

Drug Use During Lactation

What we are looking for? 1- Drug effect on the production of milk.
2- If it cause toxic reaction or adverse reactions in the amount taken by the baby.

- Breast milk is the best form of nutrition for young infants.
- Mothers should breast feed exclusively for 6 months, and continue until at least 12 months while other foods are introduced.
- Breast milk provides all the energy and nutrients required for the first 6 months of life.

Breast feeding provides:

- 1) Protection of the infant against gastric, respiratory, and urinary tract infections.
 - 2) Reduction in the rate of obesity, and juvenile-onset diabetes mellitus.
 - 3) Reduction in the rate of atopic diseases.
- Adults who were breastfed as infants have lower blood pressure and lower cholesterol levels.

Maternal benefits of breast feeding include:

1. Reduced risk of developing pre-menopausal breast cancer.
2. Strengthening of the mother-infant bond. *تقوية العلاقة / يكون أقرب*

- Breastfeeding mothers frequently require treatment with drugs. *بعضهم مثل نورهام*
- There are few contraindications to breast feeding.
- Some mothers may self-medicate with over-the-counter medications, nutritional supplements and herbal medicines.
- Nursing mothers need advice about safe drug use during lactation to protect the infant from drug-related adverse effects, and to allow necessary maternal treatment.

Transfer of Drugs into Breast Milk:

هو شوية pharmacokinetics :

- Most drugs pass to breast milk to some extent, but breastfeeding may be continued in most cases. *السبب إنه يكون تركيز الدواء بالليب تليل وما يشكل خطورة مالم طفل*
- The drug dose ingested by the infant via breast milk only rarely cause adverse effects. *Most drugs enter breast milk, but in different concentrations*
- Almost all drugs enter milk by passive diffusion of un-ionized, protein un-bound drug through the lipid membrane of the alveolar cells of the breast. *hydrophobic / lipophilic*
- Factors affecting rate and extent of passive diffusion include maternal plasma drug level, physiological differences between plasma and milk, and physicochemical properties of the drug.
- Milk differs from blood in having lower pH (ranges from 6.8 - 7.0 vs 7.4 in serum), less buffering capacity, and higher fat content. *more acidic*
So, alkaline drugs that penetrate alveolar membranes and enter to breast milk will become ionized → trapped & accumulate → higher amount taken by the infant

Drug parameters affecting the extent of transfer into milk:

1. pKa:

- It determines drug ionization at a given pH. *According to Henderson - Hasselbalch equation (determine the proportion of ionized to un-ionized drug)*
- Highly ionized drugs tend NOT to concentrate in milk.
- For basic drugs (erythromycin), a greater fraction will be ionized at an acidic pH, so that the milk compartment tends to trap weak bases.
- Acidic drugs (penicillin) are more ionized at higher pH values and will be trapped in the plasma compartment.
- Drugs with higher pKa values generally have higher milk/plasma ratios. *↑ pKa = ↑ concentration in the milk (acidic)*

2. Protein binding:

- Drugs that are highly bound to plasma proteins (warfarin) are likely to be retained in the plasma, because there is lower protein content in milk (~1%). *[Albumin] in the plasma = around 5 gm/dL (%)*
Should not be given during pregnancy, but women who take warfarin can breastfeed
- Milk concentration of highly plasma protein-bound drugs is usually low.

3. Lipophilicity:

- Water-soluble drugs will NOT effectively cross the alveolar epithelium of the breast.
- CNS-active drugs usually cross to breast milk. → cross blood-brain barrier = hydrophobic/lipophilic

4. Molecular weight:

- Drugs with low molecular weight (<200 ^{daltons}) readily pass into the milk through small pores in the cell wall of alveolar cells. ⇒ irrespective of its lipophilicity or hydrophilicity
- Drugs with higher molecular weights cross cell membranes by dissolving in the lipid layer.
- Protein molecules (very large molecular weights > 6000 daltons) are virtually excluded from milk. (does not cross)
↳ include proteins/heparin & fractionated heparin

• Therefore, drugs that pass minimally to breast milk would be:

