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Modern Solutions for the Mechanisms of Taking Medications during Pregnancy

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Annotation: The article is devoted to the issues of pharmacotherapy of pregnant women, taking into account the specific features of drug metabolism in the body of a pregnant woman and the fetus. The issues of complications of drug therapy are highlighted. A list of drugs for the treatment of certain types of somatic pathology in pregnant women is given.

Keywords: pregnancy, pharmacotherapy, side effects and complications.

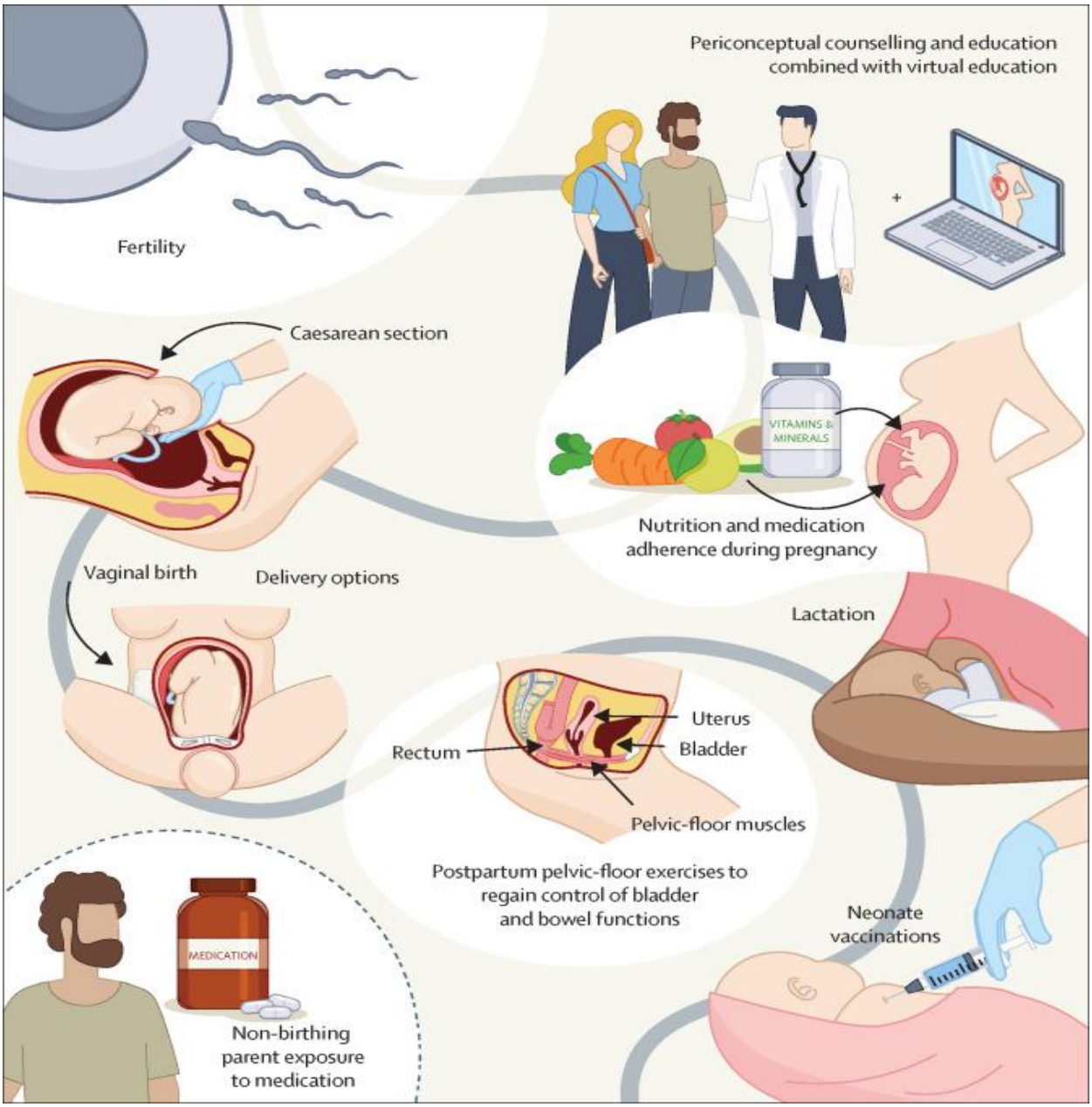
INTRODUCTION

Various somatic diseases accompanying pregnancy are an urgent problem in modern obstetric and gynecological practice. Unfortunately, as confirmed by the literature, the main indicators of the level of health of women and children in Ukraine do not have a tendency to improve. Almost 69% of pregnant women suffer from diseases of internal organs, 48% suffer from anemia. Over the past decade, anemia has increased 9 times, cardiovascular diseases 2.5 times, and kidney diseases 4.5 times. However, the main factor in predicting the health of the unborn child is the health of the mother. The increase in extragenital pathology that threatens the health of the pregnant woman and the fetus forces clinicians to treat with drugs that are not indifferent, but sometimes toxic both for the mother's body and for the developing embryo-fetal structures.

RESEARCH METHODS AND APPROACHES

According to domestic and foreign statistics, from 10 to 18 percent of children are born with certain developmental anomalies. If we take into account spontaneous abortions, miscarriages and stillbirths, this percentage increases significantly, which in half of these cases are accompanied by histologically confirmed fetal anomalies. As a rule, in the vast majority of congenital anomalies, the etiological factor cannot be identified. It is believed that these are combined effects (hereditary

