DRUGS AND PREGNANCY

IMPORTANCE

- many drugs can harm the fetus
- 2 to 3% of all birth defects result from drugs
- Sometime – essential for the health of the pregnant woman
  - risks and benefits of taking the drug
- More than 80% of pregnant women take some drugs during pregnancy
- prescription drugs over-the-counter drugs, dietary supplement – medicinal herbs social drugs (such as tobacco and alcohol) or illicit drugs

HOW THE DRUGS AFFECT THE FETUS?

- directly
  - damage, abnormal development (leading to birth defects), death
- can alter the function of the placenta
  - vasoconstriction
  - underweight and underdevelopement
- inducing intense uterin muscle contraction
  - injuring the fetus by reducing its blood supply
  - preterm labor and delivery.
- indirectly
  - blood pressure lowering drugs →reduce blood flow to the placenta →reduce the supply of oxygen and nutrients to the fetus

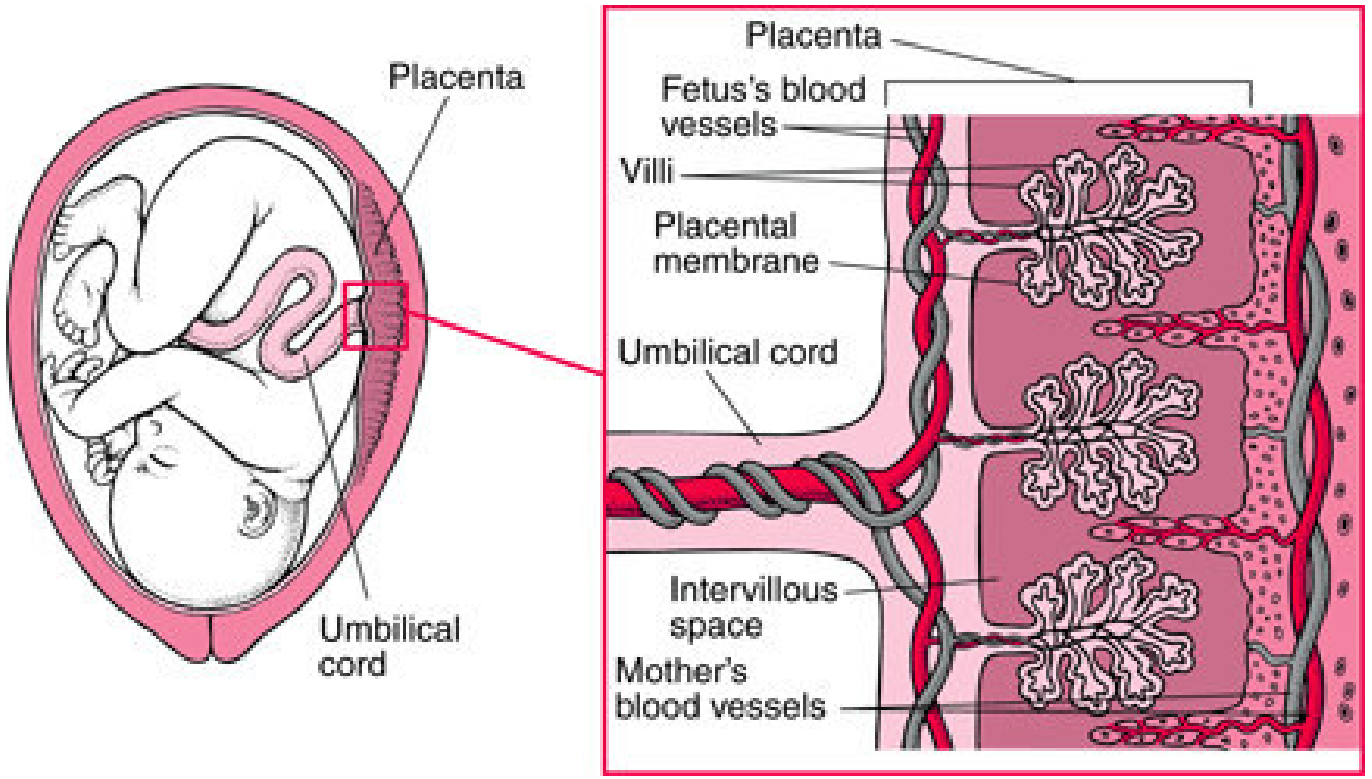
FACTORS AFFECTING PLACENTAL DRUG TRANSFER AND DRUG EFFECTS ON THE FETUS

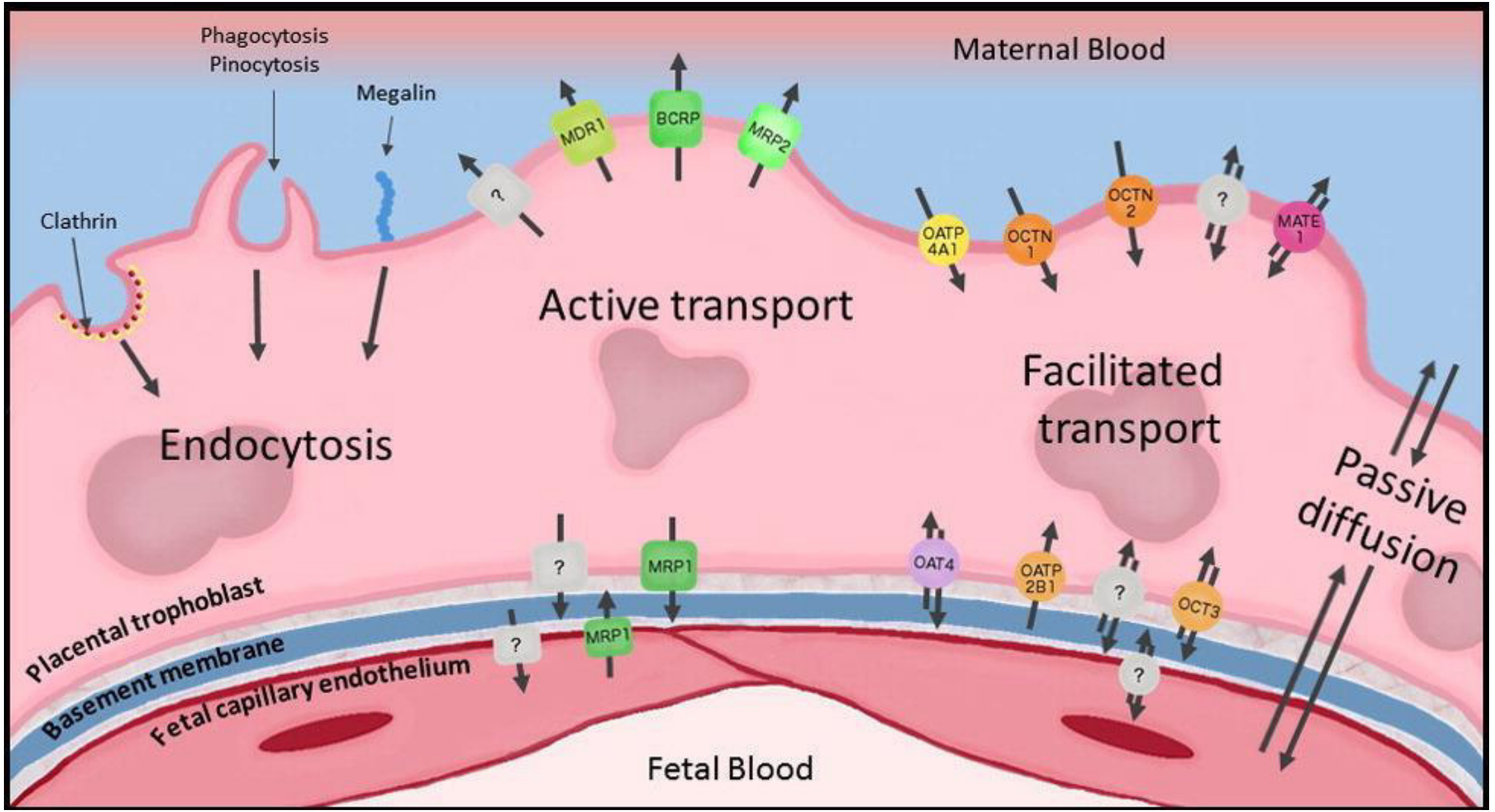
- the physicochemical properties of the drug
- the rate at which the drug crosses the placenta and the amount of drug reaching the fetus
- the duration of exposure to the drug
- distribution characteristics in different fetal tissues
- the stage of placental and fetal development at the time of exposure to the drug
- the effects of drugs used in combination

