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TERATOGENIC EFFECT OF DRUGS ON EMBRYONIC FETAL DEVELOPMENT

Qurbonov H. U
Termiz Abu Ali Ibn Sina Technical College of Public Health is a Teacher of Pharmacology

Ernazarova Mavluda Shernazarovna
Scientific Supervisor, Samarkand State Medical University

Abstract

The issues of the influence of drugs on the embryonic development of fetuses continue to remain quite relevant today.

The modern scientific and medical community of today has a lot of information about the effect of various drugs on the fetus, but it is still clearly insufficient to be sure of conducting optimal and safe pharmacotherapy in pregnant women. The ongoing COVID-19 pandemic and the use of new antiviral vaccines have exacerbated the general problem of the effect of drugs on the course of pregnancy and fetal health. Unfortunately, there are currently insufficient statistics on the use of these vaccines during pregnancy, which limits the ability of doctors to use them without compromising the health of the mother and her unborn child. At the same time, aggressive advertising, advice from non-professionals, popular medical literature, which is not always professional, are used by pregnant women to choose and take medications during pregnancy, often without thinking about what harm the medicine used can cause to the health of the mother and her unborn child. Pediatricians have repeatedly drawn attention to the problem of the effect of drugs on the embryonic development of fetuses. But the recent appearance of new drugs: antitumor antibiotics, drugs for the treatment of oncology, anti-inflammatory drugs and vaccines for the treatment of viral diseases have again attracted the attention of doctors to the health of pregnant women and their fetus. The problem of drug teratogenesis, which began with the thalidomide scandal, still remains relevant. Today, the safety of pharmacotherapy is being given significant importance, which certainly has a significant priority in the treatment of pregnant women. The use of modern diagnostic techniques allowed doctors to predict the development of the embryo and the effect on it of drugs used during pregnancy in more detail. In this review, the authors attempt, using mainly domestic literature, to focus the attention of interested parties on the negative factors and consequences of the use of certain drugs, in particular, antibiotics, nonsteroidal anti-inflammatory drugs and their analogues on fetal development and the health of mothers and their children.

Keywords: teratogenicity, embryo, pregnancy, drug, antibiotics.

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Introduction

The problem of uncontrolled, often unjustified consumption of a large number of medicines without consulting doctors, based only on the advice of non-specialists or under the influence of advertising in the media, continues to be relevant in practical medicine. This situation leads to an aggravation of the pathologies that have occurred in the body, loss of time for their treatment, which is a risk to the lives of the patients themselves. This is especially true for pregnant women, who may have a violation of fetal embryonic development under the influence of teratogenic factors, which include some physical, chemical and biological agents, including exposure to viruses. And in order to emphasize the special importance of antimicrobial therapy in pregnant women, the "European Committee on Pathogenic Medicinal Products" in 1977, in its first declaration, banned clinical trials of any medicinal products, placing special emphasis on antibacterial drugs. The development of the embryo can be affected by medications, self-treatment of which, as well as their uncontrolled use during pregnancy, can cause death or pathological changes in the embryo. In modern medicine, there is such a thing as the teratogenic termination period (TTP), during which a damaging factor can cause fetal malformation. Against this background, critical periods of embryogenesis are distinguished, during which the impact of an external unfavorable factor is most dangerous.

The main part

The fact that the fetus reacts to the drug, even if it does not pass through the placenta, is confirmed by functional changes in the body of a pregnant woman. The effect of the teratogenic effect of drugs is already evident on the 18th-60th day of embryo development. This is an important period of fetal development, because at this time, tissues and organs that are diverse in morphological features and functions are formed from homogeneous cells of the embryo. and there is also a proliferation of epithelial tissues of the skin and mucous membranes of the respiratory tract and gastrointestinal tract. Long-term exposure to teratogenic substances can affect the growth of fetal organs, which will lead to functional immaturity of internal organs. In embryogenesis, the most sensitive periods are distinguished, when the influence of external factors has a negative impact on embryogenesis. This is the first 3 weeks of the so-called preimplantation period of embryogenesis. The use of medications during this period can lead to termination of pregnancy or death of the fetus. Despite the high regenerative ability of the embryo development, a born child may have severe or multiple internal organ defects or further physical development problems. The most dangerous part of this period is taking antibiotics, sulfonamides, salicylates, and other active pharmaceutical drugs. Laboratory experiments conducted on pregnant animals have shown that sulfonamide preparations lead to the development of persistent jaundice of the fetus, and subsequently of the unborn child, due to the displacement of bilirubin from the complex with plasma albumins.

