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Pharmacotherapy in children, elderly, in pregnant women and in lactation

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Overview of factors affecting drug effects

A.Factors related to drug:
Physical and chemical properties
Dose
Drug form
Combination of drugs
Food administered together with a drug
Repeated administration

B. Factors related to organism:
Age
Gender
Weight and body constitution
Circadian rhytms
Pathological state of organism
Genotype/fenotype (Race group/ethnic group)

Age

Administration of medicinal product (MP)

to children

to elderly people

Administration of MP to children

A child is not small adult

particularities of PD
particularities of PK

Changes of PK of drugs in young age - A

- Higher pH in stomach
- Large surface area/volume ration + thinner skin – increased skin absorption

TABLE 59–3 Oral drug absorption (bioavailability) of various drugs in the neonate compared with older children and adults.

Drug	Oral Absorption
Acetaminophen	Decreased
Ampicillin	Increased
Diazepam	Normal
Digoxin	Normal
Penicillin G	Increased
Phenobarbital	Decreased
Phenytoin	Decreased
Sulfonamides	Normal

Changes of PK of drugs in young age - D

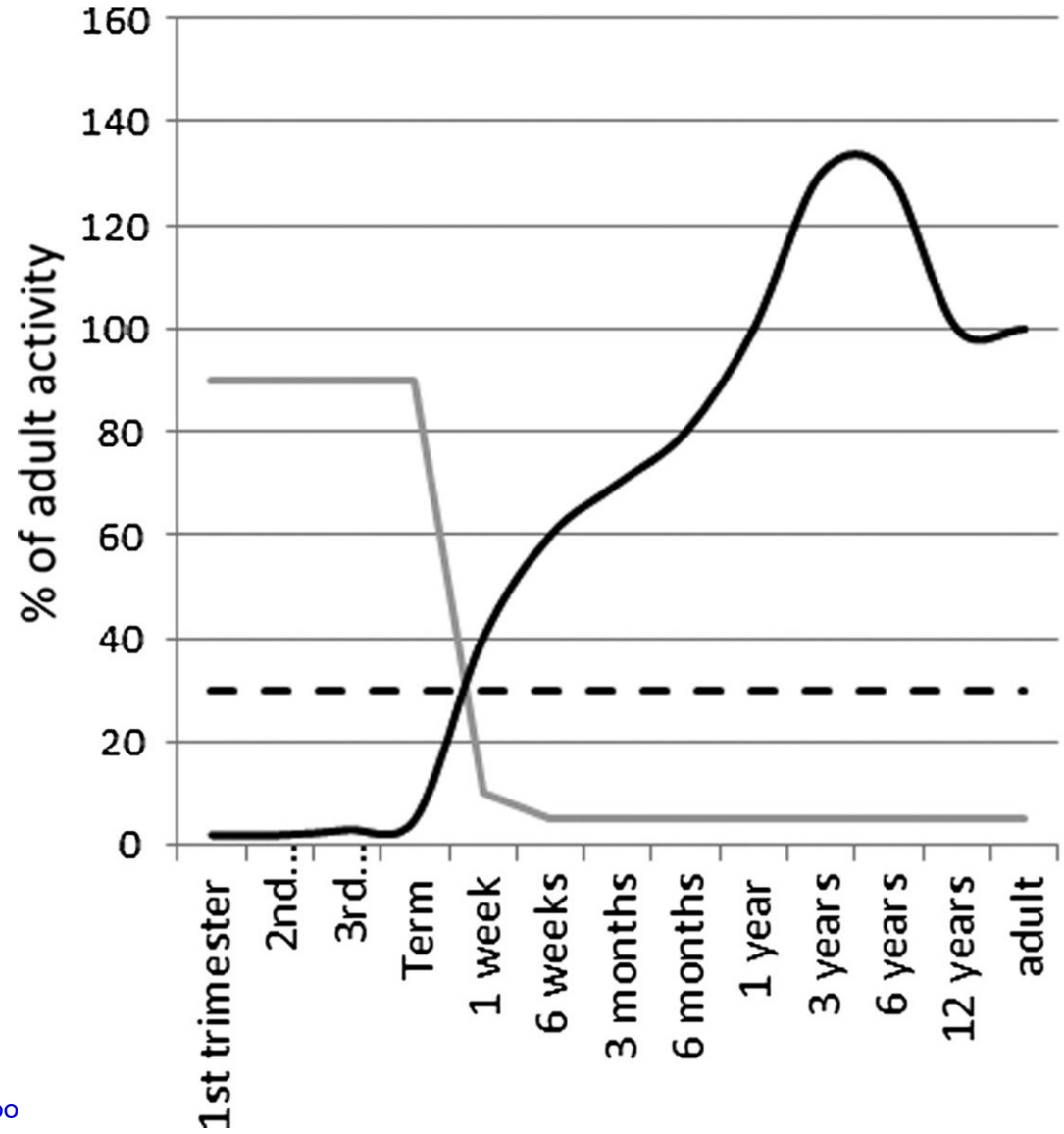
- Higher total body water
- Increase of body fat with age
- Lower plasma proteins in infants
- Unfinished development of HEB