diseases, various defects of the hereditary apparatus, including the effect of drugs). Statistics show that more than 80% of women take one or more medications during pregnancy, both prescribed by a doctor and independently. Sometimes the embryo (fetus) has to come into contact with more than a dozen different drugs during its development, which, naturally, cannot be indifferent to it.



Prescribing medications to a pregnant woman is one of the most difficult tasks for a family doctor. Nevertheless, no family doctor can avoid this problem. In order to prescribe medications rationally, a family doctor must have an understanding of the pharmacokinetics of drugs in the pregnant woman's body and in the complex system "mother - placenta - fetus - amniotic fluid".

The specific features of drug metabolism in the body of a pregnant woman depend on many factors, including hemodynamic changes. In pregnant women and newborns, starting from the second half of pregnancy, the amount of intracellular and extracellular fluid increases, the volume of circulating plasma increases by 50%, which affects half of the heart; drug life. Normal pregnancy is characterized by an increase in renal blood flow, glomerular filtration and creatinine clearance. It is these factors that determine the increase in renal clearance of drugs in pregnant women. Among the many physiological changes characteristic of pregnancy and affecting drug metabolism, there is a change in the hormonal status (increased steroidogenesis in the placenta). In pregnant women, the detoxification function of the liver decreases, which plays a major role in