- 1) an acidic drug.
- 2) a drug with high plasma protein binding.
- 3) a drug with low-to-moderate lipophilicity. (most NSAIDs)



• Therefore, drugs that pass significantly to breast milk would be:

- 1) A basic drug.
- 2) A drug with low plasma protein binding.
- 3) A drug with relatively high lipophilicity. (sotalol)/benzodiazepines

- In the first few days of life, large gaps exist between alveolar cells that permit enhanced passage of drugs into milk. = more drugs pass
↳ physicochemical properties of the drug
- By the end of the first week, the gaps close under the influence of prolactin. = less drugs pass
- Colostrum is secreted in the first 2 days after birth and has high amounts of immunoglobulins, maternal lymphocytes, and maternal macrophages. = more thick & little in amount
- Greater amounts of drugs are present in colostrum but the amounts received by infants are low because of the low volume of colostrum produced.
- Some drugs are pumped ^(active transport) actively into breast milk, such as **iodides**, which pass into milk with high concentration. ↳ radio-active material
→ Women should not breastfeed if they take radio-active material for treatment of certain conditions

Assessing the Risk to the Infant:

Infant may damage thyroid gland
Adult hyper- hypo-thyroidism

Many factors should be considered:

1. **Inherent toxicity of the drug:** Antineoplastic drugs, radionuclides, and **iodine-containing compounds** would be of concern. ↳ may damage the thyroid of the suckling infant, because it will be taken actively to the thyroid

Agents Contraindicated During Lactation Because they are Hazardous to Infants:

- ^{Amiodarone} Antiarrhythmic drugs
- ^{Cocaine/Amphetamine} CNS stimulants
- ^{Addictives} Cytotoxic agents
- ^{Addictives} Illicit substances
- ^{sulfonamides / Trimethoprim / Dapsone} Antiinfective drugs
- Immunosuppressants
- Thalidomide
- Lithium
- MAOIs
- Radioactive substances
- Skeletal muscle relaxants
- Tetracyclines
- Tricyclic antidepressants
- Retinoic acid derivatives

Should not be given; you should find alternative if there is no alternative, the mother should not breastfeed during taking of these drugs

2. Multiple maternal therapy with drugs having similar adverse effects (anticonvulsants, and psychotropic drugs) will increase the risk for the infant.
3. Active metabolites (benzodiazepines) may prolong infant drug exposure and lead to drug accumulation.
4. Drugs with long half-lives (fluoxetine) may be problematic. *metabolic capacity of the suckling infant may not be as young adults*
5. Gestational age: premature infants are more susceptible because of low clearance.
6. Maternal drug regimen: single doses or short courses have lower risk than chronic therapy or multiple medications.

Reducing Risk to the Breastfed Infant: (هذا مهم .. ← ويعنيهم متى دائما ممكن

Strategies to reduce the risk of drugs in breast fed infants:

1. Select medication considered safe for use in infants.
2. Give the maternal dose immediately after the infant has been fed, to avoid feeding at peak concentration of the drug in milk (if possible depending on frequency of feeding). → هذا متى دائما ممكن .. وكذا بتحتي هذا الـ infant عبارة عن adult به يرضع ٣ وجبات في اليوم ، وهو ممكن يرضع ١٠ وجبات في اليوم أو أكثر
3. If the mother is receiving a single dose of a hazardous material (radiopharmaceuticals), avoid breast feeding and resume after a reasonable washout period (5 half-lives). If the half-life is long, the washout period will be very long. → You pump milk out of the breast, to prevent reduction in milk producing capability of the breast & to reduce infections, and you don't use this milk
4. If the mother is using a once-daily medication, administration before the infant's longest sleep period may be advised to increase the interval to next feeding. You need to know about the frequency of breastfeeding of that infant
5. Breastfeeding mothers should avoid self-medication. وهي تبني الـ peak concentration وتحدد للسيدة متى تاخذ الدواء
6. When drug use is indicated, the lowest effective dose should be used for the shortest possible period of time.
7. Simplify maternal regimen as much as possible. → to be able to control it
8. New drugs are best avoided if a therapeutic equivalent is available for which data on safe use during lactation is available.
9. Infants exposed to drugs through breast milk should be monitored for adverse effects.
10. Select drugs with short half-lives and high protein binding to reduce accumulation.
11. For drugs taken multiple times per day, administration immediately after breast feeding provides the longest interval of back diffusion of the drug from breast milk into mother's serum (?). → This one also not always possible
12. During short-term drug therapy, and if the medication is NOT compatible with breastfeeding, the mother can pump milk out and discard it to preserve here milk-producing capability.
 - Information regarding drug use during breastfeeding can be obtained from www.toxnet.nlm.nih.gov