→ increased Vd
→ obese children – higher risk in drugs not distributed into fat
→ higher distribution and lower peak concentrations of protein-bound drugs

Changes of PK of drugs in young age - M

- The most complex difference between adults and children
- Activity of CYP begins in foetus and increases with age (in 2 y exceeds adult levels)
- Glucuronidation takes at least 3 years to mature
- Liver blood flow is relatively higher

→ higher first pass effect
→ without adjustment of dose and dosing intervals there is a risk of cummulation and toxicity especially in newborns



Prenatal pattern: CYP3A7, FMO1, SULT1A3

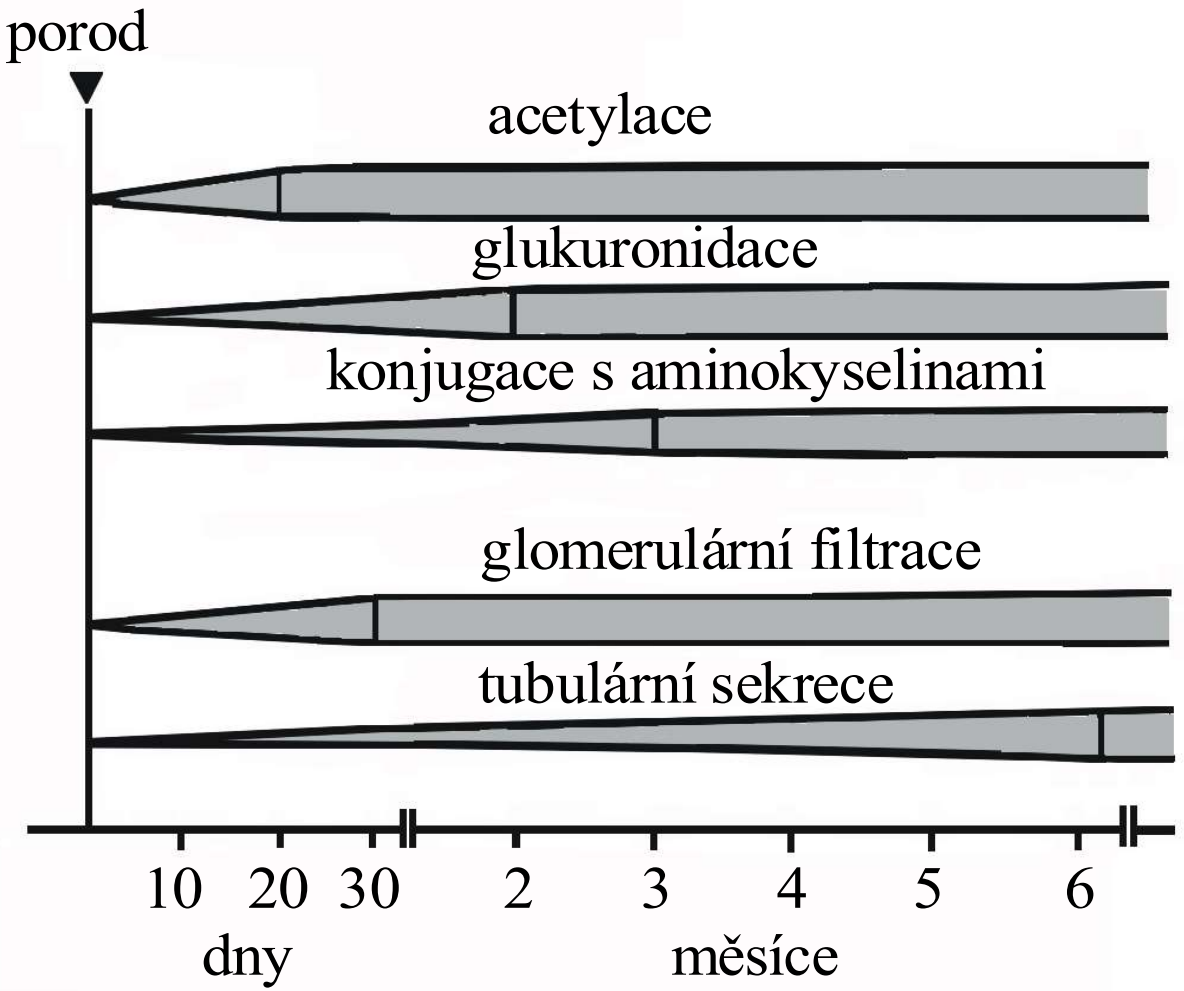
Constant pattern: CYP3A5, SULT1A1, TPMT

Postnatal pattern: CYP2C9, 2C19, 2D6, 2E1, 3A4, FMO3, most UGTs

Changes of PK of drugs in young age - E

- Decreased GF, but still is more advanced than TS
- Decreased TS (aminoglycosides!!)

→ preterm infants develop renal excretion pathways more slowly than term neonates


porod
acetylace