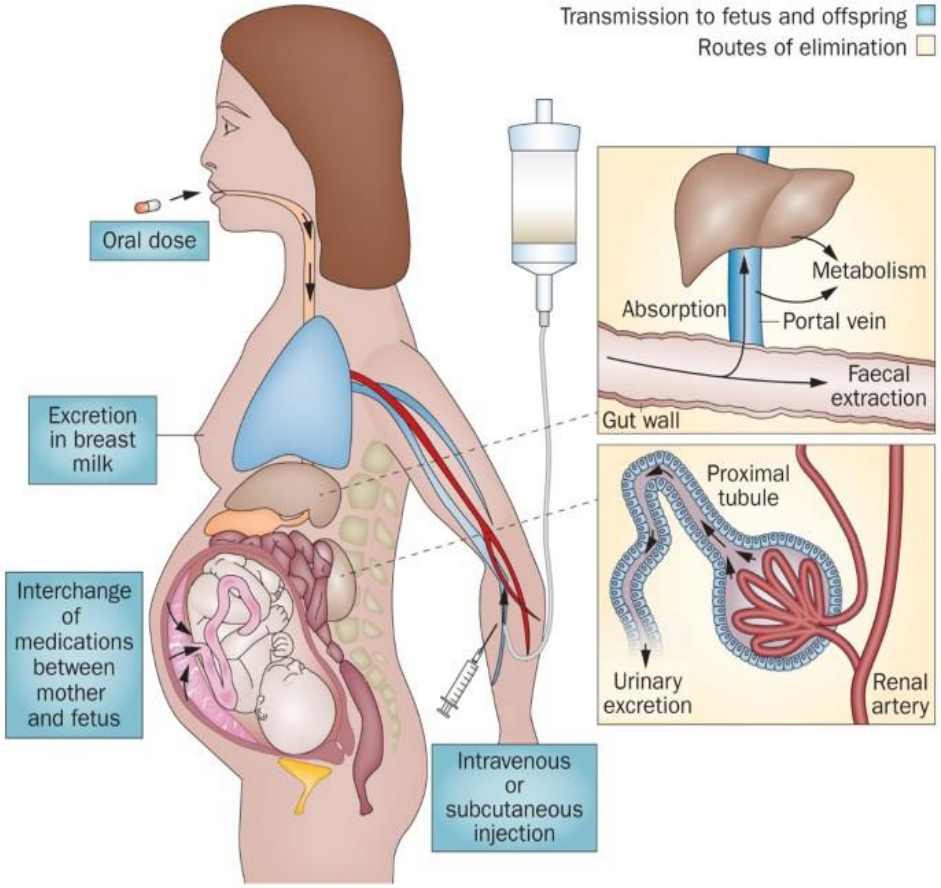
maintaining the hormonal balance necessary for pregnancy. The result is a change in the sensitivity of the pregnant woman's body to drugs and a significant increase in the risk of drug allergies. This factor should always be taken into account, especially when prescribing several drugs at the same time.

When prescribing drugs to a pregnant woman, it should be remembered that the metabolism of drugs in the body of a healthy woman is different from the metabolism of drugs in the body of a woman with late gestosis, decompensated heart disease, hypertension, and chronic liver and kidney diseases.

When choosing therapy for a pregnant woman, the family doctor must take into account that a number of medications can affect the ability of the uterus to contract, weakening it or, conversely, increasing it and leading to premature birth. The state of uteroplacental blood circulation.

In particular, adrenomimetics (berotek, fenoterol, ritodrine, salbutamol), indomethacin, aspirin, mefenamic acid, calcium antagonists (verapamil, corinfar, nifedipine) and magnesium sulfate inhibit uterine contractions and reduce the rate of uteroplacental blood flow. The use of these drugs in late pregnancy can lead to preeclampsia and prolonged labor. On the contrary, beta-blockers and digoxin increase the contractile ability of the uterus, which leads to early and rapid labor, so they should be canceled two weeks before the expected birth. Pregnant women should not be prescribed drugs containing ergotamine. These drugs cause uterine contractions and spasm of its vessels, which can lead to abortion.

When prescribing a number of antihypertensive drugs (dihydralazine, methyldopa), an increase in regional blood flow in the uterus is observed due to a decrease in peripheral resistance of the placental vessels. The use of peripheral vasodilators, clonidine, and some myotropic antispasmodics leads to a sharp decrease in blood pressure, which leads to a sharp deterioration in uteroplacental and fetal-placental blood circulation.



The transfer of the drug and its metabolites from the body of a pregnant woman to the fetus and vice versa can occur transplacentally or paraplacentally (through the fetal membranes). Starting

from the second half of pregnancy, the distribution of drugs occurs in the system "mother - placenta - fetus - amniotic fluid". An important factor determining the effect of drugs on the fetus is their transplacental passage. The greater the degree of penetration of a pharmacological agent through the placental barrier, the higher the likelihood of its negative effect on the fetus.

Of great importance for the transplacental passage of drugs are:

a. molecular weight of the drug;

b. intensity of uteroplacental blood circulation;

c. morphofunctional maturity of the placenta;

d. the ability of the drug to ionize and dissolve in lipids;

e. degree of binding to plasma proteins.

In severe late gestosis of pregnancy, as well as in a number of extragenital diseases, the distribution of drugs is significantly slowed down. This is also facilitated by dystrophic and necrobiotic processes in the placenta that accompany these diseases.

