МЕДИЦИНА, ПЕДАГОГИКА И ТЕХНОЛОГИЯ: ТЕОРИЯ И ПРАКТИКА
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EFFECTS OF DRUGS ON THE FETUS

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Abstract: This article provides information on the effect of drugs on the fetus. In particular, there is detailed information about drugs prohibited for women during pregnancy and their negative effects on the fetus.

Key words: medicines; pregnancy; embryotoxic effect; teratogenic effect; fetotoxic effect; embryo; fetus.

The effect of drugs on the embryo, fetus and newborn, in terms of probable medical and social consequences, is one of the pressing problems of modern medicine. Its importance is determined by the fact that, according to statistical data, about 80% of pregnant women take medications either as prescribed by a doctor or on their own. The need for pharmacotherapy during childbirth is constantly increasing. During pregnancy, the mother-placenta-fetus triad is considered as a single biological, pharmacological and pharmacokinetic complex. The main target of influence of drugs administered during pregnancy is the mother's body, but the fetus is often also a target for drugs. This dependence is associated with the possibility of penetration of many drugs through the placental barrier. This ability of the drugs is maintained throughout the entire period of pregnancy. The effect of drugs on the embryo and fetus is mainly toxic or undesirable, which has become a serious problem for the correct prescription of drugs during pregnancy. Research by the World Health Organization (WHO) has shown that drugs, as well as alcohol, tobacco, drugs and hallucinogens, are taken during pregnancy by more than 90% of women. Epidemiology of drug use by pregnant women in the Russian Federation (data from a multicenter retrospective study in 6 cities - 18 consultations, 543 pregnant women):

1) the average number of drugs during pregnancy is 11 ± 5.3 (1–26);
2) in the first trimester, 72% of women – 3.2 ± 1.9 HP (from 1 to 16);
3) mineral and vitamin preparations – 92.4%;
4) iron supplements – 80.9%;
5) antimicrobial drugs for local use – 50.3%.

Information about the safety of drugs during pregnancy is insufficient for more than 80% of drugs available on the market. Potential consequences of using medications during pregnancy:

- congenital anomalies;
- intrauterine death;
- sensitization;
- slowdown of intrauterine development;
- intoxication with withdrawal syndrome in a newborn;
- neurobehavioral teratogenicity;
- spontaneous abortions and premature births and other complications of pregnancy;
- complications in the postpartum period.

The effect on the embryo can be determined by the destructive effect of drugs or the formation of developmental defects according to organogenesis: central nervous system (CNS), skeleton - from 3 weeks to the end of pregnancy (especially 3–16 weeks); heart – 3–6 weeks (especially 3–4 weeks); upper limbs – 4–5 weeks; eyes – 4–8 weeks; lower limbs – 4–6 weeks; teeth – 6–8 weeks; sky – 6–9 weeks; external genitalia – 7–9 weeks; ears – 4–9 weeks [5]. Individual unusual reactions to medications may be determined by the genetic makeup of the fetus. Ontogenetic factors, causing disturbances in the activity of enzyme systems, can change the pharmacodynamics and pharmacokinetics of drugs, modulating their pharmacological activity and biotransformation in the fetus. The most dangerous periods of pregnancy are the 1st, 3rd–6th and last weeks before birth. Medicines prescribed to a pregnant woman can cause embryotoxic, teratogenic and fetotoxic effects. The result of the action of a medicinal substance on the embryo and fetus can be miscarriages, prematurity, post-maturity, malformations, death of the embryo and fetus, intrauterine malnutrition, hemorrhagic syndrome, respiratory and cardiac depression, cardiac arrhythmias, neurological disorders , acute renal failure,

dysfunction of the endocrine glands (thyroid gland, adrenal glands) and other forms of pathology.