Throughout the entire period of pregnancy, it is necessary to treat biological supplements with great caution, the benefits of which and the need for their use cause some skepticism. There is no reliable information in the literature about the use and impact of dietary supplements during pregnancy, and this is the reason for a critical approach to their use.

Even the size of the active molecule of the drug can have a teratogenic effect on the fetus. Thus, heparin, being a polymer with a large molecular size, is retained in the hemo-placental barrier and does not affect the fetus, whereas warfarin, having a small molecule of the active substance, can

pass through the placenta and have a direct effect on the fetus. Drugs such as tetracycline antibiotics and streptomycin have the same effect. Streptomycin, when administered for a long time during 3 to 5 months of pregnancy, can pass through the hematoplacental barrier and lead to deafness and violation of the skeletal bones of the unborn child. Erythromycin leads to liver damage, as well as, with possible pathologies of the birth of completely deaf offspring, kidney underdevelopment and impaired contractile function of the heart. Therefore, erythromycin in pregnant women is used only when the intended benefit to the mother does not exceed the potential risk to the fetus. When it is necessary to make a decision on the use of the drug, there is a table for assessing the risk of antibacterial therapy. Antibiotics of the tetracycline group pose a certain danger to the unborn baby. This group includes Tetracycline and Doxycycline, which show their effectiveness against a wide range of gram-positive microorganisms. Good dissolution in lipids, promotes their rapid penetration through the placenta. These antibiotics can disrupt the normal development of teeth, which is expressed in enamel hypoplasia, inhibition of the growth of fetal skeletal bones, and there is also a risk of fatty liver infiltration. Under laboratory conditions, newborn rat pups with a completely absent bone system were observed on the background of doxycycline. Therefore, taking tetracycline antibiotics is contraindicated during pregnancy. According to some studies, tetracycline affects the intestinal-hepatic circulation of estrogens, reducing it and thereby lowering the concentration of estradiol. If necessary, tetracycline-containing drugs are prescribed only taking into account the antibioticogram, provided that the pathogen reacts exclusively to tetracycline and in the absence of an alternative to therapy with another antibacterial drug. If a pregnant woman needs antibacterial therapy, then therapy is started with penicillins or cephalosporins. The use of tetracycline has certain advantages over antibacterial agents of other groups. It suppresses intracellular protein synthesis in microorganisms at the stage of translation, including the synthesis of necessary enzymes, thereby disrupting the process of reproduction of bacterial colonies. There is a certain danger that when breastfeeding in the second and third trimester, taking tetracycline can cause persistent staining of the child's teeth in brown color. However, we did not find any concrete confirmation of this fact in the literature. Apparently, this can be explained by the fact that only the smallest part of the drug gets into breast milk itself, from which even less gets into the baby's blood (calcium, which is contained in milk, prevents the absorption of tetracycline). Restriction of the use of tetracyclines applies to all dosage forms of this drug, including topical use of tetracycline and ocular tetracycline ointments, since tetracycline is well absorbed and distributed in tissues, having a systemic effect. Even after birth, the baby can "receive" antibiotics with mother's milk, which contains almost all the antibiotics taken by nursing mothers.

Antibacterial agents of the phenicol group, for example, chloramphenicol (levomycetin) can also have a teratogenic effect. Their use leads to inhibition of the process of tissue respiration, and affect the cardiovascular system, resulting in the development of heart failure ("gray syndrome of newborns"). No less dangerous is the development of hypoplastic anemia due to damage to the hematopoietic organs.

Macrolides can be attributed to teratogenic antibiotics. such drugs as erythromycin, midekamycin (macropen), oleandomycin, clarithromycin (claricin, klacid), azithromycin (sumamed), roxithromycin (rulid) and similar. They also cause the development of hyperbilirubinemia and inhibition of embryogenesis. Pregnant women taking such drugs have kidney damage and damage

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to the VIII pair of cranial nerves, and the child, in turn, also has damage to the VIII pair of cranial nerves, as well as various disorders in the structure of the bones of the skeleton.

Sulfonamides have a teratogenic effect. Prolonged-acting sulfonamide preparations (sulfadimethoxine, sulfalen), including combined preparations: sulfonamides + trimethoprim (co-trimoxazole) are not prescribed to pregnant women, due to the fact that they have a teratogenic effect at the end of the gestational period, and can manifest in the fetus and / or newborn in the form of nuclear jaundice, methemoglobinemia, hemolysis of red blood cells, bilirubin encephalopathy. Trimethoprim, which is present in co-trimoxosol, disrupts the exchange of folic acid in the mother and fetus. If the use of co-trimoxosol is unavoidable (in such cases as a pregnant woman with HIV infection in stage IIB or in stage IV with the addition of pneumocystis pneumonia), then additional administration of folic acid or calcium folate from 5 mg per day is recommended.