Based on the above, the principles of rational pharmacotherapy should be developed taking into account the following important aspects:

a. Features of drug metabolism in the body of a pregnant woman;

b. the effect of drugs on the contractile ability of the uterus and the state of uteroplacental blood circulation;

c. results of studies of transplacental transfer of pharmacological antigens and their metabolism in the placenta;

d. stage of intrauterine development at the time of drug administration;

e. results of studies of embryotoxic and teratogenic effects;

f. study of fetal pharmacokinetics;

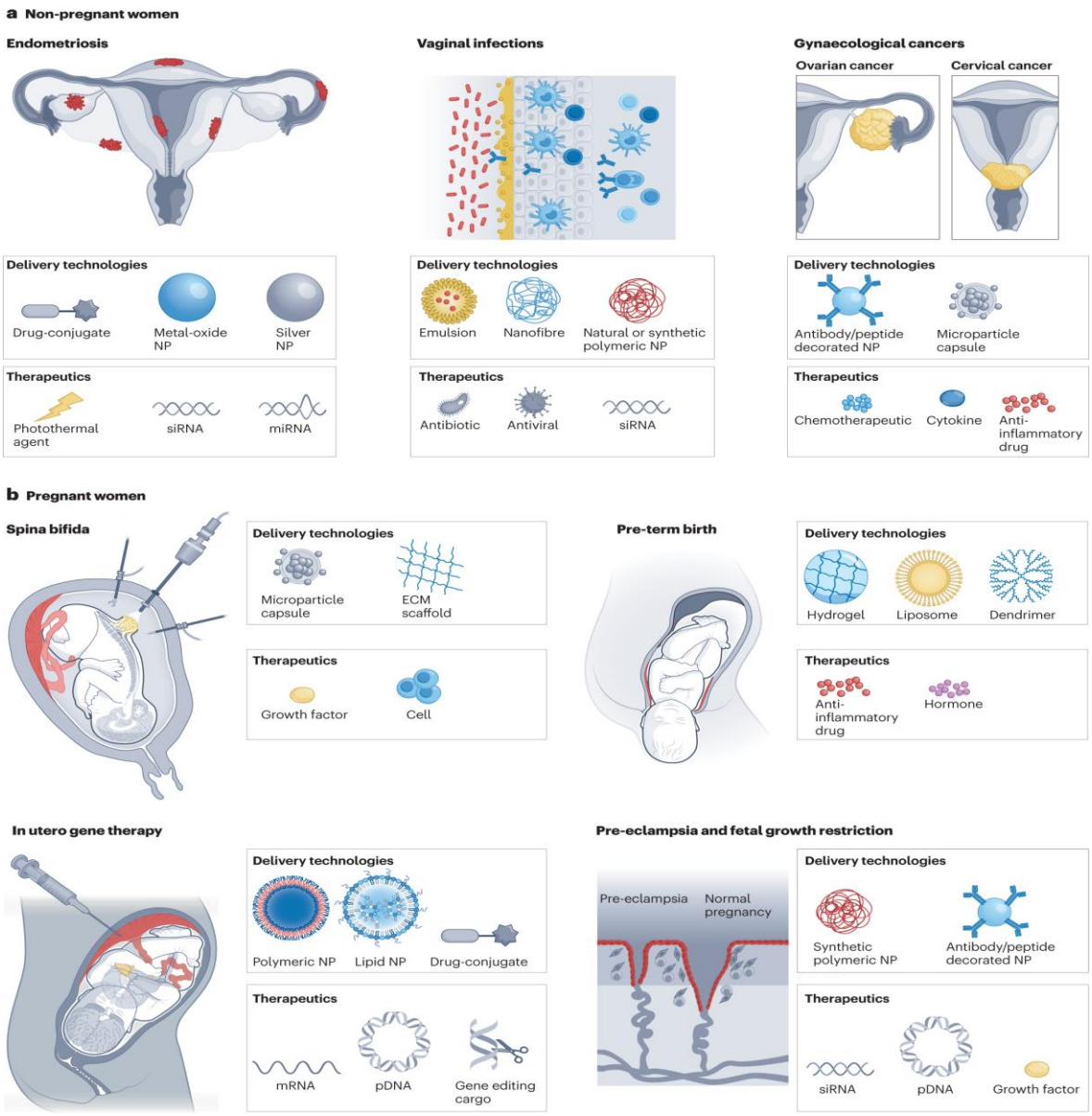
g. distribution characteristics of medicinal substances into amniotic fluid.