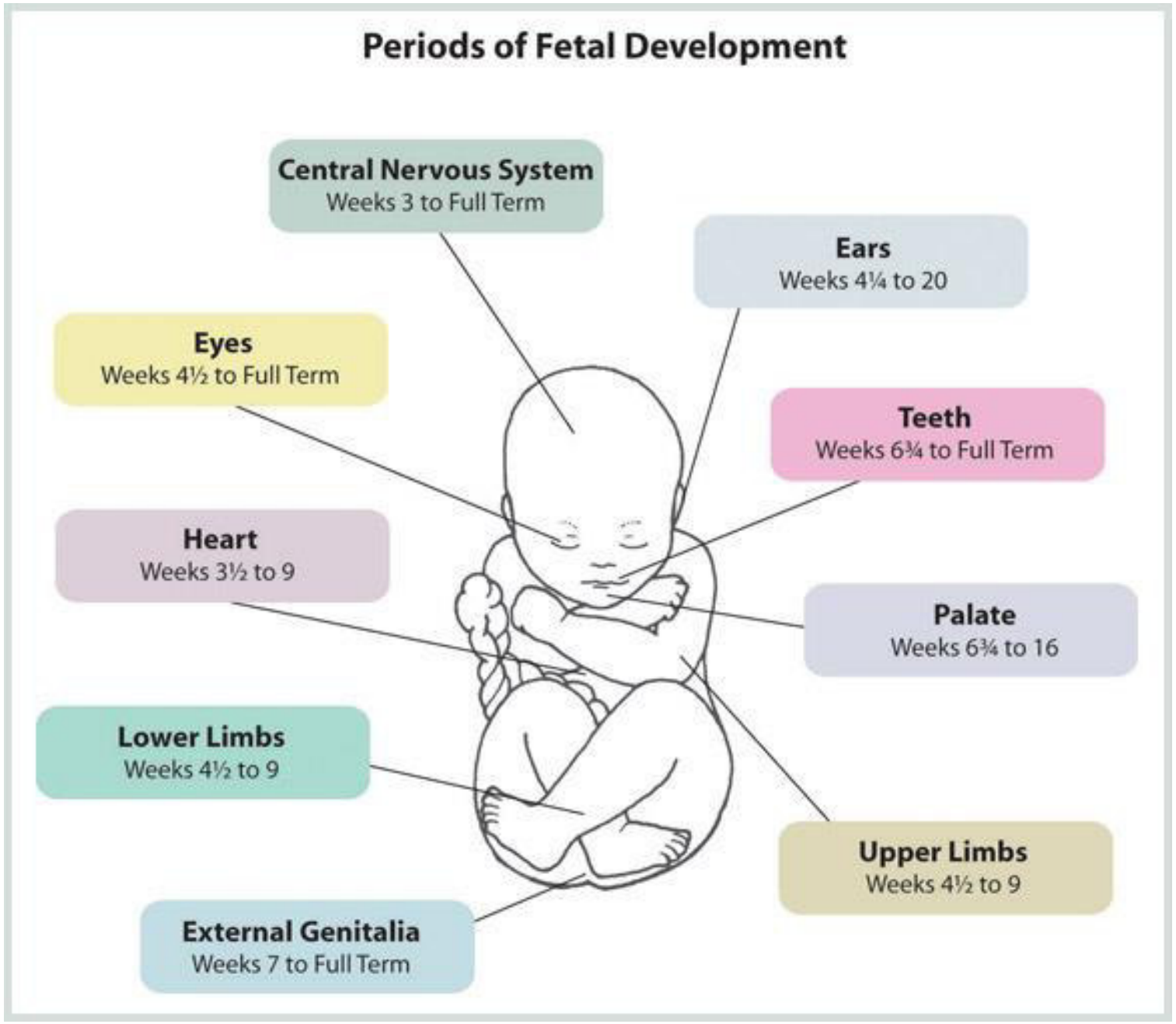
FACTORS AFFECTING PLACENTAL DRUG TRANSFER AND DRUG EFFECTS ON THE FETUS

- Lipid solubility and the degree of drug ionization
  - lipid soluble, non-ionized
- Molecular Size and pH
  - molecular weights of 250–500
  - molecular weights of 500–1000
  - molecular weights >1000 cross
  - ion trapping
    - maternal blood pH of 7.4, fetal blood is 7.3
    - basic drugs with a pKa above 7.4 will be more ionized in the fetal compartment, leading to higher fetal levels
- Protein Binding
- Placental and Fetal Drug Metabolism
  - hydroxylation, N-dealkylation, demethylation
  - creation of toxic metabolites, eg, ethanol, benzpyrenes
  - 40–60% of umbilical venous blood flow enters the fetal liver

