Reviewed by

Drugs affecting breast milk and lactation

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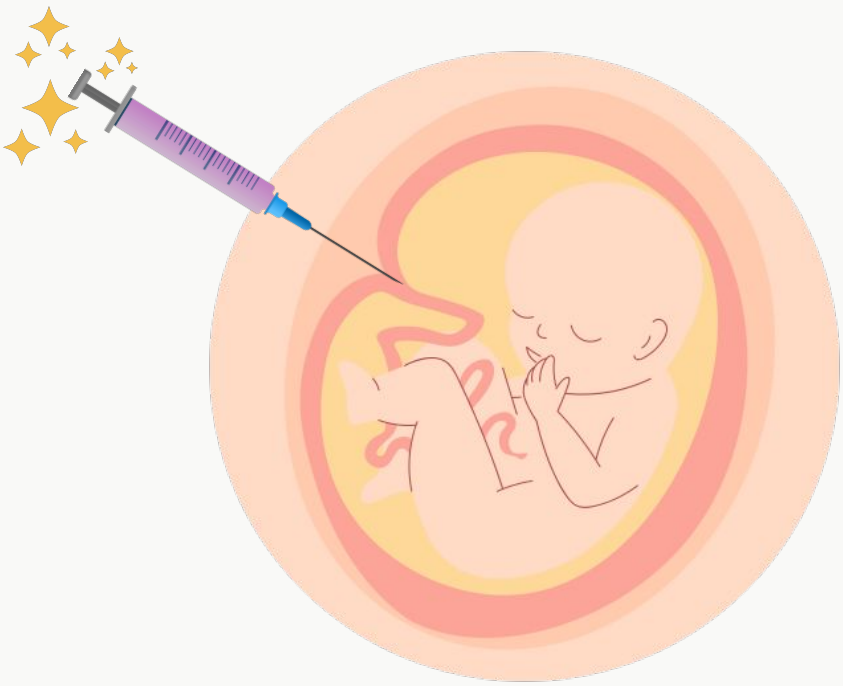


- Main text
- Male slide
- Female slide
- Important
- Dr, notes
- Extra info

EDITING FILE

Objective

- Recognize the main pharmacological characteristics that affect the passage of drugs to breast milk.
- Identify the adverse effects of major pharmacological categories on breast fed baby.
- Describe the best and safest medication during breastfeeding in cases of epilepsy, infections , diabetes, heart failure, hypertension.
- Know drugs that can inhibit lactation.
- Know drugs that may enhance lactation.

Drugs & Lactation

Lactation

- Breastfeeding is very important because breast milk is the healthiest form of milk for babies.
- It provides the baby with immunoglobulins (IgA, IgM) that are essential for protection against gastroenteritis.
- Monoclonal antibodies, pass very poorly into milk after the first 1st week postpartum.

Drugs & Lactation

- The epithelium of the breast alveolar cells is most permeable to drugs during the 1st week postpartum, so drug transfer to milk may be greater during the 1st week of infant's life.
- Drugs ingested by the mother diffuse or are transported from the maternal plasma to the alveolar cells of the breast.
- The concentration of drugs achieved in breast milk is usually low (<1%).
- However, even small amounts of some drugs may be of significance for the suckling child.
- Number of drugs are absolutely **contraindicated**.
- Some drugs may **increase or decrease** milk yield.

Pharmacokinetics

Compared to adults neonates have:

Higher	Lower
↑Gastric pH (↓Gastric acid output) ↑Gastric emptying time ↑Concentration of free drug ↑Percentage of body water	↓Serum albumin ↓Efficiency of renal clearance (↓ renal blood flow & GFR) ↓Rate of metabolism Due to immaturity of liver enzymes ↓Percentage of adipose tissue

Premature babies have very limited capacity for metabolism & excretion.

Factors controlling passage of drugs into breast milk

Drug related factors

- Molecular weight
- Lipid solubility
- Degree of ionization
- Drug pH
- Protein binding
- Half-life
- Oral bioavailability

Metrenal factors

- Dose of drug
- Route of administration
- Time of breastfeeding (& drug administration)
- Health status
- Maternal concentration of drug

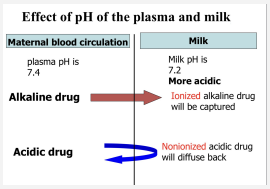
Infant factors

- Age
- Body weight
- Health status

Factors Controlling Passage of Drugs into Breast Milk

A. factors related to the drug

Molecular weight	• **Very small molecules** (<200 daltons) such as alcohol, **equilibrate rapidly** between plasma & breast milk via the aqueous channels surrounding alveoli (more transfer).
	• **Large molecules drugs** (> 800 daltons) are **less likely to be transferred to breast** milk.
	  ○ Insulin: MW > 6,000 daltons(ability to be excreted in milk are limited due to ↑MW)
	  ○ Heparin: MW = 40,000 daltons (ability to be excreted in milk are limited due to ↑MW)
	Aim: ↑Molecular Weight**