Drug metabolism in the human placenta, as well as in the liver, involves four main processes: oxidation, reduction, conjugation, and hydrolysis. These changes can, in some cases, produce chemical metabolic intermediates that are toxic to the fetus.

RESEARCH RESULTS

The stage of intrauterine development at the time of drug administration plays a major role in the nature of the fetal body's response to the pharmacological effects of drugs. In the embryonic and fetal periods of development, 3 periods are distinguished.

The blastogenesis period lasts up to 3 weeks. Detailed histological and embryological analysis has shown that the effects of drugs during this period are characterized by a general toxic effect, and the most important days in this regard should be considered 5-7 days, that is, the preimplantation period.



The period of organogenesis (4-9 weeks of pregnancy) is the most important in terms of causing birth defects. By the 56th day (8 weeks of pregnancy), the main organs and systems are already formed. The exceptions are the nervous system, sensory organs and genitals, the histogenesis of which lasts up to 150 days, and if a pregnant woman takes the drug for a long time, the fetus may develop several deformities.

The fetal period, when the differentiation of the main organs has already occurred, is characterized by histogenesis and fetal growth. At this time, biotransformation of drugs is already occurring in the “mother - placenta - fetus - amniotic fluid” system. The use of drugs during this period usually does not cause gross structural defects and malformations, but can slow down the development of the fetus and lead to disorders of the nervous system, organs of vision (optic nerve atrophy), hearing (deafness), teeth. reproductive system (especially in women), the development of which occupies a significant part of the fetal period. Exposure to drugs during pregnancy can lead to various metabolic disorders (acidosis), functional disorders (thrombocytopathies), and can also have a long-term effect on the child's behavior and psychological reactions.

Medications can have the following types of harmful effects on the fetus:

Embryolethal effect - when a drug causes the death of an embryo;

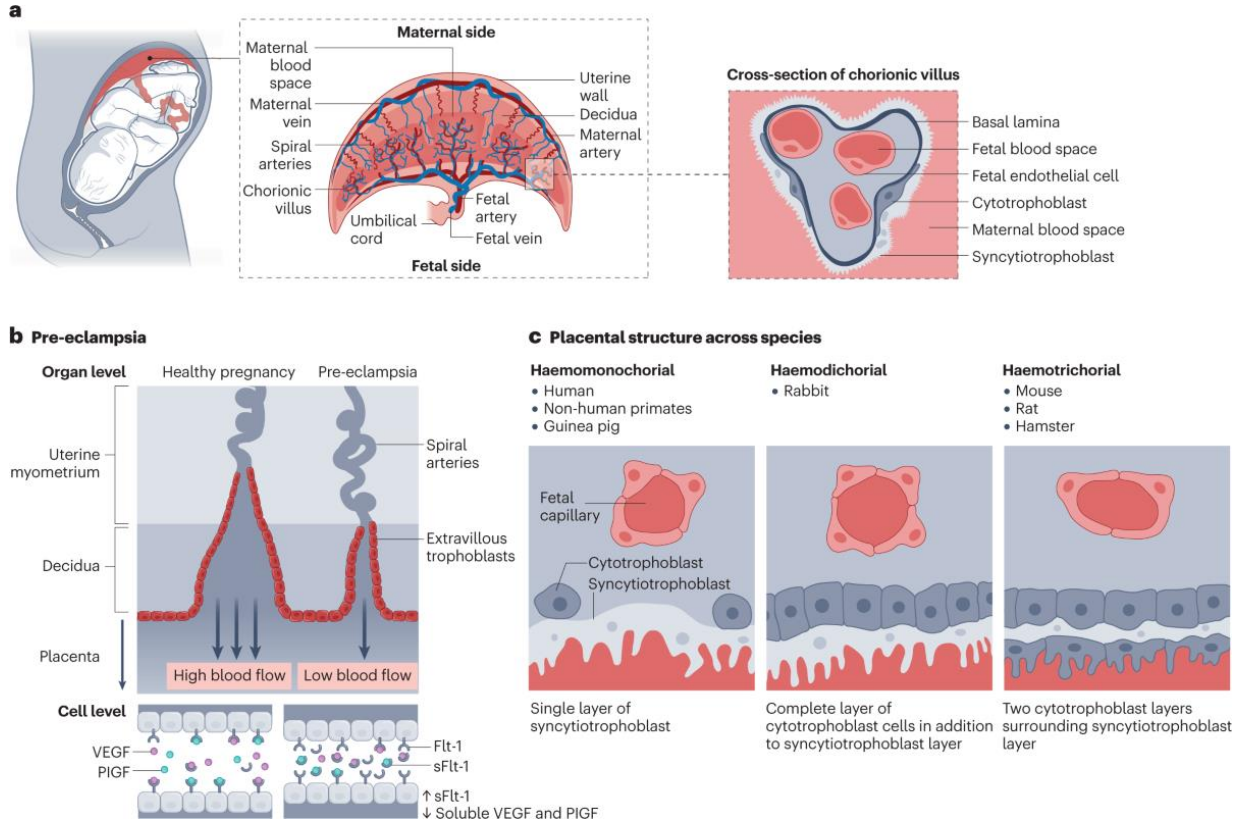
teratogenic effect (from the Greek teratosis (teratos) - "deformation"), that is, the effect on the formation of fetal organs and systems. Teratogenic effect can develop from the 3rd to the 10th