HOW DRUGS CROSS THE PLACENTA

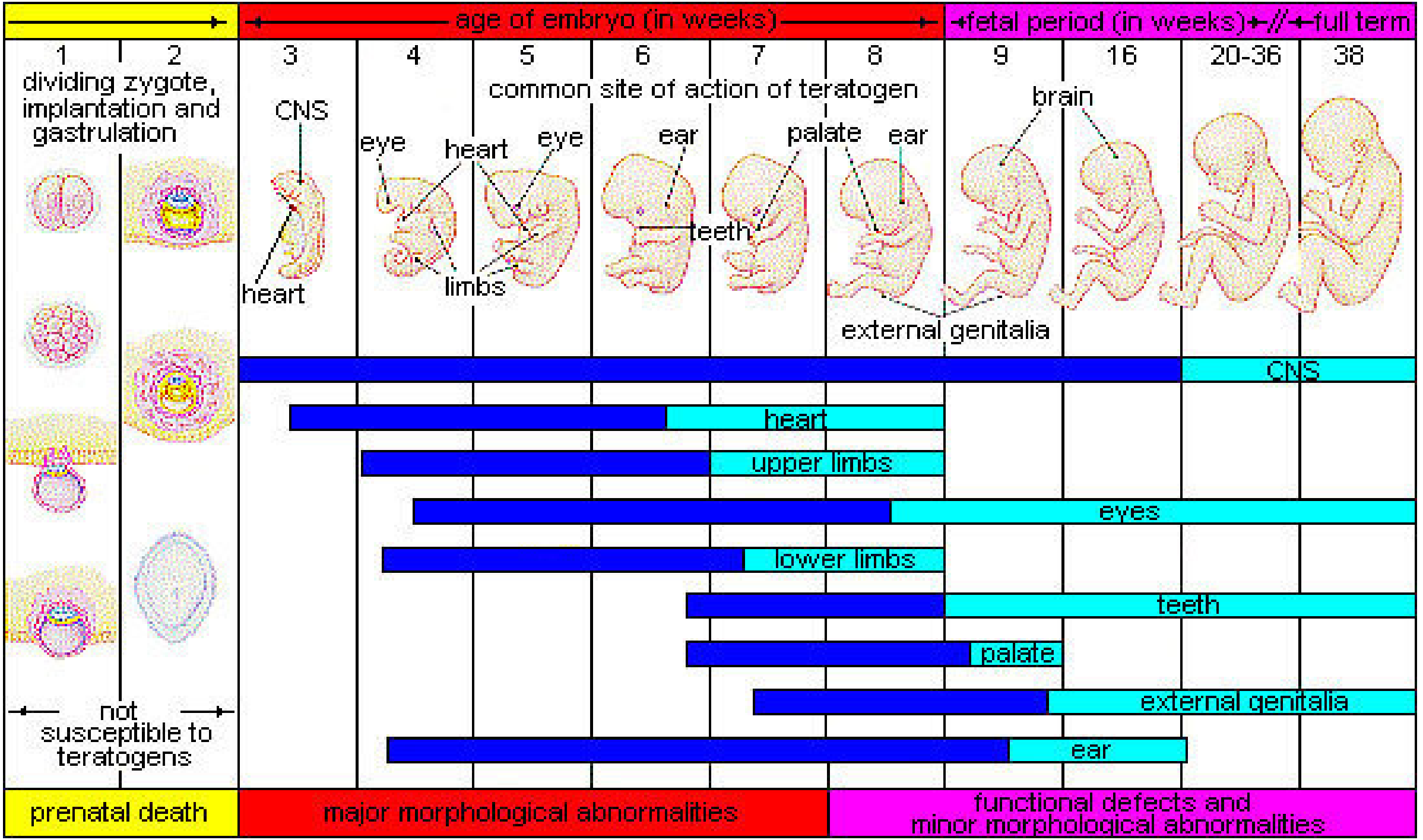



Phagocytosis
Pinocytosis
Megalin
Clathrin
Endocytosis
Maternal Blood
MDR1
BCRP
MRP2
?
Active transport
OATP 4A1
OCTN 1
OCTN 2
?
MATE 1
Facilitated transport
Passive diffusion
?
MRP1
MRP1
?
OAT4
OATP 2B1
?
OCT3
?
Placental trophoblast
Basement membrane
Fetal capillary endothelium
Fetal Blood


Periods of Fetal Development
Central Nervous System
Weeks 3 to Full Term
Ears
Weeks 4¼ to 20
Eyes
Weeks 4½ to Full Term
Teeth
Weeks 6¾ to Full Term
Heart
Weeks 3½ to 9
Palate
Weeks 6¾ to 16
Lower Limbs
Weeks 4½ to 9
Upper Limbs
Weeks 4½ to 9
External Genitalia
Weeks 7 to Full Term

FETAL AGE

- **Before the 20th day after fertilization:**
  - all-or-nothing effect
  - killing the embryo or not affecting it at all
  - Teratogenesis is unlikely during this stage
- **During organogenesis** (between **20 and 56 days** after fertilization):
  - Teratogenesis is most likely at this stage
  - spontaneous abortion
  - a sublethal gross anatomic defect (true teratogenic effect)
  - covert embryopathy (a permanent subtle metabolic or functional defect that may manifest later in life)
  - increased risk of childhood cancer (eg, when the mother is given radioactive iodine to treat thyroid cancer)
  - the drugs may have no measurable effect.
- **After organogenesis** (in the **2nd and 3rd trimesters**):
  - Teratogenesis is unlikely
  - drugs may alter growth and function of normally formed fetal organs and tissues


age of embryo (in weeks)
fetal period (in weeks)
full term
1
2
3
4
5
6
7
8
9
16
20-36
38
dividing zygote, implantation and gastrulation
common site of action of teratogen
CNS
heart
eye
heart
eye
limbs
ear
teeth
palate
ear
external genitalia
brain
not susceptible to teratogens
CNS
heart
upper limbs
eyes
lower limbs
teeth
palate
external genitalia
ear