glukuronidace
konjugace s aminokyselinami
glomerulární filtrace
tubulární sekrece
10
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30
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TABLE 59–4 Comparison of elimination half-lives of various drugs in neonates and adults.

Drug	Neonatal Age	Neonates $t_{1/2}$ (hours)	Adults $t_{1/2}$ (hours)
Acetaminophen		2.2–5	0.9–2.2
Diazepam		25–100	40–50
Digoxin		60–70	30–60
Phenobarbital	0–5 days	200	64–140
	5–15 days	100	
	1–30 months	50	
Phenytoin	0–2 days	80	12–18
	3–14 days	18	
	14–50 days	6	
Salicylate		4.5–11	10–15
Theophylline	Neonate	13–26	5–10
	Child	3–4	

Changes of PD in children

Antihistamins:
In adult patient sedation (sleppines, tiredness)
In children excitation (cramps)

Chloramphenicol – gray baby syndrome

Salicylates – Reye syndrome

Barbiturates – paradoxical reaction (excitation, agressivity)

Administration of MP to children

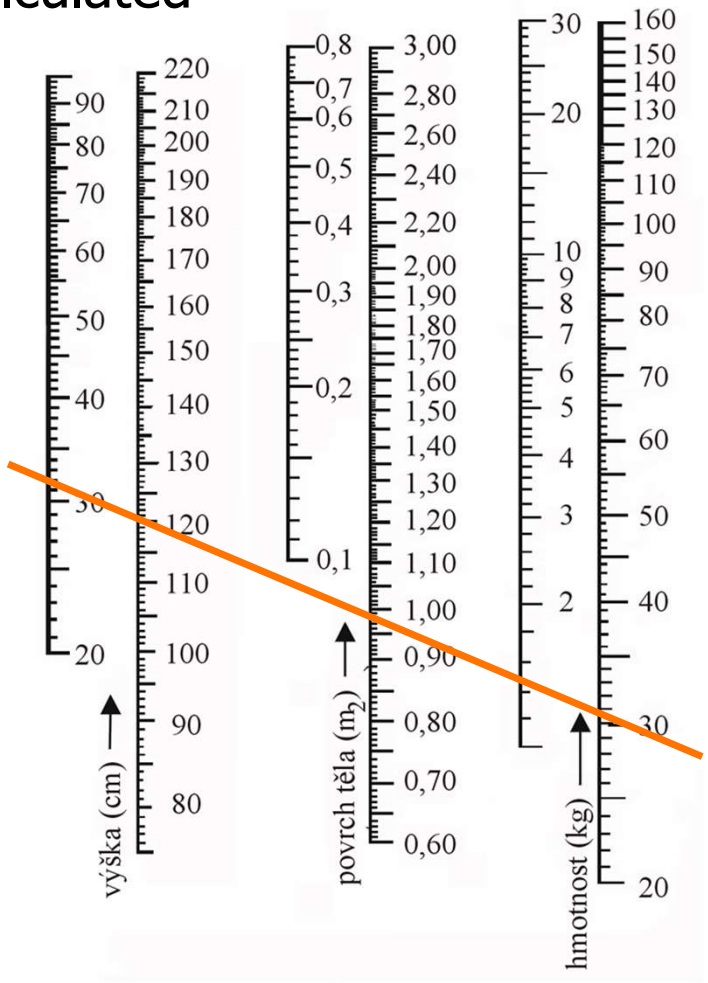
Doses are given in SPC or have to be calculated