week of pregnancy. The mechanisms of teratogenic effect of various drugs have not yet been established. According to many authors, teratogenesis is based on a violation of folic acid metabolism or hormone metabolism when taking drugs. This mechanism of action has been established for methotrexate, aminopterin, antithyroid drugs, synthetic gestagens and estrogens. The teratogenic effect of drugs can have a negative effect on maternal tissues, contributing to the development of a secondary (indirect) effect on fetal tissues, as well as by disrupting the penetration of oxygen or nutrients through the placenta or by a pronounced direct effect on differentiation processes in developing tissues;

a. The embryotoxic and fetotoxic effects of drugs are due to the fact that drugs do not cause various anomalies in the fetus, but rather affect the functioning of its organs and systems;

b. Mutagenic effects occur as a result of damage to the genetic apparatus of somatic or germ cells.

In accordance with the recommendations of the US Food and Drug Administration (FDA), all drugs are divided into 5 categories depending on the level of risk and the degree of negative, primarily teratogenic, effects on the fetus.



Category A - Controlled studies in pregnant women have not demonstrated a risk to the fetus when used during the first trimester of pregnancy (unless there is a risk of use of the drug in later stages). The possibility of harm to the fetus appears doubtful.

Category B - Animal studies have not shown a risk to the fetus, but there are no data from controlled studies in pregnant women. Or, animal studies have shown adverse effects (other than decreased fertility) that have not been confirmed in controlled studies in women during the first trimester of pregnancy. The risk of using these drugs in other trimesters of pregnancy has also not been proven.

Category C - for these drugs, animal studies have shown a risk to the fetus (teratogenic, embryogenic or other effects), if controlled studies have not been conducted or there are no data from laboratory tests in animals. The drug should be prescribed only if the need for use justifies the potential risk to the fetus.

Category D - the risk of adverse effects on the fetus is confirmed, but the expected effect of the

drug on the pregnant woman makes the risk acceptable (for example, life-threatening conditions). The drug can be used only if there is no safer alternative.

Category X - Studies in humans or animals have shown an adverse effect on the fetus, or there is reliable empirical evidence of such an effect, i.e. the adverse effects of the drug outweigh the potential benefits.