Plasma proteins binding	• Drugs circulate in maternal circulation in unbound (free) or bound forms to albumin. • **Only unbound** form gets into maternal milk. • definition of good plasma protein is > 90% binding (e.g. Warfarin). **Aim**: ↑Plasma protein binding.**
Degree of ionization	• Ionized form of drugs are less likely to be transferred into breast milk. ○ Heparins (Charged and ↑ MW) pass poorly into breast milk. **Aim**: ↑Polarity→ ↑water solubility (Does't cross easily)**
Volume of distribution	Transfer of drugs from maternal blood to milk is low with drugs that have large volume of distribution (↑VD=↑ tissues, ↓in blood of the mother= ↓to milk) **Aim**: ↑Volume of distribution.**
Lipid solubility	Lipid-soluble drugs pass more freely into the breast milk than water-soluble drugs. Aim: ↓lipid solubility**
Drug PH 	• pH of milk (7.2) is slightly more acidic than maternal blood (7.4). • **Weak basic drugs tend to concentrate in breast milk & become trapped secondary to ionization.** • Weak acidic drugs don't enter the milk to a significant extent and tend to be concentrated in plasma. • [Base + acid → ionization: if a basic drug passes through alveoli then interacts with the acidic milk, it will be ionized (trapped) & harder to return to maternal circulation, hence, excreted in milk]. **Aim: ↑ acidity of drug****
Half-life	• Avoid the use of drugs with long half-lives; short half-lives are preferable. • Oxazepam (short half-life) vs Diazepam (long half-life). **Aim: Short half-life****

B. Factors related to the mother

Route of Administration *(topical > oral > injection)*	• Route of administration affects the concentration of the drug in maternal blood. • Maternal use of topical preparations (creams, nasal sprays, inhalers) is expected to carry less risk to a breastfed infant than systemically administered drugs.
Time of breastfeeding	• The concentration of the drug in the milk at the time of feeding. • Lactating mother should take medication just **after nursing** and **3-4** hours before the next feeding (to allow time for drug to be cleared from the mother's blood–drug concentration in milk will be low *"after the ½ life"*).
Health status	**Breastfeeding is contraindicated in case of:** • HIV-positive women • Active, untreated TB in mother • Herpes on breast • Use of illegal drugs by mother • Certain medications used on chronic basis

Factors Controlling Passage of Drugs into Breast Milk

C.factors related to the infant

Age	**Pediatric population is classified into:**
	• **Newborn:** less than 1 month
	  ○ **Preterm neonates** (more sensitive)**:** born before 38 weeks of pregnancy
	  ○ **Full-term neonates:** 38-42 weeks of gestational age
	• **Infants (babies)**: 1-12 months
	• **Children**: 1-12 years
	• **Adolescents**: 13-18 years

Health status	**Special caution is required in:** • Premature infants. • Low birth weight. • Infants with G6PD deficiency. • Infants with Impaired ability to metabolize/excrete drugs (e.g. hyperbilirubinemia)

Neonatal Hyperbilirubinemia

Premature infants or **infants with inherited G6PD deficiency** are susceptible to oxidizing drugs that can cause → RBC hemolysis → ↑ bilirubin (hyperbilirubinemia) → kernicterus (irreversible brain damage).
Any drug that displaces bilirubin from albumin → ↑ free bilirubin → kernicterus
Examples for oxidizing drugs:
- **Antibiotics**: Sulfonamides, Trimethoprim
- **Antimalarials**: Primaquine

Neonatal Methemoglobinemia

- **Infants under 6 months** of age are particularly prone to develop methemoglobinemia upon exposure to some oxidizing drugs.
- **Methemoglobin** is an oxidized form ferric [Fe3+] of hemoglobin that has decreased affinity for O2 → tissue hypoxia.

The amount of a drug to which the baby is exposed as a result of breastfeeding depends on:

- The **amount** of milk consumed.
- The **amount** of drug absorbed from the GIT.
- The **ability** of the baby to eliminate the drug.

Characteristics of Drugs Safe in Lactation (summary)

- Route of administration (Local or topical e.g. inhalation) instead of an oral form.
- Short acting.
-**Ionized drug** (non-ionized can pass)
-**Acidic drug** (high pH "basic" can be trapped)
- Highly protein bound (the drug will be trapped in the mother's circulation)
- Low lipid solubility (water soluble drug)
- Poor oral bioavailability
- No active metabolites.
- **High** molecular weight.
- Well-studied in infants.

General considerations

- Infants should be monitored for ADRs (e.g. feeding, sedation, irritability, rash).
- Drugs with no safety data should be avoided or lactation should be discontinued.
- Drugs known to have serious toxic effects in adults are avoided.
- Do not guess; use reliable sources.

Drugs **Contraindicated** in Lactation:

Only few drugs are totally contraindicated:

- **Anticancer drugs**: (cytotoxicity & neutropenia) Doxorubicin, Cyclophosphamide, Methotrexate.
- **Radiopharmaceuticals**: Radioactive Iodine.
- **CNS acting drugs** (due to their high lipid solubility) : Amphetamine, Heroin, Cocaine.
- **Immunosuppressants**: Cyclosporine.
- **Alcohol & Lithium** (high milk-to-plasma ratio).
- **Chloramphenicol** (bone marrow suppression).
- **Atenolol** (CVS drugs "risk of bradycardia & hypoglycemia").
- **Potassium iodide** (thyroid effect).
- **Ergotamine** (for migraine headaches; causes vomiting, diarrhea, convulsions in infants).
- **Tobacco smoke** (nicotine can cause vomiting, diarrhea & restlessness for the baby, decreased milk production and increase the incidence of respiratory & ear infections).

