

# Teratogenesis

# Teratogenic factors

Widely distributed. During pregnancy, each woman takes an average of 3.8 items of drugs. In the US, 10-20% of pregnant women take drugs.

In addition, harmful substances are found in the home (microwave, electronic clock) and at work.

# Teratogenic factors

- Chemical
- Physical
- Biological

# Criteria of teratogenic factors

- The connection between the action of the factor and the formation of malformation is proved
- Epidemiological studies confirm this link
- The effect of the harmful factor coincides with critical periods of intrauterine development
- With rare exposure to the damaging factor characteristic malformations are rarely formed

# Main groups of teratogenic factors

- Drugs and chemicals (tetracycline, trichopol, androgens, mercury, lead, phosphorus)
- Ionizing radiation (radioactive fallout, radioisotope diagnostics, radiation therapy)
- Viral and bacterial infections (herpes, rubella, syphilis, toxoplasmosis)
- Metabolic disorders and bad habits (diabetes mellitus, endemic goiter, phenylketonuria;
- Smoking, alcoholism, drug addiction

# Features of influence of teratogenic factors (TF)

- Dose-dependent character.
- For each TF there is a dose of teratogenic action.
- Usually it is 1-3 orders of magnitude lower than lethal.
- Sensitivity to different TF during fetal development may vary.

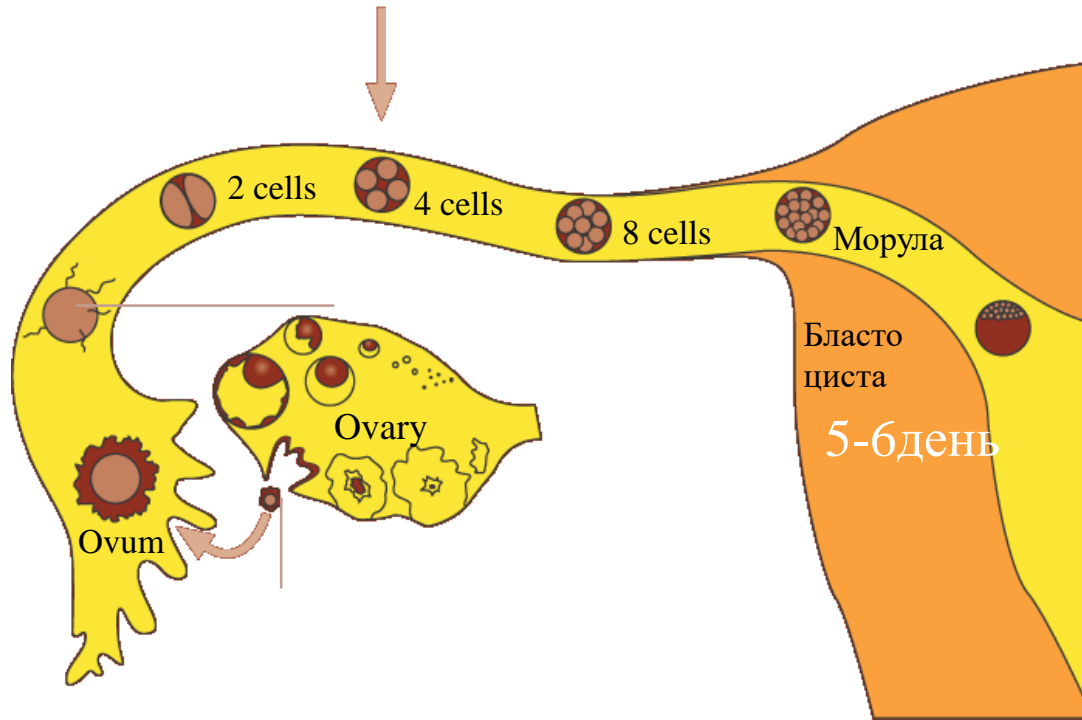
Infectious agents as teratogenic factors do not have a threshold dose and dose dependent nature

# Periods of intrauterine human development

- **Initial** - from the moment of fertilization to implantation of blastocysts (up to 11 days).
- **Embryonic** (18-60 days after fertilization)
- **Fetal** (from 9 weeks of pregnancy to birth)

# Initial period

It is characterized by large compensatory and adaptive capabilities of the embryo. The law "all or nothing" - when a large number of cells are damaged, the embryo dies, when individual blastomeres are damaged, further development is not violated



# Embryonic period

The embryo is most sensitive to the action of TF.  
gross malformations are Formed



# The fetal period

Malformations are not characteristic. Under the influence of the external environment, growth inhibition and/ or cell death occurs, which is further manifested by underdevelopment or functional immaturity of organs



# Major malformations

- Malformations of the Central nervous system – anencephaly, spina bifida, hydrocephalus. Formed as a result of cleft of the neural tube when folic acid deficiency, infections, diabetes.
- Congenital heart disease - ASD, tetralogy of Fallot, stenosis of the aorta and so on (phenylketonuria, lupus, rubella virus, genetic factors, alcohol, NSAIDs, diabetes mellitus)
- Cleft lip, firm palate
- Congenital clubfoot
- Congenital hip dislocation
- Malformations of the gastrointestinal tract-stenosis of the pylorus, Hirschsprung's disease, atresia of the esophagus, anus, etc.