Special Situations:

Neonates and premature Infants:

1. They are at greater risk of developing adverse effects to drugs after exposure via breast milk. low elimination capacity لأنه عندهم
2. Gastric emptying time is prolonged and may alter drug absorption.
3. Protein binding is decreased.
4. Total body water is higher.
5. Renal function is limited.
6. Conjugation capacity is deficient (oxazepam).

استمرااد
vitamin B12 deficiency & Folic acid deficiency الـ الفرق بين الـ ✓

→ both associated with neurologic abnormality, but that of folic acid d. is different from B12 d. (distinct)

paracetamol is hepatotoxic at high dose, and cause toxicity in the lung by the same mechanism ✓

Glucose-6-phosphate dehydrogenase deficiency:

⇒ Inheritance is sex-linked co-dominant
 & in newborns the possibility is equal between males & females, and it may be more in females.

الرجلين بنفس القوة، فمن واحد منهم تشارك الثاني مستحي
 Females.

1. It makes erythrocytes more susceptible to oxidative stress which results in hemolysis.
2. Only small amounts of the drug in breast milk are needed to produce hemolysis.
3. Breastfeeding should be avoided or alternative drugs should be used if the infant is G6PD deficient.

Recreational Drug Use:

1. Substances such as cannabis, LSD, and cocaine should be avoided during breastfeeding.
2. Chronic or heavy consumers of alcohol should NOT breastfeed.
 - High intake of alcohol in breastfeeding mothers:
 - a) decrease milk let down reflex.
 - b) disrupt nursing.
 - c) causes infant sedation, fluid retention, and hormone imbalances in infants.
3. Nicotine decreases basal prolactin production.

Mothers should be encouraged NOT to smoke whilst breastfeeding.

4. Caffeine appears in breast milk rapidly after maternal intake. ~ 10 or more cups of coffee per day by the mother produce fussiness, jitteriness, and poor sleep patterns in breast fed infants.
 - Preterm and newborn infants metabolize caffeine slowly and are at increased risk.

Drug Effects on Lactation:

1. Drugs that affect dopamine activity are the main cause of effects on milk production.
 - A. Dopamine agonists (cabergoline) decrease milk production.
 - B. Dopamine antagonists (domperidone) increase milk production.
2. Early postpartum use of estrogens may reduce the volume of milk.
 - Milk production can be abolished by the use of estrogens or oral contraceptives.
 - Breast milk production can be increased by metoclopramide (10 mg po, 3 times daily for 714 days) if nonpharmacological means are ineffective. It stimulates prolactin secretion.

Drugs Contraindicated during Lactation:

Table 1-5. Agents Contraindicated During Lactation, Hazardous to Milk Production

Drug Class	Agents	Comments
Antiestrogens	Danazol	Ovarian suppression through pituitary-ovarian axis, inhibiting hormone production
	GNRH agonists (e.g., leuprolide)	
	Anastrozole	Estrogen suppression through aromatase inhibition
Antiviral	Amantadine	Can suppress lactation by increasing dopamine
Dopamine agonists	Ropinirole	Lower serum prolactin concentrations, preventing lactation
	Selegiline	
	Rotigotine	
	Dopamine	
Decongestants	Pseudoephedrine	Oral intake can suppress milk production with single doses; topical application has a significantly lower risk unless overused
	Propylhexedrine	
	Phenylephrine	
Ergots	Ergotamine	Inhibit prolactin, preventing lactation
	Dihydroergotamine	
Ergot derivatives	Bromocriptine	Likely safe if treating hyperprolactinemia; otherwise contraindicated
	Cabergoline	
Ethanol	Alcohol	Chronic ingestion will suppress milk production
Nicotine	Cigarettes	Decreased prolactin concentrations, reduced antioxidant properties of breast milk
Selective estrogen receptor antagonists	Tamoxifen	Inhibit estrogen effects in breast tissue
	Raloxifene	

GNRH = gonadotropin-releasing hormone.

