Developmental toxicology
Pharmacotherapy during pregnancy
Murphy’s law:
If anything can go wrong, it will
Teratology is the science that studies the causes, mechanisms, and patterns of abnormal development.

Progress during 20th century: genetics, Hiroshima, rubella, thalidomide.....
Causes of congenital anomalies

**Figure 9-1.** Graphic illustration of the causes of human congenital anomalies. Note that the causes of most anomalies are unknown and that 20 to 25% of them are caused by a combination of genetic and environmental factors (multifactorial inheritance).
Anomalies caused by environmental factors

- **Teratogens** are exogenous agents that may cause developmental defects:
  - **Drugs** (warfarin, valproic acid, phenytoin, vitamin A, thalidomide, lithium carbonate, cytostatic drugs – i.e. cyclophosphamide, methotrexate etc.)
  - **Chemicals** (PCBs, methylmercury, alcohols)
  - **Infections** (rubella, cytomegalovirus, herpes virus, toxoplasma, syphilis)
  - **Ionizing radiation** (X-rays)
  - **Maternal factors** (diabetes mellitus, hyperthermia, phenylketonuria, hyper-/hypo-thyreosis)
Causes of congenital defects caused by environmental factors:

Chemical compounds - i.e. drugs –(thalidomide), environmental factors (Minamata disease–organic compounds of mercury)
Thalidomide

- Firm Gruenewald brought it on market in 1957
- 1958-1961 cases of irreversible polyneuropathia

Widukind Lenz (1961) reports on accumulation of specific malformations (focomelia) data on 52 infants born to mothers taking thalidomide during pregnancy at a meeting of the German Society for Pediatric Medicine, and he later received 115 additional reports of similarly affected infants from physicians in Germany, Belgium, Sweden, and England

- Thalidomide was gone out of market
- 8000 -12000 malformed newborns
- Critical period 38. – 50. day after ovulation
- Risk 1-2:10, if exposed during critical period, i.e. 20% risk.
Anomalies caused by environmental factors

2. Ionizing radiation
3. Infections (rubella, syphilis, Zika)
Syphilis connata recens

Příznaky 2-12 týden

The influence of maternal diseases

- Caudal Regression Syndrome - sirenomelia
- It occurs more frequently in diabetic mothers
Birth defects

- 3% of all live-born infants have a major anomaly (immediately in time of birth)
- Additional anomalies are detected during postnatal live – about 6% at 2 year-olds, 8% in 5-year-olds, other 2% later
- Single minor anomalies are present in about 14% of newborns
- Major anomalies are more common in early embryos (up to 15%) than they are in newborns (3%). Most severely malformed embryos are spontaneously aborted during first 6 to 8 weeks.
Teratogen

- Teratogen is a factor that is present in the environment in such a high amount that it can increase the occurrence of embryotoxicity manifestation up to the basic frequency in non-exposed populations.

- Every chemical substance may be a poison (teratogen). This effect depends on quantity. In small amounts, it is without any effect.

- Teratogenesis is a process with a threshold-level effect.

- Teratogenicity is a manifestation of developmental toxicity representing a particular case of embryo/fetotoxicity, by the induction or the increase of frequency of structural disorders in the progeny.
Basic principles in teratogenesis

- Critical periods of development
- Dosage of the drug or chemical substance
- Genotype (genetic constitution) of the embryo and mother
Prenatal progress of losses

Nearly 70% of embryos is aborted

40% - 50% of embryos is aborted during the first 2 weeks
Figure 9-12. Schematic illustration of critical periods in human prenatal development. During the first 2 weeks of development, the embryo is usually not susceptible to teratogens; a teratogen either damages all or most of the cells, resulting in death of the embryo, or damages only a few cells, allowing the conceptus to recover and the embryo to develop without birth defects. Pink denotes highly sensitive periods when major defects may be produced (e.g., amelia, absence of limbs). Green indicates stages that are less sensitive to teratogens when minor defects may be induced (e.g., hypoplastic thumbs).
Critical and sensitive periods of development
Dose-response relation in teratology

- A - afflicted
- B - malformed
Testing for teratogenicity

- Standardized procedures for the drug testing for teratogenic potential are used.
- They use at least two common mammalian laboratory species, that are given several different doses of the test agent once or several successive days during organogenesis and early fetal period (acute and chronic toxicity).
- Teratogenicity: 3 doses are administered conventionally; the highest causing maternal toxicity, during organogenesis.
- Evaluation of human case reports and epidemiological investigation (retrospective and prospective).
Correlation data obtained from animal studies

- Dose, way of administration, resorption ability
- Plasma level, bound on proteins
- Metabolism in liver – effective metabolites, (different metabolic pathways can be used)
- Transfer through placenta, plasma level in fetus
- Mechanism of the effect, bond on receptors
The process estimating reproductive and embryo- or fetotoxic drug effect

- The sudden increase in the prevalence of specific malformations
- The link between increase of the drug use or start of drug taking and increase of specific malformations prevalence is confirmed
- The drug should be used during sensitive periods to cause a specific malformation
- Drug or its metabolite which is suspected teratogen, must reach the fetus
- It is necessary to confirm that the drug caused malformations, never conditions (illness)
- The findings must be confirmed by other independent studies
- Outcome studies on laboratory animals should confirm epidemiological findings
About 80% pregnant women use prescribed or over-the-counter drugs. The drugs should only be taken when essential thereby avoiding unnecessary and unknown risks. The same is obviously applied to social drugs like tobacco, alcohol and additive drugs.
Labeling of some prescription drugs includes information about the level of risk for the fetus and the extent of caution necessary in their use. The FDA has established five categories (A, B, C, D, and X) to indicate a drug's potential for causing teratogenicity. This format was first announced in the September 1979 FDA Drug Bulletin. Because of labeling revisions, products should not be classified in this format.

