

FEATURES OF DRUGS ACTION DURING PREGNANCY, LACTATION AND IN CHILDREN

Drug use in pregnancy

Drugs can be harmful for the unborn child!!!

THE PLACENTA

- Drugs pass placenta by passive diffusion
- lipid barrier between maternal and embryonic/fetal circulations
- slow process (used during caesarean section)
- non-ionized drugs pass more rapidly
- most drugs are small enough to pass exceptions: growth hormone, conjugated steroids
- cuts peak concentrations in maternal plasma

Drug use in pregnancy

effects of toxic drugs

- malformation
- growth retardation
- fetal death
- functional defects in newborn
- premature birth

Drugs should be used with caution during pregnancy

Drug use in pregnancy

Use of drugs in pregnancy is not always wrong

Some examples:

- High fever is harmful for the fetus in the first months.

Use of paracetamol is better than no treatment

- Diabetes during pregnancy needs intensive therapy with insulin
- Folic acid protects against spina bifida
- Anti-epileptics are teratogenic. But an epileptic insult may provoke harmful anoxia for the fetus.

Drug use in pregnancy

Toxic chemicals and irradiation can damage

Oocytes:

- all female germ cells develop prenatally. No germ cells are formed after birth
- Oocytes are in situ and not multiplying.
- teratogenic effects can become apparent after fertilization, maybe long after the presence of damage
- **EMEA** does not allow women with childbearing potential to take part in first in man studies

Drug use in pregnancy

Is damaged sperm teratogenic?

- Spermatozoa are continuously produced
- Damaged spermatozoa are slower and arrive late when the oocytes is already fertilized → mostly not harmful?
- May lead to infertility
→ paternal teratogenicity cannot fully be excluded.
- advice: use of condoms when the man is taking products that are suspected to be harmful
- termination of pregnancy because of paternal teratogenicity is not justified

Drug use in pregnancy

The first trimester (day 8 – end of month 2)

- Is the most important period for teratogenicity
- Is period of formation of organs

3rd – 9th month

- Less risk for malformations
- except for urogenital tract and central nervous system
- More functional effects
- i.e. aminoglycosides nephro- & ototoxicity
- salicylates increased risk of bleeding

Drug use in pregnancy

drugs have effects in newborn

- **avoid CNS depressants**

floppy infant syndrome

- **avoid drugs with increased bleeding risk**

like anticoagulants, salicylates

increased risk of cerebral hemorrhage

during delivery

- **NSAIDs and salicylates ↓ uterine**

contractility

Drug use in pregnancy

spontaneous malformations (=unknown origin)

2-4 %

Additional risk from drugs is small for most drugs
evidence for teratogenic effects

- golden standard is randomized controlled trial (RCT). ethical objections
 - epidemiologic studies cannot establish proven causality
 - large species differences in teratogenic effects
- No drug is proven free from teratogenic effects

Drug use in pregnancy

Risk classification (FDA)

Category A:

Controlled studies in women fail to demonstrate a risk to the fetus in the first trimester (and there is no evidence of a risk in later trimesters), and the possibility of fetal harm appears remote.

Drug use in pregnancy

Category B:

Either animal reproduction studies have not demonstrated a fetal risk but there are no controlled studies in pregnant women, or animal-reproduction studies have shown an adverse effect (other than a decrease in fertility) that was not confirmed in controlled studies in women in the first trimester (and there is no evidence of a risk in later trimesters).

Drug use in pregnancy

Category C:

Either studies in animals have revealed adverse effects on the fetus (teratogenic or embryocidal or other) and there are no controlled studies in women,

or

studies in women and animals are not available.

Drugs should be given only if the potential benefit justifies the potential risk to the fetus.

Drug use in pregnancy

Category D:

There is positive evidence of human fetal risk, but the benefits from use in pregnant women may be acceptable despite the risk (e.g., if the drug is needed in a life-threatening situation or for a serious disease for which safer drugs cannot be used or are ineffective).

Drug use in pregnancy

Category X:

**Studies in animals or human beings have demonstrated fetal abnormalities, or there is evidence of fetal risk based on human experience or both,
and
the risk of the use of the drug in pregnant women clearly outweighs any possible benefit.**

The drug is contraindicated in women who are or may become pregnant.