→ Can reduce milk production

الاسم هذا عبارة عن تصنيف من الرتبة، يعني مش رافينين يحكوا : Addictive Drug Use

Table 2. Botanical galactagogues

Oral botanical galactagogue	How it might work	Harms	Reference(s)
Fenugreek (<i>Trigonella foenum-graecum</i>) الحلبة	Increases milk flow by its phytoestrogens and diosgenin contents Stimulates sweat production, which would enhance milk secretion because the breast is a kind of sweat gland May stimulate milk production through dopamine receptor antagonism	Digestive upset, loose stools, light headedness, maple smell in the urine and sweat, mild allergic reaction. Possible peanut allergen cross sensitivity	Abascal 2008, Bingel 1994, Bruckner 1993, Capasso 2009, Humphrey 2007, Low Dog 2009, MacIntosh 2004, Mortel 2013, Romm 2010
Blessed thistle (<i>Cnicus benedictus</i>)	Stimulates the flow of blood to the mammary glands	Increased risk of bleeding	Abascal 2008, Bingel 1994, Zapantis 2012
Torbangun leaves (<i>Coleus amboinicus</i> Lour)	May stimulate proliferation of secretory mammary cells	Hypoglycaemia and stimulation of the thyroid gland	Bingel 1994, Zapantis 2012, Mortel 2013
Goat's rue (<i>Galega officinalis</i>)	Contains galegin, a precursor to metformin. May exert effects via contents of steroidal saponins Reputedly stimulates mammary growth	No data for humans. Minor abnormalities in blood and pathological specimens in rats	Abascal 2008, Bruckner 1993, Humphrey 2007, MacIntosh 2004, Rasch 2008, Romm 2010
Fennel (<i>Foeniculum vulgare</i>) الشومر	Contains anethole, considered weakly estrogenic; may increase breast milk production or assist with the 'let-down' reflex. Reputedly stimulates mammary growth	Essential oil, may be toxic in large amounts	Abascal 2008, Bingel 1994, Bruckner 1993, Humphrey 2007, Low Dog 2009, Mills 2006, Mortel 2013, Romm 2010
Shatavari (<i>Asparagus racemosus</i>)	Estrogenic; may stimulate production by increasing prolactin. Increases weight of mammary gland in animal studies	Runny nose, itchy conjunctivitis, contact dermatitis and cough. May have laxative effect	Bingel 1994, Chaudhury 1983, Mortel 2013, Zapantis 2012
Anise or Aniseed (<i>Pimpinella anisum</i>) اليانسون	Contains anethole, considered weakly estrogenic; the aromatic compound in anise may act as a dopamine receptor antagonist	Possible allergen for some people	Abascal 2008, Bingel 1994, Bruckner 1993, Humphrey 2007, Low Dog 2009, Romm 2010
Milk thistle (<i>Silybum marianum</i>) الخرقيش	Appears to stimulate prolactin; possibly estrogenic	None known	Abascal 2008, Bingel 1994, Capasso 2009, Low Dog 2009, Mills 2006, Mortel 2013
Barley (<i>Hordeum vulgare</i>) الشعير	Polysaccharide stimulates prolactin	None known. Commonly consumed grain, also used to make beer	Bingel 1994, Humphrey 2007, Koletzko 2000, MacIntosh 2004, Sawagado 1988
Malunggay or Drumstick (<i>Moringa oleifera</i>)	Increases prolactin	None known. Commonly consumed as a vegetable in the Phillipines and elsewhere	Bingel 1994

→ Drugs that increase milk production

× الاسم العلمي
✓ تأثيره على milk production
× mechanism ما يثبت كبر

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