Drugs Affecting Milk Supply

Increase Lactation	Suppress Lactation
Drugs that: ↑Prolactin.	Drugs that: ↓ Prolactin.
Dopamine antagonists: **Stimulate prolactin secretion & galactorrhea.** • **Metoclopramide** (antiemetic). • **Domperidone** (antiemetic). • **Haloperidol** (antipsychotic). • **Methyldopa** (antihypertensive). • **Theophylline** (used in asthma).	• **Levodopa** (dopamine precursor). • **Bromocriptine** (dopamine agonist). • **Estrogen & combined oral contraceptives** that contain high-dose of estrogen & progestin. • **Androgens.** • **Thiazide diuretics.**

Drugs of Choice in Lactation

Antibiotics	• Cephalosporins.	• Penicillins.
Antidiabetes	• Insulin.	• Oral antidiabetics.
Anticoagulants	• **Heparin.**	• **Warfarin.**
Analgesics	• Acetaminophen (Paracetamol).	
Antithyroid drugs	• **Propylthiouracil** is preferable over others.	
Anticonvulsants	• Carbamazepine	• Phenytoin
Oral contraceptives	• **Progestin-only pills (mini pills)** are preferred for birth control.	
Antiasthmatics	• Inhaled corticosteroids.	• Prednisone.

Drugs & Lactation

Group	Drugs that may be used ✓	Drugs that should be avoided ✕
Antibiotics Penicillins are the first choice.	• **Penicillins** (e.g. Ampicillin, Amoxicillin): no significant ADRs but mostly allergic reactions & diarrhea. • **Cephalosporins & Macrolides** (e.g Erythromycin, Clarithromycin): no significant ADRs but alterations to infant bowel flora.	• **Quinolones:** theoretical risk of arthropathies. • **Chloramphenicol:** grey baby syndrome. • **Sulfonamides** (Co-trimoxazole): hyperbilirubinemia - neonatal jaundice; should be avoided in premature infants or infants **with G6PD deficiency.** • **Tetracycline:** possible risk of teeth discoloration; absorption by the baby is probably prevented by chelation with milk calcium.
Sedatives (Hypnotics)	• **Benzodiazepines** (e.g Diazepam, Lorazepam): ○ Single use of low dose → probably safe ○ Prolonged use → lethargy & sedation in infants.	• **Barbiturates** (e.g Phenobarbitone): lethargy, sedation, & poor suck reflexes with prolonged use.
Antidiabetics	• **Insulin:** safe. • **Oral antidiabetics:** compatible. ○ **Metformin:** risk of **lactic acidosis**; use with caution while nursing newborns, premature infants and those with renal impairment.	

Drugs & Lactation (Cont.)

Group	Drugs that may be used ✓	Drugs that should be avoided ✕
Antidepressants	• **Selective Serotonin Reuptake Inhibitors (SSRIs):** Paroxetine is the preferred SSRI.	
Oral contraceptives	• **Progestin-only pills (mini pills):** preferred for birth control. • **Non-hormonal methods.**	• **Estrogens-containing pills:** ↓ milk quantity.
Antithyroid drugs	• **Propylthiouracil**: should be used rather than Carbimazole or Methimazole	• **Carbimazole, Methimazole, Potassium Iodide**: may suppress thyroid function in infants
Anticoagulants	• **Heparin:** safe; not present in breast milk. • **Warfarin:** can be used; very small quantities found in breast milk, **so monitor infant's prothrombin time during treatment.**	
Anticonvulsants	• **Carbamazepine:** preferable over others; compatible with breastfeeding • **Phenytoin:** amounts entering breast milk are not sufficient to produce ADRs	• **Valproic acid:** infants must be monitored for CNS depression, hepatotoxicity. • Lamotrigine: **avoid** **Lactation:** Use with caution. **Pregnancy:** Absolutely contraindicated due to proven teratogenicity.
Antihistamines	• **Non-sedating antihistamines** 2nd & 3rd gen (e.g. Loratadine): safe at lower doses	• **Sedating antihistamines** 1st gen (e.g. Diphenhydramine)
Analgesics	• **Paracetamol:** safe. • **Ibuprofen:** compatible.	• Aspirin, theoretical risk of reye's syndrome

Physiologic Differences between Neonates & Adults of Pharmacokinetic Importance

Pharmacokinetics Changes

Dr: numbers are not important	Neonates	Adults
Gastric acid output (mEq /10 kg/h)	0.15 ↓	2
Gastric emptying time (min)	87 ↑	65
Total body water (% of body weight)	78 ↑	60
Adipose tissue (% of body weight)	12 ↓	12-25
Serum albumin (g/dL)	3.7 ↓	4.5
GFR (mL/min/m2)	11 ↓	70

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