The effect of teratogenic effects can be reduced by using drugs – cephalosporins, which have recently been prescribed by doctors during pregnancy most often. These antibiotics cause fewer side effects and are less teratogenic than other antibiotics.

At the same time, semi-synthetic cephalosporins of the second and third generations are used in the treatment of pregnant women, which are also active against gram-negative bacteria and have a weaker toxic effect on the kidneys that work during the period of carrying a child with an increased load.

However, their use is possible only after the doctor evaluates the patient's condition and in the case when it is impossible to cope with the infection without antibiotics. Due to the fact that the absolute safety of using cephalosporins during pregnancy is not clinically sufficiently verified, these antibacterial drugs can be prescribed to pregnant women only in limited cases of infectious inflammation: ent organs and respiratory tract (tonsillitis, pharyngitis, otitis media, sinusitis, bronchitis, pleurisy and pneumonia); abdominal and pelvic organs (endometritis); genital tract (chlamydia, gonorrhea, cercevitis, etc.); urinary tract and kidneys (cystitis, urethritis, nephritis, pyelonephritis); biliary tract (cholangitis); joints and periarticular tissues; pustular skin lesions (streptoderma, erysipelas, etc.).

The use of nitro imidazole derivatives, such as metronidazole, increases the frequency of chromosomal aberrations in human lymphocytes, exerting a carcinogenic effect on the fetus. In the first trimester, metromedazole derivatives are not used, as they have an embryotoxic effect. And in the II and III trimesters, they are prescribed with great caution.

The use of nitrofuran drugs such as furadonin, furagin, furazolidone, furacillin is also undesirable, since their use can cause blood hemolysis and hyperbilirubinemia in the postpartum period.

Non-steroidal anti-inflammatory drugs can also have a certain effect on the fetus, even if they are used in dental practice. During pregnancy, the use of analgesics is carried out with caution and if necessary, but in small doses and for a short time. Long-term use of analgesics in the late stages can lead to complications, for example, to an increase in the duration of pregnancy, the occurrence of bleeding in the fetus and pregnant woman, impaired renal function of the newborn, and premature closure of the Botall duct. In the case of dental manipulations or preventive rehabilitation of the oral cavity, in which there is a need to use painkillers, it is advisable for pregnant women to choose the period between the 13th and 32nd weeks of pregnancy. During this period, organogenesis mostly ends and the placenta is formed with functioning fetal blood circulation. But the later period of pregnancy from 37 to 40 weeks is considered "critical". During

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this period, the risk of spontaneous miscarriages or premature birth is significantly increased. Caution should be exercised when using steroid medications as anesthetics. Taking into account their good lipid solubility, which ensures their penetration through cell membranes and into the placenta, they should be taken with caution and, if the expected effect of therapy does not exceed the potential risk to the fetus. Objective data from the use of anesthetics during pregnancy are not sufficient. In laboratory studies on animals, anomalies of development in the fetus of the head and limbs were observed.

Conclusion

In the treatment of pregnant and lactating mothers, doctors of any specialty face the problem of choosing a safe drug therapy. According to statistics, at least 5% of all congenital anomalies of the fetus are associated, in one way or another, with the use of medicines. The penetration of a drug through the placenta depends on a number of factors — the physical and chemical properties of the substance itself,the state of the placenta, and the placental blood flow itself. If it is necessary to use medicines, it should be taken into account that the rate of their inactivation and excretion in the embryo and fetus is not high enough, and this circumstance increases the risk of their adverse effect on the fetus.

Unfortunately, teratogenicity has not yet become an objective field of research in evidence-based medicine, but recently, thanks to a large number of observations on the effects of drugs on the fetus, a significant amount of evidence has been accumulated, which made it possible to reconsider the concept of reliable protection of the fetus from harmful substances. This contributed to the continuation of the study of the mechanisms of teratogenesis and variants of the effect of drugs on the fetus. Before recommending new drugs for medical use, it becomes relevant to check drugs for safety for the fetus and determine their teratogenesis. A good help for the use of antibacterial drugs in modern medical practice was the creation and introduction into active practice of tables and scales for assessing the risk of drugs used, which greatly simplified the doctor's work in choosing the right drug. Modern medicine can no longer do without risk stratification according to the drugs used. In this regard, feedback from the attending physician and the patient is very important, who informs the doctor about side effects. It is the duty of the doctor to inform the manufacturer of the drug-the pharmaceutical company. Based on this information, the texts of instructions for use are constantly being improved and relevant statistics on the effects of teratogenicity are kept, which is a necessary factor in modern gynecology and pediatrics.

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