prenatal death
major morphological abnormalities
functional defects and minor morphological abnormalities

FDA PREGNANCY CATEGORIES

- A, B, C, D and X risk categories
- in use since 1979
- replaced with narrative sections and subsections:
- Pregnancy (includes Labor and Delivery):
  - Pregnancy Exposure Registry (now **REQUIRED**)
  - Risk Summary (always required, even if no data is available)
  - Clinical Considerations
  - Data
- Lactation (replace the "Nursing Mothers" subsection)
  - Risk Summary
  - Clinical Considerations
  - Data
- Females and Males of Reproductive Potential
  - Pregnancy Testing
  - Contraception
  - Infertility

- Pregnancy and Lactation Labeling Final Rule (PLLR)
  - went into effect on June 30, 2015
  - the pregnancy letter category must be removed by June 29, 2018

FDA PREGNANCY CATEGORIES

Category	FDA drug risk classification in pregnancy	Examples
A	Controlled studies in women fail to show a risk to the fetus and the possibility of fetal harm appears unlikely.	levothyroxine, folic acid, liothyronine
B	Animal-reproduction studies have not shown a fetal risk or adverse effect. Risks have not been confirmed in controlled studies in women.	metformin, hydrochlorothiazide, cyclobenzaprine, amoxicillin, pantoprazole
C	Either studies in animals have revealed adverse effects on the fetus and there are no controlled studies in women or studies in women and animals are not available.	tramadol, gabapentin, amlodipine, trazodone
D	There is confirmation of human fetal risk, but the benefits from use in pregnant women may be acceptable despite the risk.	lisinopril, alprazolam, losartan, clonazepam, lorazepam
X	Animal and human studies have shown fetal abnormalities. The drug is contraindicated in women who are or may become pregnant.	atorvastatin, simvastatin, warfarin, methotrexate, finasteride

