk (P <0.01)	[327]
Levonorgestrol (Norplant)	Clinical, nonrandomized trial: 220 breastfed infants in Norplant group and 222 infants in copper intrauterine device group; breastfeeding pattern and infant growth similar in both groups; in first year breastfed infants in	[328–332]

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Table 2 (*continued*)

Drugs	Reported findings in infant	Reference
	Norplant group had higher incidence rates (P <0.05) of mild episodes of respiratory infections (adjusted RR 1.17, CI 1.08–1.27), skin conditions (adjusted RR 1.46, CI 1.20–1.79), and eye infections (unadjusted RR 1.49, CI 1.03–2.18) than control group	
Nesterone	Clinical trial: 100 women of Nesterone subdermal implant versus copper intrauterine device (n = 100); no effect on lactation and infant growth; no serious adverse events; Nesterone concentration in breast milk 54–135 pmol/L; safe in breastfed infants because steroid is inactive by the oral route	[333]
Nomegestrol acetate (Uniplant)	Clinical, nonrandomized trial of Uniplant (n = 120) versus intrauterine device (n = 120); no significant difference between two groups in infant weight, weight gain per day, or infant linear growth; no significant differences in incidence of health problems in both groups; there were seven infant deaths, six in Uniplant group	[334]
Immunosuppressives		
Cyclosporine	Case report: M:P ratio of 0.84, but undetectable levels in infant; infant grew and developed normally; in another study (n = 7), breastfed infants of mothers treated with CsA received <300 μg/d and absorbed undetectable amounts; no demonstrable nephrotoxic effects or other side effects	[335,336]
Tacrolimus	Prospective cohort: 21 female liver recipients treated during pregnancy; on day of delivery, mean concentrations of 1.5, 0.7, and 0.5 ng/mL in maternal, cord, and child plasma, and 0.6 in breast milk specimens; infants with 36% incidence of transient perinatal hyperkalemia (K^+ >7 mEq/L) and mild reversible renal impairment, thought to reflect in part maternal homeostasis; all 25 babies had satisfactory postnatal growth and development	[337]
Cough/cold medicines and antihistamines	Review: overall, few data from human studies on use of antihistamines, decongestants, and cough products during breastfeeding; studies of pseudoephedrine, triprolidine, and loratadine in humans conclude that low levels of each drug would reach a breastfed infant; triprolidine and pseudoephedrine considered compatible with breastfeeding (should be first-line choices); codeine compatible with breastfeeding and is an acceptable choice for short-term use as a cough suppressant; many liquid cough and cold medicines contain alcohol; many combination products mixture of an antihistamine and a decongestant and may contain aspirin, acetaminophen, ibuprofen, or caffeine; preferable for nursing mothers to only take medications that are necessary and avoid such combination products; The American Academy of Pediatrics considers alcohol, acetaminophen, ibuprofen, and caffeine compatible	[338]

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Table 2 (*continued*)

Drugs	Reported findings in infant	Reference
Cough/cold medicines and antihistamines	with breastfeeding; aspirin has been associated with significant negative effects on some nursing infants, and the American Academy of Pediatrics recommends giving aspirin to nursing mothers with caution; mothers taking cough/cold products should watch for adverse events in their breastfed infants; infants may experience paradoxic central nervous stimulation from antihistamines, irritability, and insomnia from decongestants	
Terfenadine	Multiple-dose pharmacokinetic study: four lactating mothers 60 mg Terfenadine every 12 h × 48 h; terfenadine not detected in milk or plasma; metabolite M:P ratios 0.12–0.28; newborn dosage estimates suggests maximum newborn exposure not >0.45% of recommended maternal weight-corrected dose; estimated amounts consumed by neonate not likely to result in plasma levels producing untoward effects	[339]

Drugs of specific concern for the breastfed infant

The American Academy of Pediatrics publishes periodic updates on the transfer of drugs and other chemicals in human milk because of the advent of new medications in the formulary [340]. Certain classes of drugs deserve mention because of their potential toxicity in infants. Cytotoxic and immunosuppressive drugs, such as cyclophosphamide, cyclosporine, doxorubin, and methotrexate, may interfere with cellular metabolism of the nursing infant and are potentially harmful. Drugs of abuse, such as amphetamine, cocaine, heroin, marijuana, and phencyclidine, should not be used by the breastfeeding mother because of the hazards to the health of the mother and her infant. If used, radioactive compounds, such as copper 64, gallium 67, indium 111, iodine 123, 125, 131, radioactive sodium, and technetium 99, should be an indication to withhold breastfeeding temporarily. Certain classes of drugs have been classified as drugs of concern, particularly when given for a prolonged period. These drug classes include antianxiety, antidepressant, and antipsychotic drugs (Table 2). Although most of these drugs have low concentrations in breast milk and few case reports of adverse effects in infants, psychotropic drugs, by virtue of their mechanism of action, could affect short- and long-term development and function of the central nervous system of an infant.

Caffeine, nicotine (smoking), and alcohol are drugs of special category. As a rule, smoking should be discouraged in the breastfeeding mother because of its inherent hazard to her health. The milk-to-plasma ratio of nicotine is 1.5 to 3, but so far there has been no evidence that this concentration is a health risk to the infant. One study reported that infants of women who continued to smoke while breastfeeding had lower incidence of respiratory illness compared with bottle-fed infants of smoking women. Breastfeeding and smoking may be less detrimental to the infants than smoking and bottle feeding. For this reason, the American

Academy of Pediatrics has revised its previous position on nicotine as a contraindicated drug for breastfeeding and has not categorized nicotine into any specific drug for caution. It is strongly hoped that breastfeeding per se may be enough motivation for a mother to stop smoking.

Summary

In general, drugs that are taken by a mother during pregnancy or after birth may be transferred to the fetus or her infant (through breastfeeding). Many factors are involved that determine the amount of drugs that are transferred and their potential effects on the fetus or infant. A careful assessment of the risk versus benefit is necessary and should be individualized. In the breastfed infant, many measures can be undertaken so that the amount of drug transferred to the infant is minimized.

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