

# Teratogenesis

**Teratogenesis** – disorders of prenatal development, which lead to developmental defects (cleft palate, malformations of limbs, sensory and internal organs)

## Effects of teratogens

Teratogens affect prenatal development in many different ways, i.e., not just by inducing mutations! It is any agent that is responsible for a developmental defect or for increasing its **incidence in the population**.

Some newborns are affected by **congenital malformations (CM)**, in the Czech Republic the frequency of CM is about 5% at birth. The frequencies depend on the **gene pool of the population**, the exposure load of the environment and also on the setting of the spectrum of their **monitoring**.

CM is defined as a **deviation from a structure or function** that exceeds the limits of normal **species variability**. Organ defects that occurred during prenatal development are present at the **birth of the individual** (whether diagnosable or not at the time). Other CMs are diagnosed only during life, when the **intensity of congenital malformations** is one of the basic qualitative population and medical indicators.

This deviation puts its bearer at a disadvantage compared to other individuals.

They can have a **variety of genetic and non-genetic causes**, different mechanisms of origin, different phenotypic manifestations and, based on that, **different end effects**.

They can manifest **at birth** as a morphological disorder of varying intensity or later growth failure, fertility disorders, sterility, eye disorders, IQ depletion, learning disabilities, hyperactivity,... CM also includes metabolic disorders.

## Types and description of congenital malformations

– malformation, disruption, deformation, dysplasia, sequence, syndromes, association

### 1. Malformation

- **organ development** disorders that result from changes in **genetic information**
- **monogenic**, multifactorial hereditary
- birth defects affecting only **individual organs**
- they occur most often between the **3. and 8. week**
- e.g., heart defects, spina bifida, polydactyly, clefts

### 2. Disruption

- **organ disorders** caused by **external influences**
- limb malformations caused by amniotic bands (wrapping, limb strangulation as a result of amniocentesis)

### 3. Deformation

- defects caused by **unusual mechanical forces** on a normally established organ
- Talipes equinovarus due to lack of **amniotic fluid**
- caused **by forced foot misalignment**

### 4. Dysplasia

- caused by **abnormal organization** of cells in tissues
- the cause is a **disorder** of induction, differentiation, apoptosis
- Osteogenesis imperfecta, renal dysplasia

### 5. Sequence

- **multiple defects** arise as a cascade of subsequent events
- in renal agenesis, lack of amniotic fluid leads to deformity of the face by pressure of the uterine walls and hypoplasia of the lungs (without sufficient amniotic fluid, they cannot develop properly)

### 6. Syndroms

- **multiple defects**, with a known common cause
- described several **thousands of syndromes** of various genetic etiologies

- **monogenically** inherited, chromosomal, teratogen-induced
- for the diagnosis of the necessary **syndrome database**

## 7. Association

- **combinations** of multiple defects that are not a sequence or a syndrome
- **VACTERL association** (vertebral-anal-cardiac-tracheal-esophageal-renal-limbs abnormalities)
- caused by **teratogens** on the development of multiple organs simultaneously

Wilson's table of teratogenic effects

Causes	Mechanisms	Speeches
<b>Radiation and ionizing radiation</b>	gene, chromosomal and genomic mutations	disturbed genetic programs of differentiation, intrauterine death
<b>Chemical effects of the environment</b>	mitotic division disorders	disorders of biosynthetic mechanisms
<b>Medicines, drugs, alcoholism, smoking</b>	transcription and translation disorders	erroneous cell interactions, developmental defects
<b>Maternal infections; metabolic or hormonal imbalance</b>	lack of precursors, failures of energy sources	disorders of cell mass proliferation and movement, delayed growth
<b>Deficiency of nutrients and vitamins</b>	membrane receptor disorders	tissue detachment
<b>Fetal hypoxia, placental dysfunction</b>	enzyme inhibition	unprogrammed cell death, functional disorders
<b>Mechanical damage</b>	ionic imbalance	

The real cause and effect relationship is complex in teratogenesis. The resulting effect depends on the teratogen, the intensity and duration of action, on the genotype of the fetus and mother.

## Examples of teratogens

**Teratogens** - substances that cause abnormal prenatal development, which leads to developmental defects

### Physical teratogens

- **radioactive radiation** - causes mainly chromosomal breaks
- risk is increased by higher doses of radiation, such as those used in the treatment of tumors
- large doses of ionizing radiation can cause anencephaly, spina bifida and microcephaly depending on the stage of embryonic development at the time of exposure
- **high temperature** (hyperthermia) can adversely affect the development of the CNS in particular

### Chemical teratogens

- all mutagenic substances are potential teratogens
- in medicine, possible teratogenic effects of drugs are evaluated - Contegran (Thalidomide) - malformations of limbs, ears and other defects
  - **antiepileptics** - especially in combination, up to 10 % risk of fetal defects - cleft lip and palate, cleft spine
  - **hydantoin antiepileptics** cause **hydantoin syndrome** - heart defects, cleft palate, distal phalangeal hypoplasia
- co-administration of folic acid reduces the risk - it favorably affects nucleic acid metabolism
- **antibiotics** - streptomycin, tetracycline
- **cytostatics**
- **alcohol** - fetal alcohol syndrome (delayed psychomotor development, restlessness and facial dysmorphism - narrow eye slits, long philtrum)

### Infection

- the highest risk is the primary infection of the mother and the fetus at the beginning of pregnancy
- the presence of antibodies in the mother's blood after a disease or vaccination before pregnancy usually protects the fetus from infection
- the most important teratogens - rubella virus (CNS disorders, heart defects), herpes virus, cytomegalovirus, HIV
- toxoplasmosis (eye defects, CNS damage), syphilis

### Mother's diseases

- unrecognized or insufficiently treated diseases of the mother can adversely affect the conditions for fetal development and cause developmental defects
- Typical diseases with a risk to the fetus include **diabetes mellitus** (poorly treated diabetics have an increased risk of miscarriages and newborns with birth defects)
- **maternal phenylketonuria** (high levels of phenylalanine cause fetal CNS damage with subsequent severe psychomotor retardation regardless of fetal genotype)

- **obesity** (BMI > 30) – higher risk of neural tube defects

### Dose factor

- **the dose** of the teratogenic agent is often critical
- **low doses** of teratogen may not cause a birth defect at all, they may cause a **milder disability**, or even another **type of defect**

### Time factor

- **the sensitivity to the effect** of individual teratogens is not the same throughout pregnancy
- the effect of teratogens in the **first trimester** of pregnancy has the worst prognosis
- **critical period** = time for which the fetus is most sensitive to a certain teratogen, more precisely when an organ that is sensitive to the effect of a given **teratogen** develops
- "All or nothing" = a reaction of the very **early stages of the embryo** that can either correct the effect of the teratogen or lead to an abortion

### Species genotype factor

- **sensitivity** to the action of individual **teratogens** is also affected by the genetic makeup of a **particular individual**
- significant **interspecies variability**
- important in **teratogen testing** on non-human species
- for example, the effect of **thalidomide** in the rat is 100 times smaller than in humans

## Links

- **FDA Drug Category** (2015): <https://www.drugs.com/pregnancy-categories.html>

### Related articles

- Teratogens
- Congenital malformations
- Drugs in pregnancy

### Source

- ŠTEFÁNEK, Jiří. *Medicína, nemoci, studium na 1. LF UK* [online]. [cit. 11. 2. 2010]. <<http://www.stefajir.cz>>.

### References

- SADLER, Thomas W. *Langmanova lékařská embryologie*. 10. edition. Praha : Grada, 2011. ISBN 978-80-247-2640-3.