Drugs (D, X)	TRIMESTER	Effect
Aminopterin	I.	Multiple gross anomalies
Carbamazepin (Tegretol)	I.	Neural tube defects
Cyclophosphamide	I.	Various congenital malformations
Lithium (Liticarb)	I. and III.	Ebstein's anomaly, neonatal toxicity after third trimester exposure
Methotrexate	I.	Multiple malformations
Misoprostol (Cytotec)	I.	Möbius sequence
Mycophenolate mofetil	I.	Major malformations of the face, limbs, and other organs
Penicillamin (Byanodine)	I.	Cutis laxa, malformációk
Organic solvents	I.	Multiple malformations
Penicillamine	I.	Cutis laxa, other congenital malformations
Thalidomid (Contergan)	I.	phocomelia
Topiramate	I.	Oral cleft
Warfarin	I.	Hypoplastic nasal bridge, chondrodysplasia punctata

Drugs (D, X)	TRIMESTER	Effect
Amphetamines	I-III.	Suspected abnormal developmental patterns, decreased school performance
Barbiturates	I-III.	Chronic use can lead to neonatal dependence
Benzodiazepines	I-III.	Cleft lip, Chronic use can lead to neonatal dependence
Busulfan	I-III.	Various congenital malformations; low birth weight
Chlorpropamide	I-III.	Prolonged symptomatic neonatal hypoglycemia
Cocaine	I-III.	Increased risk of spontaneous abortion, abruptio placentae, and premature labor; neonatal cerebral infarction, abnormal development, and decreased performance
Danazol (Danoval)	I.	Teratogenic
	II.-III.	Virilisatio
Diazepam	I-III.	Chronic use may lead to neonatal dependence
Diethylstilbestrol	I-III.	Vaginal adenosis, clear cell vaginal adenocarcinoma
Ethanol	I-III.	Risk of fetal alcohol spectrum disorder
Ergotamin	I.	Abortion
	II.-III.	Fetal hypoxia and death
Etretinate	I-III.	High risk of multiple congenital malformations
Heroin	I-III.	Heroin

Drugs (D, X)	TRIMESTER	Effect
Iodide	I-III.	Congenital goiter, hypothyroidism
Isotretinoin	I-III.	Extremely high risk of central nervous system (CNS), face, ear, and other malformations
Methadone	I-III.	Chronic use may lead to neonatal abstinence syndrome
Methylthiouracil	I-III.	Hypothyroidism
Phencyclidine	I-III.	Abnormal neurologic examination, poor suck reflex and feeding
Phenytoin	I-III.	Fetal hydantoin syndrome
Propylthiouracil	I-III.	Congenital goiter
Smoking	I-III.	Intrauterine growth restriction; prematurity; sudden infant death syndrome; perinatal complications
Statines	I-III.	Various congenital malformations
Streptomycin	I-III.	n. VIII. (inner ear) damage
Tamoxifen	I-III.	Increased risk of spontaneous abortion or fetal damage
Tetracycline	I-III.	Discoloration and defects of teeth and altered bone growth
Trimethadione	I-III.	Multiple congenital anomalies
Valproic acid	I-III.	Neural tube defects, cardiac and limb malformations; developmental delay; possibly autism

Drugs (D, X)	TRIMESTER	Effect
ACE inhibitors	All, (!!!) II.-III.	Renal damage, hypocalvaria
Androgens	II.-III.	Masculinization of female fetus
Warfarin	II.	CNS malformations
Clomipramine (TCAs)	III.	Neonatal lethargy, hypotonia, cyanosis, hypothermia
Serotonin reuptake inhibitors	III.	Neonatal abstinence syndrome, persistent pulmonary hypertension of the newborn
Warfarin	III.	Risk of bleeding. Discontinue use 1 month before delivery.