Embryotoxic effects are observed in the first 3 weeks after fertilization and consist in the fact that the drug causes the death of the embryo or morphofunctional disturbances in the activity of the cellular systems of the zygote or blastocyst. Teratogenic effects develop mainly during 4–8 weeks of pregnancy and are characterized by the fact that the damaging agent induces abnormalities in fetal development. According to the WHO definition, teratogenic are medicinal substances that cause the development of structural (morphological), functional (behavioral) and biochemical disorders in the antenatal period. Fetotoxic effects are observed from the beginning of the 14th to 38th week of pregnancy. They are expressed by morphofunctional disorders of individual cellular systems of the fetus against the background of the effects of drugs taken by a pregnant woman. Fetotoxic effects are expressed mainly by dysfunction of various systems and correspond to side, undesirable reactions to medications. An example is the closure of the ductus arteriosus in the fetus with a deterioration in the oxygenation of its tissues when anti-inflammatory drugs such as indomethacin are prescribed to pregnant women. The development of atrioventricular block in the fetus when anaprilin is prescribed to pregnant women can also serve as an example fetotoxic effect of drugs. The embryotoxic effect of drugs is manifested by damage or, more often, death of the blastocyst. Medicines that can have an embryo-lethal effect include estrogens, gestagens, mineralocorticoids, antitumor agents, antibiotics, sulfonamides, salicylates, barbiturates and nicotine. The teratogenic effect of drugs is accompanied by morphological damage to the organs and systems of the fetus. It is assumed that the likelihood of developing a fetal anomaly is determined by the age of the pregnant woman, genetic predisposition to the development of defects, gestational age, type and dose of the prescribed drug, and the functional state of the biotransformation and clearance organs of the drug. The highest likelihood of developmental defects is observed in pregnant women under 17 and after 35 years of age. The risk of teratogenic effects in these age periods is higher in cases of pregnancy diseases and genetic predisposition to the development of defects. The likelihood of developing heart and central nervous system defects is higher during weeks 3–6 of pregnancy, arms and legs – during weeks 4–7, palate – 6–8 weeks, external genitalia – 7–9 weeks, ears – 4–8 weeks. On the other hand, minor morphological abnormalities may occur from 9 to 38 weeks.

According to the degree of danger of teratogenic effects on the fetus, drugs are classified into three groups . The first includes the main teratogens, which are highly dangerous for the fetus and therefore are absolutely contraindicated for use during pregnancy. Their use should be stopped 6 months before the planned pregnancy. If pregnancy occurs, the woman must be warned about the danger of maintaining it, the high probability of developing fetal anomalies, and insist on interrupting its course. Medicinal substances that are definitely known to cause teratogenic effects include anbiotics such as actinomycin and tetracycline, antifolic drugs (methotrexate, trimethoprim), antitumor drugs (dopane, sarcolysine, vincristine, cis-platinum, doxorubicin, lomustine , carminomycin, mytoxantrone, etoposide, etc.), hormonal contraceptives, thalidomide, radioactive drugs (radioactive iodine, etc.) and antithyroid drugs (propylthiouracil, mercazolil). The second group includes medicinal substances with a certain teratogenic risk. These include oral hypoglycemic agents (butamide, glibenclamide, chlorpropamide, gliclazide, etc.), immunostimulants (thymalin, tactivin, myelopid), immunosuppressants (azathioprine, cyclophosphamide, cyclosporine), antiepileptic drugs (barbiturates, valproates, diphenine), estrogens and their antagonists (diethylstilbestrol, clomiphene, etc.), med-roxyprogesterone, aminoglycosides, antihistamines (terfenadine, diphenhydramine, Fervex), analgesics (codeine), indirect anticoagulants (vitamin K antagonists), some neuroleptics (fluphenazine, haloperidol), antiparkinsonian drugs (bromocriptine), some benzodiazepines (sibazon, midazolam, chlozepid). The third group includes drugs that can cause malformations in the fetus in the presence of special conditions (old age of the pregnant woman, very high doses of drugs, etc.). This group of medicinal substances includes salicylates, indomethacin and its analogues, anti-tuberculosis drugs (rifampicin), general anesthetics (fluorotan). The pharmacokinetics of drugs in pregnant and healthy women differs in that it requires a certain adjustment of dosages, frequency of administration and choice of route of drug administration. Taking into account the characteristics of pharmacokinetics, medicinal substances are divided into three groups:

1) medicines that do not cross the placenta and do not cause harm to the fetus;
2) drugs that cross the placenta but do not harm the fetus;
3) drugs that cross the placenta and can cause harm to the fetus.