# General approaches to prenatal prevention

1. Environmental protection
2. Family planning (consanguineous marriages, childbearing after 35 years)
3. Prenatal diagnosis – the elimination of embryos with abnormal
4. Identification of heterozygous carriers
5. Periconceptional preparation
6. Invasive and non-invasive methods of intrauterine diagnosis

# Periconceptional preparation

- medical and genetic counseling;
- carrier diagnosis and treatment of viral and bacterial infection;
- exclusion of occupational hazards;
- giving up bad habits;
- the intake of folic acid and Tocopherols)

# Methods of intrauterine diagnosis

## 1. Noninvasive method:

- Ultrasound (10-14, 22-24, 32-34 weeks),
- Biochemical marker:
  - 9-14 weeks b-HCG, rarr-A From 17 to 19 weeks AFP, 17 MIC, b-HCG, estradiol

## 2. Invasive method:

- Chorionic villus sampling (9-11 weeks)
- Cordocentesis (22-24 weeks)

# Drugs and chemicals

**For the transplacental transition are important:**

Molecular weight of the drug (up to 600 easily pass, 600-1000 limited, more than 1000 almost do not penetrate). Most drugs are less than 600 and easily penetrate to the fetus. Fat-soluble substances easily diffuse through the placenta (ether, nitrous oxide). Binding to blood proteins. The greater the bond, the slower the penetration through the placenta and accumulation in the fetus. The method of introducing the material Stage of intrauterine development

# Categories of drug safety

Risk categories of drug use during pregnancy FDA (Food and Drug Administration)

**A - no risk to the fetus;**

**B - the risk to the fetus is not established in animals or humans;**

**C - risk to the fetus has not been established in humans; controlled human studies have not been conducted;**

**D - there is a risk to the fetus, but can only be used at risk to life; it is necessary to assess the degree of risk and benefit;**

**X-proven risk to the fetus. When pregnancy is contraindicated.**

# Absolute teratogens

Drugs used in Oncology:

1. Antimetabolites (6-mercaptopurine)
2. Alkylating agents (cyclophosphamide)
3. Antitumor antibiotics (actinomycin, sarcolysin)

# Antibacterial drugs during pregnancy (Gurtov B. L. et al. 2004)

Group I - contraindicated in pregnancy:  
tetracyclines, chloramphenicol, trimethoprim.

Group II - apply only on vital indications:  
aminoglycosides, nitrofurans, sulfonamides.

Group III - antibiotics without embryotoxic action:  
penicillins, cephalosporins, macrolides.

# Effects of antibiotics

- Tetracycline and its derivatives in the early stages lead to malformations, in the late-slows the growth of the fetus, the defeat of the rudiments of the teeth, hepatotoxic effect
- Chloramphenicol – aplastic anemia
- Aminoglycosides-ototoxic effect

# Hormonal preparation

- Estrogens lead to the development of adenosis and light cell adenocarcinoma of the vagina and cervix in girls

# Ionizing radiation

The effect of radiation on the female body occurs according to the General laws of radiation damage-  
radiation practically does not penetrate the skin, but is very dangerous if ingested-  
b-radiation penetrates to a depth of 1-2 cm-  
g-radiation has the greatest penetrating power with the formation of free radicals, leads to gene mutations

**Transplacental transfer is the major penetration of the isotopes**

# Mechanisms of transplacental transition of radionuclides

- Hematogenic pathway-free transfer of isotopes from the mother's blood to the fetal blood through the transplacental membrane ( $^{131}\text{I}$ ,  $^{32}\text{P}$ , etc.)
- Accumulation in the tissues of the placenta with subsequent effects on the fetus (transuranic elements)
- Paraplacental transition through fetal membranes and amniotic fluid (radioactive plutonium)

# Infection (mechanisms of action)

1. Viruses (cytomegalovirus, herpes, rubella), penetrating to the embryo and fetus, can have a direct teratogenic effect
2. Infection leads to changes in the metabolism and function of the endometrium, which causes a violation of implantation or a violation of the development of the placenta

# Infection (mechanisms of action)

3. Viral and bacterial infection can affect the development of the placenta and lead to CKD and fetal STD
4. Bacterial toxins can have a toxic effect on the fetus

# Pernicious habits

- Smoking
- Use of alcohol
- Addiction

# Smoking

- Tobacco contains more than 600 harmful factors: organic and inorganic acids, proteins, esters, aldehydes, phenols, etc.
- Currently, radioactive polonium has been detected in tobacco smoke
- Nicotine has the greatest impact

# Nicotine

- Exposure to nicotine in early pregnancy can lead to impaired egg implantation and spontaneous abortion.
- Abortion and premature birth may be due to increased contractile activity of the uterus when Smoking
- Nicotine leads to contraction of the vessels of the uterus and placenta with the development of placental insufficiency and fetal hypoxia

# Nicotine

- Fetal hypoxia is also associated with increased levels of carboxyhemoglobin
- Violation of the development of the placenta contributes to the emergence of CKD and fetal STD
- Nicotine intensively penetrating through the placenta and accumulating in it, penetrating through the amnion, accumulating in the internal organs of the fetus, causes prolonged intoxication

# Alcohol

Systematic use of alcohol during pregnancy  
can lead to the development of fetal  
alcohol syndrome

# Fetal alcohol syndrome

- Violation of the structure and function of the Central nervous system (microcephaly, impaired intelligence, coordination)
- A slowdown, particularly noticeable after the baby is born
- Characteristic anomalies of the facial skull (microphthalmia, elongation of the face, low forehead, underdevelopment of the chin, small saddle-shaped nose, large wide open mouth, strabismus, flattening of the nape)

# Pathogeneses of fetal alcohol syndrome

Insufficiently studied. It is known that:

- Ethanol easily penetrates the placenta and blood-brain barrier of the fetus, accumulates in the
- Central nervous system, having a toxic effect
- In the liver of the fetus there is no enzyme alcohol dehydrogenase, which destroys ethanol, so the fetus is exposed to prolonged exposure
- Embryotoxic and teratogenic action has a metabolite of ethanol-acetaldehyde