Approximate dose for children =

$$\frac{\text{body surface area (m2) x dose for adult}}{1{,}7\ (\text{m}2)}$$

Body surface area =

$$\frac{7 \times \text{age (years)} + 45}{100}$$



Administration of MP to old people

Seniors represent 14% of population but use 35% of drugs
„Young“ senior 60 – 64y ..... 83% use medicines
„Middle“ senior 65 – 74y..... 89% use medicines
„Old“ senior above 75y..... 91-98% use medicines

Avarage amount of used preparations increase with age
Ambulant seniors 4-6
Hospitalised 5-8 prep

Administration of MP to old people

- physiological changes (organs lose their functional reserve)
- worse adaptability to changes in inner or external conditions
- polymorbidity (concomitant diseases or chain of diseases)
- polypragmasia (administration of many drugs together, risk of drug interactions is increasing)
- higher incidence and severity of adverse effects

Characteristics of morbidity in old age

- Microsymptomatology – asymptomatology
  (lack of typical symptoms – fever, leucocytosis, silent AMI)
- Mono(oligo)symptomatology
  (tachyfibrillation in thyreotoxicosis)
- Non-specific symptoms
  (tiredness, loss of appetite, weightloss)
- Syndrom of secondary impairment
  (symptoms of another organ than which is the cause of disease
  e.g. disease of kidney leads to delirant state)
- Cascade reaction (chain of diseases)
- Atypic reactions to drugs

Changes of PD in old age

Very variable
Tissue hypoxia
Dysfunction of regulatory mechanisms
Change of sensibility of target structures

= **hyperergic or paradoxical reactions**

Changes of PD in old age - examples

ATB aminoglycosides:

lower doses in case of lower GF (correction according to CL CR)

Antihypertensives:

orthostatic hypotension, psychical alternations (confusion)

Anticoagulants:

bleeding from GIT (decreased absorption of vitamin K and decreased synthesis of prothrombin)

NSAID:

in 25% hematemesis

Anticholinergic drugs:

higher toxicity, depression, confusion

The most often mistakes in prescription in old age

- **underprescribing**
  not prescribing drugs with proven benefit (statins, AD, ACE-I)
- **overprescribing**
  drugs which are not indicated (hypnotics, BZD, peripheral vazodilatants, nootropics
- **„imperative drugging“**
  prescribing drugs for each disease per se
- prescription with risk of **interactions**
- prescription of drugs with **risky profile**
  drugs CI due to comorbidities (β-blockers + COPD)

Drugs not suitable in old age

Mark H. Beers, 54, Expert on Drugs Given to Elderly, Dies Feb 28, 2009

Beers' List — Potentially Inappropriate Medications for the Elder

Fick DM, Cooper JW, Wade WE, Waller JL, Maclean JR, Beers MH. Updating the Beers criteria for potentially inappropriate medication use in older adults: results of a US consensus panel of experts. Arch Intern Med. 2003;163:2716-2724