ANTIBIOTICS I.

Penicillines (+ clavulanic acid)

- FDA B
- the most extensively studied group
- passes through placenta
- most penicillins can be used during pregnancy and breastfeeding in the usual doses

Macrolides

- FDA B
- Erythromycin – only type of macrolide that can take
- can increase serum transaminase levels

ANTIBIOTICS II.

Cephalosporins

- FDA B

Clindamycin

- FDA B

Sulphonamides and trimethoprim

- FDA B
- But near term FDA D (haemolytic anemia, Kernicterus)

Vancomycin

- FDA B
- Ototoxicity ?

ANTIBIOTICS III.

Fluoroquinolones

- FDA C
- Cartilage disorders in animal studies
- Not suitable for pregnant womens

Nitrofurantoin

- FDA B
- I-II. trimester: has no harmful effects on the fetus
- Near term: haemolytic anemia

ANTIBIOTICS IV.

Metronidazol

- FDA B
- I. trimester:
  - Theratogenic:
  - mental retardation, holotelencephaly, hip dysplasia, lip and palate cleft, vitium, hypospadias
  - II-III. trimester: can be used if there is no other alternative

ANTIMYCOTICS I.

Fluconazole (szisztémás)

- FDA C
- terathogenic and fetotoxic (animal studies)
- In high doses long-term therapy (400 mg/nap <): craniofacial abnormalities

Itraconazole (szisztémás)

- FDA C
- terathogenic and fetotoxic (animal studies)
- In short-term therapy is safe

ANTIMYCOTICS II.

Clotrimazole (local application)

- FDA B
- seem to be safe (few human data)

Econazole (local application)

- FDA C
- few human data

Butoconazole (local application)

- FDA C
- Thratogenic in high doses
- No human data available

ANALGESICS I.

Metamizol

- FDA classification has not yet happened, but has been found to be harmless so far

Paracetamol

- FDA B
- Safety in lower than1000 mg daily dose
- High dose: craniofacial and limbs deformities

ANALGESICS II.

Opioidok

- FDA B
- FDA D: in high dose long-term thearpy Csak
- can be used only in severe cases (high addictive potential, amplify nausea)
- I. trimester: polydactylia, hypospadias

MIGRAINE

Metoclopramid

- FDA B

Sumatriptan

- FDA C
- Harmful only in animal studies

AUTOIMMUN DISEASES I.

Dexamethason, betamethason

- FDA C
- Passes rapidly through placenta
- The metanolism in the placenta is very poor
- IRDS (Infant Respiratory Distress Syndrome) prophylaxis (menacing premature birth)
- may cause hypoglycaemia, leukocytosis in the newborn

AUTOIMMUN DISEASES I.

Prednisolon, methyl-prednisolon

- FDA C
- only 10-15 % crosses the placenta
- cleft palate
- Dose dependent effects

PARKINSON'S DISEASE

Selegilin

- FDA C
- In hypertensives increase the postpartum hypertension
- IUGR (intrauterine growth restriction) in animal studies
- Not recommended

DEPRESSION I.

- First psychotherapy!
- SSRI or SNRI
- Previously used SSRI or SNRI

DEPRESSION II.

Sertralin

- FDA C
- The first drug to be chosen (in the newborn, the lowest plasma level was found)
- Omphalokele risk arisen, but not proven

Citalopram

- FDA C
- It was associated with atrial septum defect, but not proven

DEPRESSION III.

Fluoxetin

- FDA C
- Long t1/2
- accumulates in the fetus
- Easily passes into breast milk

Paroxetin

- FDA D (not recommened)
- High risk of ventricular septal defect
- Neonatal hemangioma

DEPRESSION IV.

TCAs

Imipramine

- FDA D
- Cleft palate
- diaphragmatic hernia
- Cardiovascular and renal defect

DEPRESSION V.

Amitriptylin

- FDA C
- Terathogenic in animal studies
- In humans not proved

Clomipramin

- FDA C
- congenital heart defect (significantly higher risk)

DEPRESSION V.