Anti-infectives

- **Penicillins**
- **Cephalosporins**
- **Carbapenems**
- **Fluoroquinolones**
- **Macrolides**
- **Aminoglycosides**
- **Sulfonamides**
- **Miscellaneous Antibiotics**
- **Antivirals**
- **Antiretrovirals**
- **Antifungals**

Penicillins

- **Category B in pregnancy**
 - **Cross the placenta easily and rapidly**
 - **Concentrations equal maternal levels**

- **Lactation**
 - **Crosses in low concentrations**
 - **Compatible with breastfeeding**

Cephalosporins

Category B in pregnancy

- **Cross the placenta during pregnancy**
- **Some reports of increased anomalies with specific cephalosporins (cefaclor, cephalexin, cephadrine)**
- **Primarily cardiac and oral cleft defects**

Lactation

- **Excreted into breastmilk in low concentrations**
- **Considered compatible with breastfeeding**

Carbapenems

(ertapenem, imipenem, meropenem)

Category B/C/B in pregnancy

- **Likely cross the placenta**
- **Very little human data**

Lactation

- **Excreted into breastmilk in low amounts**
- **Unknown effects but likely low clinical significance**

Fluoroquinolones

Pregnancy Category C

- Not recommended in pregnancy
- Cartilage damage in animals
- Safer alternatives usually exist

Lactation

- Excreted into breastmilk
- Limited human data
- AAP says compatible with breastfeeding

Macrolides **(azithromycin, clarithromycin, erythromycin)**

Pregnancy Categories B/C/B

- **Cross the placenta in low amounts**
- **Limited data with azithromycin and clarithromycin**

Lactation

- **Erythromycin compatible**
- **Others probably compatible**

Aminoglycosides

(amikacin, gentamicin, tobramycin)

Pregnancy Category C

- **Rapidly cross placenta**
- **Enter amniotic fluid through fetal circulation**

Lactation

- **Compatible with breastfeeding**
- **Not absorbed through GI tract**

Sulfonamides

Pregnancy Category C

- Readily cross the placenta
- Concerns of use at term

Lactation

- Excreted into breastmilk in low levels
- Use should be avoided in premature infants

Tetracyclines

(doxycycline, minocycline, tetracycline)

Pregnancy Category D

- **Can cause problems with teeth and bone and other defects/effects**
- **Have been linked to maternal liver toxicity**

Lactation

- **Compatible with breastfeeding**
- **Serum levels in infants undetectable**

Miscellaneous Antibiotics

Aztreonam

- **Pregnancy Category B, likely safe in pregnancy, little human data**
- **Lactation – Compatible per AAP**

Clindamycin

- **Pregnancy Category B, commonly used**
- **Lactation – Compatible per AAP**

Miscellaneous Antibiotics

Linezolid

- **Pregnancy Category C, no human data available**
- **Lactation – unknown, myelosuppression in animals**

Metronidazole

- **Pregnancy Category B, carcinogenic in animals, avoid in 1st trimester if possible**
- **Lactation – hold feeds for 12-24hrs afterward**

Miscellaneous Antibiotics

Nitrofurantoin

- **Pregnancy Category B, possible hemolytic anemia with use at term**
- **Lactation – Compatible, avoid with G-6-PD deficiency**

Trimethoprim

- **Pregnancy Category C, potentially problematic early in pregnancy**
- **Lactation – Compatible as combination drug**

Miscellaneous Antibiotics

Vancomycin

- **Pregnancy Category B, compatible**
- **Lactation – likely compatible, not absorbed**

Antivirals

(acyclovir, famciclovir, valacyclovir)

Pregnancy Category B

- **Acyclovir and valacyclovir readily cross the placenta**
- **Can be used for HSV treatment and suppression**

Lactation

- **Acyclovir and valacyclovir are compatible**
- **Famciclovir should be avoided**

Antiretrovirals/NRTI

(abacavir, didanosine (ddI), emtricitabine (FTC))

Pregnancy Categories C/B/B

- **Maternal benefit usually outweighs fetal risk**
- **Cross the placenta**
- **Limited data with each do not show increased risk of anomalies**
- **Didanosine has been associated with severe lactic acidosis w/ or w/o pancreatitis**

Antiretrovirals/NRTI

(lamuvidine (3TC), stavudine (d4T))

Pregnancy Category C

- Maternal benefit usually outweighs fetal risk
- Cross the placenta by simple diffusion
- Data with lamivudine show no increased risk of anomalies
- Stavudine has been associated with severe lactic acidosis w/ or w/o pancreatitis
- All NRTIs have been possibly linked to mitochondrial dysfunction postnatally