Gender

Women are in general more sensitive to effects of some drugs, e.g. because of lower weight, but also of lower CL (olanzapine)

Specific periods are:
menstruation
gravidity
lactation
menopause

Pregnancy

- slowed stomach and intestinal motility
- increased volume of plasma
- body water can be raised by up to 8 litres
- occupancy rate of plasma proteins by hormones,
- relative hypoalbumineamia
- increased blood flow through kidneys and increase of GFR
- changed liver enzymes activity (some stimulated, some inhibited)

Safety of medication in pregnancy

Consider

- Dose
- Lenght of therapy
- Ability of drug to cross placentar barrier
- Ability of the baby to eliminate the drug
- Cummulation of the drug in the baby or in the water
- Period of gestation when the drug is administered

Safety of medication in pregnancy

1) **Period of implantation** – all or nothing (14 days)

2) **Organogenesis** – the most sensitive period to teratogenic effects of drugs (till 12th week)

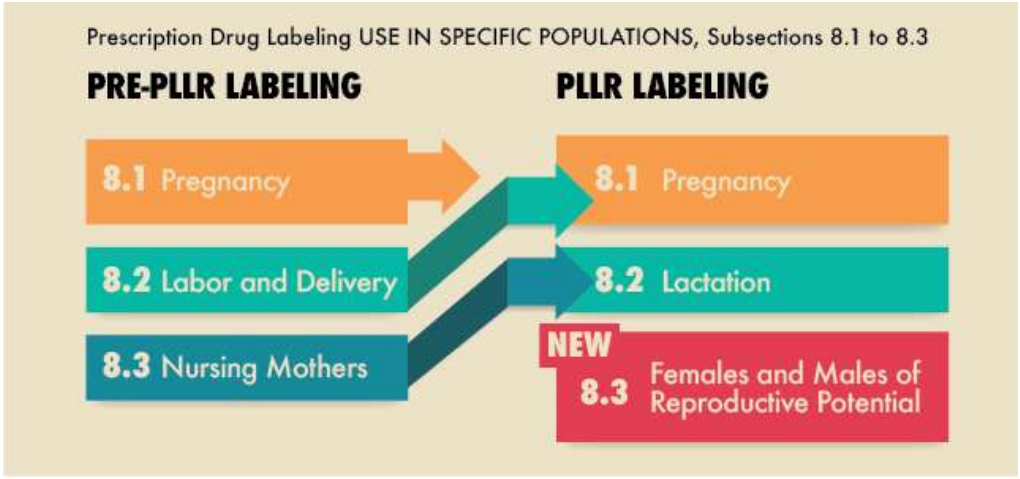
3) **Fetal period** – relatively safer when considering teratogenic effects, but risky in toxic eff.

4) **Last month of gravidity** – long acting drugs can affect newborn !

5) **Lactation**

Pregnancy and Lactation Labeling Rule

FDA Pharmaceutical Pregnancy Categories	
Category A	Adequate and well-controlled human studies demonstrate no risk.
Category B	Animal studies demonstrate no risk, but no human studies have been performed. OR Animal studies demonstrate a risk, but human studies have demonstrated no risk.
Category C	Animal studies demonstrate a risk, but no human studies have been performed. Potential benefits may outweigh the risks.
Category D	Human studies demonstrate a risk. Potential benefits may outweigh the risks.
Category X	Animal or human studies demonstrate a risk. The risks outweigh the potential benefits.



Pregnancy and Lactation Labeling Rule

The final rule requires that for the labeling of certain drug products (as described in the "Implementation" section of this document), the subsections "Pregnancy," "Nursing mothers," and "Labor and delivery" be replaced by three subsections entitled "Pregnancy," "Lactation," and "Females and Males of Reproductive Potential." The final rule also requires the removal of the pregnancy categories A, B, C, D, and X from all drug product labeling.