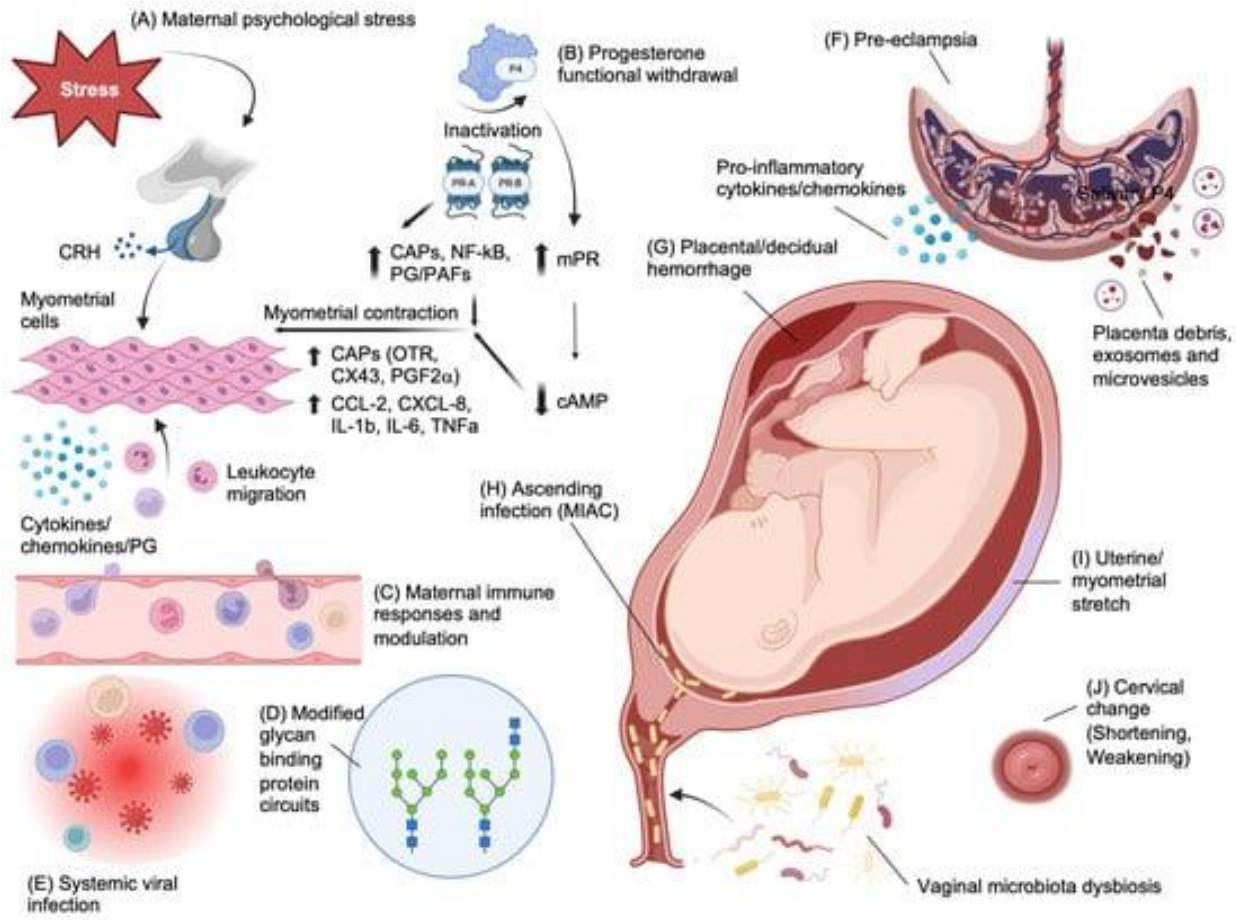
Based on the above, when prescribing medications to pregnant women, the family doctor should adhere to the following principles:

1) the use of the drug is possible only if the benefit to the mother outweighs the risk of harm to the fetus;
2) The use of any medication should be avoided during the first trimester of pregnancy;
3) During pregnancy, preference should be given to drugs with proven safety over new and untested drugs;
4) any drug should be prescribed in the minimum therapeutic dose;
5) A small number of drugs have been proven to be teratogenic, but no drug is considered completely safe in early pregnancy;
6) In cases where the mother's life is at risk, any therapy indicated in this situation is chosen.

The family doctor should also be aware of the risks or safety of the most commonly used medications for the fetus and newborn. Only knowledge of these important issues can ensure the rational use of medications in pregnant women without risk of harm to the fetus.

Below are brief recommendations for the use of a number of medications in the treatment of heart failure, arrhythmia, and hypertension in pregnant women.