Antiretrovirals/NRTI

(tenofovir, zalcitabine (ddC), zidovudine
(AZT))

Pregnancy Category B/C/C

- Maternal benefit usually outweighs fetal risk
- Cross the placenta by simple diffusion
- Limited data with zalcitabine do not show increased risk of anomalies
- Zidovudine is commonly used, but may cause neonatal anemia
- Limited data with tenofovir show low risk of teratogenicity

Antiretrovirals/NNRTI

(delavirdine, efavirenz, nevirapine)

Pregnancy Category C

- **Maternal risk usually outweighs fetal risk**
- **Likely cross into fetus (nevirapine readily)**
- **Delavirdine has possible VSD risk, but limited human data**
- **Efavirenz is associated with anomalies in monkeys, limited human data, possible NTD**
- **Nevirapine can cause hepatotoxicity and rash**
- **Nevirapine can be used as a single dose in labor to prevent HIV transmission**

Antiretrovirals/PI

- **Pregnancy Category B/C**
 - **Maternal benefit usually outweighs fetal risk**
 - **Likely cross the placenta**
 - **All PIs can cause hyperglycemia**
 - **Atazanavir can cause hyperbilirubinemia**
 - **Indinavir can cause nephrolithiasis**

Antiretrovirals/Fusion Inhibitor (enfuvirtide)

- **Pregnancy Category B**
 - **Maternal benefit usually outweighs fetal risk**
 - **Very large molecule (4492 daltons), likely does not cross placenta**
 - **Animal data does not show risk**
 - **No human data available**
 - **Hold during first trimester if possible**

Antifungals/Azoles

(fluconazole, itraconazole, ketoconazole, posaconazole, voriconazole)

Pregnancy Categories C/C/C/D/D

- **Likely cross placenta**
- **Fluconazole \geq 400mg/day seems to be associated with cranio-facial abnormalities**
- **Itraconazole appears to have low risk**
- **Ketoconazole can impair testosterone and cortisol synthesis**
- **No data in humans is available for voriconazole, increased risk in animals**

Antifungals/Azoles

(fluconazole, itraconazole, ketoconazole, posaconazole, voriconazole)

Lactation

- Fluconazole is compatible per AAP
- Itraconazole could concentrate in milk and body tissues, not recommended
- Ketoconazole is compatible per AAP
- No data with voriconazole, not recommended

Antifungals/Echinocandins

(anidulofungin, caspofungin, micafungin)

- **Pregnancy Category C**
 - **No data with anidulofungin**
 - **No human data with caspofungin, single case at UVA, animal data suggests risk**

- **Lactation**
 - **No human data, but probably compatible**

Antifungals/Polyenes

Amphotericin B

- **Pregnancy Category B, compatible, lipid complexes also compatible**
- **Lactation – no data available**

Migraine Headache Therapy

- **Triptans**
- **Ergots**
- **Butalbital**
- **Caffeine**
- **Dichloralphenazone**
- **Isometheptene**

Triptans (5-HT₁ agonists)

Pregnancy Category C

- **Limited human data exists, sumatriptan has been associated with VSDs in several cases**
- **No data available in humans for almotriptan, eletriptan, frovatriptan, or zolmitriptan**
- **Limited human data exists with naratriptan and rizatriptan, although animal data indicates moderate risks**
- **Pregnancy registry available for exposures**

Triptans (5-HT₁ agonists)

Lactation

- **Cross into breastmilk and may concentrate**
- **No reports of human lactation with almotriptan, frovotriptan, naratriptan, rizatriptan, or zolmitriptan**
- **Sumatriptan is compatible per AAP**
- **Eletriptan is likely compatible with low concentrations**

Ergots

(Dihydroergotamine, ergotamine)

Pregnancy Category X

- **Oxytocic properties could cause IUGR by vascular disruption or increased uterine tone**
- **Early exposure appears safe, not teratogens**
- **Chronic exposure is contraindicated**

•Lactation

- **Contraindicated**

Butalbital and Caffeine

Butalbital

- **Pregnancy Category C, can see neonatal withdrawal symptoms with long-term use**
- **Lactation – not recommended**

• Caffeine

- **Pregnancy Category B, doses generally lower than that in coffee**
- **Lactation – compatible**

Dichloralphenazone and Isometheptene (Midrin)

- **Dichloralphenazone**
 - **Pregnancy Category B**
 - **Lactation – similar agent considered compatible**
- **Isometheptene**
 - **Pregnancy Category C, extremely limited data**
 - **Lactation – potentially compatible**

Safe Drug Administration in children

Administration of drugs during the first year of life can be a challenge due to rapid changes in body size, body composition, and organ function.