- Previous FDA classification was not suitable for practical use
- Drugs are no more classified into categories
- Detailed characterisation of possible use of the drug in pregnancy or in lactation
- Also SPC contains information on influence of the drug on fertility

Teratogenic drugs include: remember of "TERATOWA"

Thalidomide

Epileptic medications (Valproic acid, Phenytoin)

Retinoid (Vitamin A)

ACE inhibitors, ARBs

Third element (Lithium)

Oral contraceptives, Hormones

Warfarin

Alcohol

General recommendations

Prescription for women in fertile age

1. Prescribe medicines which were tested for teratogenicity

2. Newly registered drugs should be prescribed only if older (time-proven) drugs cannot be used

3. If known teratogenic drug cannot be avoided, contraception is necessary

General recommendations

Prescription for pregnant women

1. Choose proven medication **before** pregnancy if chronic therapy is necessary

2. Sudden discontinuation may provoke worsening of the condition with possible severe consequences for both mother and child

3. Prefer monotherapy with the lowest dose possible

Lactation

Almost all of the drugs given to mother gets into her milk (apart from big molecules), however often **in very small amount**

- depends on characteristics of the molecule (size, lipophility, binding to proteins in mother´s plasma, ionisation)

- milk is mildly acidic

- drugs which cross the barrier easiest are typically small molecules, lipophylic, weak bases and non-ionised

Lactation

- drugs given to mother only locally or in small amount (nose or eye drops, inhalant sprays, topical preparations applied on small area) do not reach the baby in significant concentrations

- the **relative infant dose** is the dose received via breast milk (mg/kg/day) relative to the mother's dose (mg/kg/day). It is expressed as a percentage.

- A relative dose of 10% or above is the notional level of concern, but this is rare (e.g. Lithium)

Safety of medication during lactation

Possible risk for breast-fed child depends on

- Amount of the drug fed in breast-milk to the baby
- PK of the drug in the baby (t1/2)
- Safety profile of the drug
- Health state of the baby

General recommendations

1. Adjust **time of administrations and feeding** –
Generally the most suitable pattern is to feed baby 1-3h after administration of the drug (exceptions - amoxicilin 4-6 h, metylprednisolon 8 h, caffeine 0,5 h).

2. The safest is to use drugs, which can be administered **once a day**

3. In this case the drug should be given **after evening feeding**, before child´s longest sleep

Drugs Contraindicated During Breastfeeding

• Amiodarone	• Hypothyroidism reported
• Antineoplastic agents	• Possible immune suppression, effect on growth
• Chloramph.	• (May-->idiosyncratic BM supp. at high conc. in breast milk)
• Ergotamine	• Vomiting,diarr.,convulsion (dose≥migraine)
• Gold salts	• Possible facial edema in one infant 3 mo. after Rx in mother
• Lithium	• Severe rash reported
• Phenindione	• Increased PT & PTT in 1 infant

Drugs Contraindicated

• Retinoids	•Very lipid soluble,wide range of AEs in adult, mutagenic & carcinogenic in animals
• Tetracycline (chronic-months)	•Staining immature teeth, change in epiphyseal bone growth
• Pseudoephedrine	•Unpublished result, may inhibit prolactin & milk production significantly
• Radioactives	•Temporary cessation of BF, based on presence of radioactivity in milk
• Combined oral contraceptives	•Dec.breast milk product^{n}, dec.protein & nitrogen content of milk

Drugs stimulating milk production = galactogogues

Domperidone and metoclopramide

- D antagonists
- used off-label to stimulate prolactin and enhance milk supply
- do not have high evidence of efficacy for this indication, risk of arrhytmias!

Other drug increasing milk production – side effects

Imipramine, fenothiazin, sulpirid, haloperidol, reserpin, metyldopa, TSH

Drugs decreasing milk production

Estrogens, ergot alkaloids (very strong effect)

androgens, tamoxifen, bromocriptine, levodopa, barbiturates, apomorphin,

diuretics,1st generation of antihistaminics, pyridoxin (in very high doses)

Where to look for information?

Product information - **SPC**

State-based obstetric drug information services provide detailed advice on the use of drugs during lactation and should be able to advise about past clinical experience with the drug.