Cardiac glycosides



Digoxin freely crosses the placenta 2 hours after administration, its concentration in the fetal blood is the same as in the mother's blood. Studies of fetal cardiac activity have shown that digoxin does not have a significant effect on it. Cardiac glycosides accumulate in the fetus and amniotic fluid, which is associated with the delayed excretion of these drugs from the fetus, as well as the possibility of repeated oral administration from the amniotic fluid. The concentration of glycosides in the blood of newborns is higher than in mothers who took glycosides at the end of pregnancy. At the same time, the excretion of digitalis group cardiac glycosides (digoxin, digitoxin, celanide, cordigit) does not pose a danger to the newborn. Cardiac glycosides are among the drugs with very low toxicity to the fetus. Good transplacental passage of cardiac glycosides allows them to be used in the treatment of fetal heart failure. When prescribing cardiac glycosides to a pregnant woman, it is important to remember that digitalis has a direct tonic effect on the uterus, leading to premature and rapid labor.

Diuretics

The use of diuretics during pregnancy is limited. Teratogenic effects have been identified in potassium-sparing diuretics (veroshpiron, triamterene, amiloride) and diacarb. When using these drugs in late pregnancy, uncompensated changes in the acid-base state of fetal blood develop. There is evidence of the fetotoxic effect of thiazide diuretics. Their long-term use contributes to the development of hyponatremia, thrombocytopenia, hypotension, and neonatal jaundice.

Furosemide does not have a teratogenic effect, but after prolonged use of furosemide and urethritis, the fetus may develop symptomatic transplacental hyponatremia, leukopenia, and agranulocytosis.

Antiarrhythmic drugs

Adenosine (Adenocard) - clinical studies have not revealed any negative effects of this drug on the fetus or mother. It can be successfully used in the treatment of pregnant women due to its high efficacy in paroxysmal supraventricular tachycardia, including Wolff-Parkinson-White syndrome, or significant hypotension.

Amiodarone (cordarone) is contraindicated during pregnancy because it causes thyroid dysfunction in the fetus, which contributes to the development of cretinism, bradycardia, prolongs the PQ interval, and affects melanin metabolism. Amiodarone causes premature birth and fetal hypotrophy. However, in an emergency with paroxysmal rhythm disturbances due to WPW syndrome, it may be the drug of choice.

Calcium channel blockers - phenylalkylamines of short (verapamil, isoptin, finoptin) and long (verapamil SR, isoptin SR) action are often used to stop arrhythmias in pregnant women. These drugs do not have a negative effect on the fetus. Good results were achieved with the use of prolonged-release verapamil (St. Petersburg Association of Obstetricians and Gynecologists) - Isoptin retard at a daily dose of 120 mg to prevent the development of hypertensive complications in high-risk pregnant women. Verapamil was used from 20-24 to 34-36 weeks of pregnancy. Prophylactic use of verapamil made it possible to prevent the development of severe forms of late gestosis.

CONCLUSION

Procainamide (novocainamide) has no pronounced toxic effects. However, long-term use causes immunological disorders in the fetus. It should be remembered that intravenous administration can cause a decrease in blood pressure due to peripheral vasodilation.

Lidocaine (hicaine) can be used for ventricular arrhythmias in pregnant women. The drug accumulates mainly in the fetal brain tissue, which leads to increased convulsive readiness. Under conditions of hypoxia, the toxic effect of lidocaine on the central nervous system of the fetus increases. Long-term use of lidocaine can lead to acidosis in the fetus. With conductive anesthesia with lidocaine, which is often used in childbirth, negative side effects are noted both in the mother (hypotension, anaphylactic shock) and in the child (convulsions, excitation of the central nervous

system, opisthotonus or, conversely, toxic reactions manifested by depression, apnea, brady- or tachycardia, hypoxia, metabolic acidosis).

Mexiletine is not used in pregnant women due to the risk of side effects (loss of consciousness, hypotension, bradycardia, seizures, etc.), as well as its ability to cause neonatal hypoglycemia.

Quinidine and its derivatives (quinineline, etc.) are contraindicated in pregnant women. They cause thrombocytopenia, optic neuritis, and myasthenia gravis in newborns.

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