The Neonate – birth to 4 weeks



Neonate - Absorption

Two major factors affect the absorption of drugs

- **pH dependent passive diffusion**
- **Gastric emptying**

Gastric pH

- **Gastric pH (6-8) is directly related to the presence of amniotic fluid in the stomach**
- **Postnatally, gastric acid secretory capacity appears after the first 24 to 48 hours and gastric acidity decreases during the first weeks of life**
- **Adult values are achieved at about 3 months of life**

Gastric pH in premature infant

In the premature infants, gastric pH may remain elevated due to immature acid secretion

Delayed Absorption in neonate

- **Prolonged emptying is seen in premature infant**
- **In the neonatal period the emptying rate is variable and prolonged**
- **Delayed absorption may also be a result of diminished pancreatic enzyme function and bile acid secretion.**

Absorption from skin and muscle in neonate

- **Percutaneous absorption may be drastically increased due to immature epidermis and increased skin hydration**
- **Absorption from intramuscular site may be unpredictable and decreased due to insufficient blood flow, poor muscle tone, and compromised muscle oxygenation**

Distribution drugs in children

- **Distribution of drugs within the body is influenced by the amount and character of plasma proteins, and relative size of fluid, fat and tissue compartments of the body.**
 - **Total body water**
 - **Plasma proteins**

Total Body Water

- **85 % in pre-term infant**
- **78% in neonate**
- **60% at 1 year**
- **64 % in childhood (10 to 15 year old)**
- **60% in adults**
- **54% in elderly**

Metabolism in infants

- **Hepatic enzyme activity and plasma / tissue esterase activity are both reduced during the neonatal period**
- **The enzyme activity increases as the infant ages but can be compromised in cases of severely malnourished infants and children**
- **Plasma half-life 2 to 3 times longer in neonates**

Neonate Renal Excretion

Renal Excretion

- 1. At birth, glomerular function is more advanced than tubular function. This persists until about 6 months of age.**
- 2. This affects the efficiency at which the kidneys eliminate drugs.**
- 3. This is especially important in the administration of aminoglycosides**

Infant – 5 weeks to 1 year



Infant - Absorption

- **Low acidity in stomach until around 2 years of age**
- **Gastric emptying still delayed**
- **Percutaneous absorption: continue to be increased through childhood**

Absorption - IM

- **Injected drugs are often erratically absorbed because of variability in muscle mass amount children and illness**
- **IM generally avoided due to pain and possibility of tissue damage**

Absorption - transdermal

- **May be enhanced in young children because the stratum corneum is thin and the ratio of surface area to weight is much greater than for older children and young adults**
- **Skin disruptions (abrasions, burns, eczema) increase absorption**

Absorption – transrectal

- **Transrectal is dependent on placement of the drug within the rectal cavity**
 - **Good for drugs such as acetaminophen (Tylenol)**
 - **Diazepam in status Epilepticus**

Absorption - lungs

- **Varies less by physiologic parameters and more by reliability of the delivery device**

- **Beta agonists may be used for asthma, pulmonary surfactant for hyaline membrane disease**

Meds via mask



Infant - Distribution

- **Protein-binding capacity reaches adult values within 10 to 12 months**
- **Higher doses (mg / kg) of water-soluble drugs are required in younger children due to higher percentage of their body weight in water**

Infant – Hepatic

Metabolism

- **Complete maturation of the liver develops by one year**

- **Cytochrome P-450 enzyme system in the small bowel and liver are the most important factor in drug metabolism**

Infant – Renal Excretion

Renal elimination depends on plasma protein binding, renal blood flow, GFR and tubular secretion all are altered in the first two years of life.

Drug Dosing

- **Dosing in children less than 12 years is always of function of age, body weight or both**
- **When very accurate levels dosing is needed, dose adjustments should be based on plasma drug concentration**

Child – 1 to 12 years



Pharmacokinetics in children

- **After one year similar to adults**
- **They metabolize drugs faster than adults until around age 2 years**
- **Metabolism declines again at puberty**
- **Increase in dosage or reduction in dosing interval may be needed for drugs that are eliminated by hepatic metabolism**