A similar, but somewhat expanded, classification system was adopted by the Australian Drug Evaluation Committee (ADEC) in 1989. Germany set forth its own classification system.

The European Union-The European Medicines Agency (EMEA) standard links in leaflets
US FDA Pregnancy Category Definitions

- **A** - Adequate, well-controlled studies in pregnant women fail to demonstrate a risk to the fetus in the first (second, third, or all) trimester(s), and the possibility of fetal harm appears remote.

- **B** - Animal studies do not indicate a risk to the fetus; however, there are no adequate, well-controlled studies in pregnant women. OR Animal studies have shown an adverse effect on the fetus but adequate, well-controlled studies in pregnant women have failed to demonstrate a risk to the fetus. Despite the animal findings, the possibility of fetal harm appears remote, if used during pregnancy.

- **C** - Animal studies have shown that the drug exerts teratogenic or embryocidal effects, and there are no adequate, well-controlled studies in pregnant women, OR No studies are available in either animals or pregnant women.

- **D** - Positive evidence of human fetal risk exists, but benefits in certain situations (i.e. life-threatening situations or serious diseases for which safer drugs cannot be used or are ineffective) may make use of the drug acceptable despite its risks.

- **X** - Studies in animals or humans have demonstrated fetal abnormalities or there is positive evidence of fetal risk based on human experience, or both, and the risk clearly outweighs any possible benefit. The drug is contraindicated in women who are or may become pregnant.
QUALITY OF DATA

Proportion

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n=2240

90%

1%
Drug classification by risk factors

- The rating according to FDA classification does not provide sufficient useful therapeutic guidance.
- The characterization of different categories of drugs are ambiguous and difficult to evaluate whether reader is physician.
- The anxiety may even lead to unnecessary termination of pregnancy.
Information sources

- Animal studies
- Case-reports
- Retrospective studies
- Prospective studies
- Meta-analysis
- Randomized blinded studies are not possible in pregnant women from ethical reasons

Data known only from registration from animal studies – risk approximately 10% up to base line

100 cases – risk under 6%

600 cases risk under 3%

More than 1000 cases - risk under 1%
Surveillance and monitoring

- EUROCAT (European Concerted Action on Congenital Abnormalities and Multiple Births – 1979)
In 1990, two networks of Teratology Information Services were established, OTIS (USA and Canada) and ENTIS (Europe).

- They provide information relating to the pertinent situation of the person involved
- They carry out follow-up studies to learn about what happened during the course of pregnancy and health of the newborn
Recommendation

- Disease have to be treated in all cases! Disease without treatment is more risky than appropriate treatment.
- We should use drugs with well-known effect on pregnancy without signs of embryotoxicity. It is not recommended to change quickly a lot of drugs.
- It is not recommended to use combinations of various drugs. Undesirable effects may be multiplied.
- *Any woman in reproductive age may be pregnant!!*
Drugs classified as dangerous

- Thalidomide
- Cytostatics
- Warfarin and other coumarine derivatives
- Anti-epileptic drugs
- Retinoids and vitamin A
- Alcohol
- Androgens
- Diethistilbestrol
- Antagonists of folic acid (aminopterin)
- Lithium
- Ribavirin
- Mycophenolate mophetil
- ACE inhibitors
- Non-steroid antiphlogistic (NSAID)
Thalidomide

- Meromelia, amelia
- Cardiac and other malformation
Fetal warfarin syndrome

- Calcification disorder
- Face dysmorphism - flat face, hypoplastic nose, wide nasal bridge
- Low IQ
- Cardiac malformation
- Bleeding into tissue – mainly CNS
Embryopatia caused by retinoid acid

- Impairment of segmentation
- Impairment of CNS histogenesis – low IQ
- Cardiac malformation
- Malformed ear, small mandible, hypertelorism
Mycophenolate mophetil

- Antibiotic used as immuno suppressant for treatment of autoimmune diseases and after the organ transplantation
- Typical anomaly is impairment of ear development
- Teratogenicity was evaluated in animal studies and in prospective studies with relatively low number of exposed pregnancies
ACE inhibitors

- Drugs used for hypertension treatment – they have effect on renin-angiotensin-aldosteron signal pathway
- During first trimester they are not teratogenic
- During 2nd and 3rd trimester they impair normal regulation within kidney and also cell differentiation – resulting in kidney failure (anuria, oligohydramnios) and renal tubular dysgenesis (ACE appear during 26th week of pregnancy)
- Abortion, preterm birth, respiratory distress syndrome