Gravidity

- European Network of Teratology Information Service (ENTIS)
- UK Teratology Information Service (UKTIS)
- The Australian categorisation system for prescribing medicines in pregnancy

  https://www.tga.gov.au/prescribing-medicines-pregnancy-database

Lactation

- Drugs and Lactation Database (**LactMed**)

  https://www.ncbi.nlm.nih.gov/books/NBK501922/

LactMed11 is a freely accessible, well-resourced and peer-reviewed online database. It is updated to keep pace with new information, including published studies and drug approvals. It also incorporates information on complementary treatments.

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Drugs used in dentistry

TABLE 2

Updated Drugs and Pregnancy Categories

Generic Name	Brand Name	Pregnancy Category	Potential Risk
Local Anesthetics			
Articaine with epinephrine	Septocaine	C	
Bupivacaine with epinephrine	Marcaine	C	Fetal bradycardia
Lidocaine with epinephrine	Xylocaine	B	
Mepivicaine plain	Carbocaine	C	Fetal bradycardia
Mepivicaine with levonordefrin	Carbocaine with Neo-Cobefrin	C	
Prilocaine plain	Citanest	B	Potential methemoglobinemia
Prilocaine with epinephrine	Citanest Forte	C	Potential methemoglobinemia
Benzocaine Topical	Orajel	C	Potential methemoglobinemia
Peripherally Acting Analgesics			
Acetaminophen	Tylenol	B	
Aspirin	Bayer	C/D[3]	Postpartum hemorrhage; premature closure of ductus arteriosus
Ibuprofen	Advil, Motrin	B/D[3]	Postpartum hemorrhage; premature closure of ductus arteriosus
Ketorolac	Toradol	B/D[3]	Postpartum hemorrhage; premature closure of ductus arteriosus
Naproxen	Aleve, Anaprox	B/D[3]	Postpartum hemorrhage; premature closure of ductus arteriosus
Centrally Acting Opioid Analgesics			
Codeine with Acetaminophen	Tylenol with Codeine	C/D[3]	Neonatal respiratory depression and opioid withdrawal
Hydrocodone with Acetaminophen	Vicodin	C/D[3]	Neonatal respiratory depression and opioid withdrawal
Hydrocodone with Ibuprofen	Vicoprofen	C/D[3]	Neonatal respiratory depression and opioid withdrawal
Oxycodone	Oxycontin	B/D[3]	Neonatal respiratory depression and opioid withdrawal
Oxycodone with Acetaminophen	Percocet	C/D[3]	Neonatal respiratory depression and opioid withdrawal
Oxycodone with Ibuprofen	Combunox	C/D[3]	Neonatal respiratory depression and opioid withdrawal; premature closure of ductus arteriosus
Tramadol	Ultram	C	
Antibiotics			
Amoxicillin	Amoxil	B	
Amoxicillin and Clavulanate	Augmentin	B	
Azithromycin	Zithromax, Z-Pack	B	
Cephalexin	Keflex	B	
Clindamycin	Cleocin	B	
Doxycycline	Doryx	D	Tooth discoloration and inhibition of bone development
Erythromycin base	E-mycin	B	Avoid estolate salt
Fluconazole	Diflucan	C	Fetal brachycephaly, cleft palate, thinning of bones
Gentamicin	Garamycin	C/D[3]	Ototoxicity potential in fetus
Metronidazole	Flagyl	B	
Minocycline	Dynacin, Minocin	D	Congenital anomalies and enamel hypoplasia
Penicillin V	Pen-Vee K	B	
Tetracycline	Tetracycline generic	D	Maternal hepatoxicity and enamel hypoplasia; tooth discoloration
Sedatives/Anxiolytics			
Alprazolam	Xanax	D	Congenital malformations, withdrawal symptoms
Diazepam	Valium	D	Congenital malformations, withdrawal symptoms
Lorazepam	Ativan	D	Congenital malformations, withdrawal symptoms
Midazolam	Versed	D	Congenital malformations, withdrawal symptoms
Triazolam	Halcion	X	Congenital malformations, withdrawal symptoms
Other			
Diphenhydramine	Benadryl	B	
Epinephrine	Epinephrine	C	Potential for fetal hypoxemia
Flumazenil	Romazicon	C	Avoid during labor and delivery
Phentolamine	OraVerse	C	Avoid during labor and delivery

D[3] = Avoid in third trimester. Designated D[3] drugs are considered Pregnancy Category D when taken in third trimester.