Other antidepressives

Mirtazapine

- FDA C
- Increase the frequency of premature births

Bupropion (norepinephrine–dopamine reuptake inhibitor (NDRI))

- FDA C
- Significantly more miscarriages have been described

ANXIETY AND PANIC DISORDER I.

Benzodiazepines – Generally addictive effect

Alprazolam

- FDA D
- Terathogenic in animal studies
- Increases birth weight

Nitrazepam

- No FDA classification
- Increased risk of later suicide attempt

ANXIETY AND PANIC DISORDER II.

Diazepam

- FDA D
- Intense sedative effect
- Accumulates in the fetus (long T1/2)
- Cleft palate, bubonocele, spina bifida, neonatal hypothermia

ANXIETY AND PANIC DISORDER III.

Medazepam

- FDA D
- Neonatal haemangioma

Chlordiazepoxid

- FDA D
- Dose dependent IUGR

HYPERTENSION I.

Methyldopa

- FDA B
- Between the 16th and 20th week may slow the growth of bone, reduce the head circumference

Labetalol (α_1 antagonist, β parcial agonist, voltage gated Na channel inhibitor)

- FDA C
- Recommended

HYPERTENSION II.

Propranolol

- FDA C
- Intrauterine growth restriction (IUGR),
- Fetal bradycardia, hypoglycaemia, hypocalcaemia,
- In high dose increase the uterine contractions

Metoprolol

- FDA C
- Cross the placenta
- Most of the studies consider the metoprolol as a safe drug

HYPERTENSION III.

Pindolol

- I. trimester: FDA C
- II., III trimester: FDA D (IUGR)

Atenolol

- FDA D
- I. trimester: hypospadias
- II. trimester: fetal bradycardia, beta blockade and IUGR

HYPERTENSION IV.

Hydrochlorothiazid

- FDA B
- liquid and electrolyte loss (should be avoided)

Nifedipin

- FDA C
- safe

HYPERTENSION V.

Losartan, Valsartan

- FDA D
- Fetal renal damage, reduced fetal renal perfusion, anuria and oligohydramnios

Prazosin, Doxazosin, Urapidil

- FDA C
- Not teratogenic in animals
- Few human studies (seem safe)

THROMBOSIS

Enoxaparine, nadroparine, nalteparine

- FDA B
- does not cross the placenta
- Thromboprophylaxis during pregnancy and breastfeeding

Acetilszalicilsav

- FDA D (antithrombotic dose also)

ORAL ANTICOAGULANTS

K-vitamin antagonisták

- FDA X
- during conception is also dangerous

New oral anticoafulants (NOAC)

- No FDA classification
- Bleeding complications in animal studies (increased risk of abortion)

HERPES

Acyclovir

- FDA B
- Cross the placenta
- Little human experience (safe)

INFLUENZA

Oseltamivir (Tamiflu), amantadine

- FDA C
- altered bone growth in animal studies
- no reliable human data
- H1N1 for chemoprophylaxis (high risk of infection)

HYPEREMESIS GRAVIDARUM I.

- occurs within the first 12-14 weeks of pregnancy (I. trimester)
- Fluid and mineral supplementation, Mg, vitamin B6
- Cold liquid, ginger

Dimenhydrinat (Daedalon)

- FDA B
- 100 mg every 6 hours, max. 400 mg daily

Promethazine

- FDA C
- I. trimester: increased risk of cardiovascular anomalies

HYPEREMESIS GRAVIDARUM II.

Metoclopramide

- FDA B
- Human studies – safe
- 10 mg at every 6 hours

Ondansetron

- FDA B
- Animal studies – safe
- No harmful effects so far in humans
- 4-8 mg at every 8 hours

SEASONAL ALLERGY I.

Nasal corticosteroid administration: safe

Budenosid

- FDA B
- First choise nasal corticosteroid

Loratadin, cetirizin

- FDA B
- 10 mg daily dose
- Safe

SEASONAL ALLERGY II.

Pseudoephedrine

- FDA C
- Terathogenic in animals
- In humans: gastroschisis (not recommended)

Oxymetazoline

- FDA C
- Near term the chronic administration may induce fetal hypoxia, bradycardia
- Intranasal short-term therapy (< 3 nap) is safe