The rate of penetration of drugs through the placenta is determined by fat solubility, the size of drug molecules and their concentration, placental blood flow,

the stage of development of the placenta and the metabolism of drugs in it. Substances that dissolve in lipids diffuse faster through the placenta than hydrophilic substances. With a molecular size of more than 500 D, drugs diffuse across the placenta at a low speed. Changes in oncotic pressure, total volume and distribution of water in the body of a pregnant woman can significantly affect the transfer of drugs. Thus, impaired uteroplacental circulation, often observed in late toxicosis of pregnancy, can significantly reduce the transfer of drugs across the placenta.

Of great importance is the high permeability of the blood-brain barrier in the fetus, which is associated with its incomplete development. Peculiarities of blood circulation in the fetus also increase the risk of damage to it by the medicinal substance. After passing through the placenta, drugs enter the umbilical vein.

20-40% of the umbilical cord blood flow through the shunt enters the inferior vena cava and reaches the heart and brain, bypassing the liver. These factors lead to excessive concentrations of drugs in the fetal cerebrospinal fluid, which increases the risk of damage to the fetal central nervous system. The obstruction of the placenta to foreign substances, including medicinal substances, is always relative. Thus, in case of increased concentration, any substances can partially penetrate to the fetus. The permeability of the placenta as a result of its thinning, increase in the number of villi and exchange area increases by 32–35 weeks of pregnancy. As the age of the fetus increases, the water content in its body decreases (mainly due to a decrease in the volume of extracellular fluid) and fat deposition increases (mainly in the last trimester of pregnancy). As a result, the volume of distribution of water-soluble drugs increases. The amount of fat in the fetus affects the distribution of lipid-soluble drugs, for example, the tranquilizer diazepam [1; 7]. The main excretory organ for most drugs is the placenta. The second most important excretory organ of the fetus is the kidneys. By the end of pregnancy, the rate of urine formation is 15–20 ml/hour. Urine contains 2–5 times more urea, creatinine and uric acid than amniotic fluid. Excretion of medicinal substances by the fetal kidneys is associated with the maturation of the latter and the formation of active tubular transport processes in them. Drugs that enter the amniotic fluid can be swallowed by the fetus and reabsorbed in the intestine. The amount of substances swallowed by the fetus depends on the volume of amniotic fluid absorbed (at the end of pregnancy it is 5–70 ml/h). Since some drugs can re-circulate in the fetus, the time of their pharmacological action is prolonged and the risk of toxicity increases [8]. Based on extremely limited information, mainly experimental studies, it is assumed that the

use of teratogenic drugs by the father does not lead to the development of congenital anomalies, but may cause pregnancy loss or impaired conception. One of the steps to organize safe treatment during pregnancy was the mandatory introduction of special labeling of medicines. Labels contain information about the degree of risk of using the drug during pregnancy and the level of research proving its safety. Currently, it is customary to use risk categories for the use of drugs, which were developed by the American Drug and Food Administration (FDA): A - drugs for which, when prescribed to a large number of pregnant women, no evidence has been obtained influence on the incidence of congenital anomalies or harmful effects on the fetus;

B - drugs that have been taken by a limited number of women of childbearing age and pregnant women without evidence of their effect on the incidence of congenital anomalies or harmful effects on the fetus; C – drugs that showed embryotoxic and/or teratogenic effects in animal studies. There is a possibility that they may have a similar effect on the human embryo and fetus. No controlled studies have been conducted in humans; D – drugs that can cause congenital abnormalities or permanent damage to the fetus. The risk to the fetus should be weighed against the potential benefit of the drug; X – drugs with a high risk of developing congenital anomalies or permanent damage to the fetus, since there is evidence of their embryotoxic or teratogenic effects in both animals and humans. They should not be used during pregnancy.

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