TABLE 2

Key medication considerations during pregnancy and breast-feeding.

AGENT	FDA PR* CATEGORY	SAFE DURING PREGNANCY?	SAFE DURING BREAST-FEEDING?
Analgesics and Anti-inflammatories†			
Acetaminophen	B	Yes	Yes
Aspirin	C/D	Avoid	Avoid
Codeine	C	Use with caution	Yes
Glucocorticoids (dexamethasone, prednisone)	C	Avoid‡	Yes
Hydrocodone	C	Use with caution	Use with caution
Ibuprofen§	C/D	Avoid use in third trimester	Yes
Oxycodone	B	Use with caution	Use with caution
Antibiotics¶#			
Amoxicillin	B	Yes	Yes
Azithromycin	B	Yes	Yes
Cephalexin	B	Yes	Yes
Chlorhexidine (topical)	B	Yes	Yes
Clarithromycin	C	Use with caution	Use with caution
Clindamycin	B	Yes	Yes
Clotrimazole (topical)	B	Yes	Yes
Doxycycline	D	Avoid	Avoid
Erythromycin	B	Yes	Use with caution
Fluconazole	C/D	Yes (single-dose regimens)	Yes
Metronidazole	B	Yes	Avoid; may give breast milk an unpleasant taste
Nystatin	C	Yes	Yes
Penicillin	B	Yes	Yes
Terconazole (topical)	B	Yes	Yes
Tetracycline	D	Avoid	Avoid
Local Anesthetics			
Articaine	C	Use with caution	Use with caution
Bupivacaine	C	Use with caution	Yes
Lidocaine (with or without epinephrine)	B	Yes	Yes
Mepivacaine (with or without levonordefrin)	C	Use with caution	Yes
Prilocaine	B	Yes	Yes
Benzocaine (topical)	C	Use with caution	Use with caution
Dyclonine (topical)	C	Yes	Yes
Lidocaine (topical)	B	Yes	Yes
Tetracaine (topical)	C	Use with caution	Use with caution
Sedatives			
Benzodiazepines	D/X	Avoid	Avoid
Zaleplon	C	Use with caution	Use with caution
Zolpidem	C	Use with caution	Yes
Emergency Medications			
Albuterol	C	Steroid and β_2-agonist inhalers are safe	Yes
Diphenhydramine	B	Yes	Avoid
Epinephrine	C	Use with caution	Yes
Flumazenil	C	Use with caution	Use with caution
Naloxone	C	Use with caution	Use with caution
Nitroglycerin	C	Use with caution	Use with caution

* FDA PR: U.S. Food and Drug Administration Pregnancy Risk. See Table 1 for FDA PR category definitions.

† In the case of combination products (such as oxycodone with acetaminophen), the safety with respect to either pregnancy or breast-feeding is dependent on the highest-risk moiety. In the example of oxycodone with acetaminophen, the combination of these two drugs should be used with caution, because the oxycodone moiety carries a higher risk than the acetaminophen moiety.

‡ Oral steroids should not be withheld from patients with acute severe asthma.

§ Ibuprofen is representative of all nonsteroidal anti-inflammatory drugs. In breast-feeding patients, avoid cyclooxygenase selective inhibitors such as celecoxib, as few data regarding their safe use in this population are available, and avoid doses of aspirin higher than 100 milligrams because of risk of platelet dysfunction and Reye syndrome.

¶ Antibiotic use during pregnancy: The patient should receive the full adult dose and for the usual length of treatment. Serious infections should be treated aggressively. Penicillins and cephalosporins are considered safe. Use higher-dose regimens (such as cephalexin 500 mg three times per day rather than 250 mg three times per day), as they are cleared from the system more quickly because of the increase in glomerular filtration rate in pregnancy.

Antibiotic use during breast-feeding: These agents may cause altered bowel flora and, thus, diarrhea in the baby. If the infant develops a fever, the clinician should take into account maternal antibiotic treatment.

Thank you for your attention