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CURRENT ASPECTS OF THE PROBLEM OF PLACENTAL DYSFUNCTION AND MISCARRIAGE OF INFECTIOUS AND INFLAMMATORY GENESIS

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Abstract. Placental dysfunction and miscarriage of infectious and inflammatory origin remain urgent problems in modern obstetrics, significantly contributing to perinatal morbidity and mortality. This article reviews the etiopathogenetic mechanisms of placental insufficiency, emphasizing the role of viral and bacterial infections, immune responses, and systemic inflammatory reactions. Special attention is given to ozone therapy as a promising complementary approach in treating such conditions. The biological effects of ozone—antibacterial, anti-inflammatory, antioxidant, and immunomodulatory—are discussed as potential tools to improve maternal and fetal outcomes in high-risk pregnancies.

Key words: placental dysfunction, miscarriage, inflammation, infection, ozone therapy, perinatal complications, obstetrics.

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Annotatsiya. Platsentaning disfunksiyasi zamonaviy akusherlikning dolzarb muammolari bo'lib qolmoqda, bu perinatal kasallik va o'limga sezilarli hissa qo'shadi. Ushbu maqolada platsenta yetishmovchiligining etiopatogenetik mexanizmlari ko'rib chiqiladi, virusli va bakterial infeksiyalar, immunitet reaksiyalari va tizimli yallig'lanish reaksiyalarining rolini ta'kidlaydi. Bunday sharoitlarni davolashda istiqbolli qo'shimcha yondashuv sifatida ozon terapiyasiga alohida e'tibor beriladi. Ozonning biologik ta'siri — antibakterial, yallig'lanishga qarshi, antioksidant va immunomodulator — yuqori xavfli homiladorlikda ona va homila natijalarini yaxshilash uchun potensial vositalar sifatida muhokama qilinadi.

Kalit so'zlar: platsenta disfunksiyasi, abort, yallig'lanish, infeksiya, ozon terapiyasi, perinatal asoratlar, akusherlik.

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One of the most significant problems of modern obstetric practice remains miscarriage (MP) [36,46]. This term refers to spontaneous termination of pregnancy at any stage – from the moment of conception to 37 weeks, which corresponds to the period from the first day of the last menstrual period to the 259th day. [55]

According to WHO, premature birth is considered to be a birth that occurs between 22 and 37 completed weeks of gestation, counted from the first day of the last menstrual period, with a fetal weight of 500 g or more. [46,55]

Miscarriage occurs in 10-25% of all pregnancies, with 5-10% ending in premature birth. More than half of stillbirths occur in premature babies, who also account for 70-80% of early neonatal mortality and 60-70% of infant mortality. The probability of death of a premature baby is 30-35 times higher than that of a full-term baby, and the perinatal mortality rate in miscarriage exceeds the same indicator for term births by 30-40 times. [55] In recent years, the proportion of premature births in Uzbekistan has ranged from 9 to 15%, with about 70% of early neonatal mortality cases due to prematurity. [34]

These data confirm that the problem of miscarriage remains relevant for modern medicine.

When treating miscarriage, specialists are faced with a limited number of attempts, which places great responsibility on the doctor when conducting diagnostics and choosing the optimal treatment tactics. It is important to consider that each lost pregnancy not only becomes a serious psychological trauma for a woman, but also negatively affects her reproductive health. This is due to both the consequences of the termination of pregnancy itself and the need for invasive interventions. Thus, each unsuccessful pregnancy intensifies the pathological processes that contribute to miscarriage, which further complicates its treatment. Termination of pregnancy after 16 weeks is usually caused by pathological processes such as infections, isthmic-cervical insufficiency and thrombophilic disorders. These factors provoke the development of placental insufficiency and severe pregnancy complications, including placental abruption, intrauterine growth retardation, gestosis and other complications [36].

It has been proven that one of the main causes of early premature birth is local inflammation of the chorion and decidua in the cervix. In most cases, it is associated with the persistence of opportunistic mycoplasma-viral microflora in the endometrium. [44]

The results of a number of studies have shown that the cause of pregnancy termination can be both severe systemic inflammatory diseases and asymptomatic urogenital infections. [27]. Risk factors for the development of infectious diseases in pregnant women and the fetus can be divided into three main groups (31,32). The first group includes women with chronic foci of extragenital infection, among which are: long-term nonspecific diseases of the respiratory system, chronic inflammatory processes in the gastrointestinal tract, chronic tonsillitis, chronic pyelonephritis. The second group includes pregnant women with chronic inflammatory diseases of the reproductive system, which include: colpitis, lower genital tract infections, endometritis, salpingo-oophoritis. The third group includes patients who experienced an exacerbation of chronic infectious diseases during pregnancy, as well as those who suffered acute inflammatory processes during the gestational period (57).

In recent decades, the need to find and justify new or additional methods of therapy has become especially urgent due to the increase in morbidity, the emergence of microorganism

resistance to existing drugs, and the development of new forms of diseases. Modern medicine faces challenges related to the limited effectiveness of traditional treatment methods, side effects, and their insufficient universality for different groups of patients.

The importance of finding and implementing new methods of therapy is also reinforced by the need to adapt medicine to changes in population health and the rapid progress of scientific technologies.

The purpose of this literature review is to analyze existing approaches to the treatment of placental dysfunction and miscarriage caused by infectious and inflammatory factors, as well as to determine the place of ozone therapy among alternative and traditional treatment methods. The review examines the effectiveness of various therapeutic strategies aimed at correcting infectious and inflammatory processes and improving placental functioning, with a special emphasis on the possibility of using ozone therapy. Based on the systematization of available data on the effectiveness and safety of various therapeutic strategies, it is proposed to substantiate the prospects of further studies aimed at clarifying the mechanism of action and expanding the indications for the use of ozone therapy in obstetric practice.

Etiopathogenetic mechanisms of formation of placental dysfunction in women with infectious and inflammatory diseases of the reproductive system.

Placental dysfunction is a complication of pregnancy that is accompanied by intrauterine fetal distress, growth retardation and developmental delay, and is also one of the significant factors of perinatal morbidity and mortality [5, 64]. This syndrome is characterized by morphofunctional changes in the placenta and is a consequence of a complex adaptive response of the fetoplacental complex to various pathological processes in the mother's body. Its development is based on a violation of compensatory-adaptive mechanisms at the molecular, cellular and tissue levels [19, 62]. As a result, the main functions of the placenta are impaired - transport, trophic, endocrine, metabolic and detoxification, which negatively affects the condition of the fetus and newborn. Placental dysfunction accompanies almost all complicated forms of pregnancy. In patients suffering from viral and bacterial infections, its frequency reaches 50.0% - 60.0%. The morphological basis of this condition is pronounced changes in the vascular network of the placenta, including narrowing and tortuosity of the spiral arterioles, their heterogeneity in caliber, a decrease in the density of the arterial bed, as well as a decrease in the lumen of the capillaries with foci of stasis, aggregation and adhesion of cellular elements of the blood [2, 7].

According to T. S. Kachalina and co-authors [26], massive fibrin deposits in the intervillous space, pronounced edema and fibrosis of the chorionic villi are detected in the placental tissue, which is caused by primary vascular disorders. At the same time, J. Aplin [3] proved the possibility of secondary changes in the placental vessels, which arise due to thinning of the walls of large vessels, which leads to a decrease in the volume and area of terminal villi during placentation.

There are two main types of placental dysfunction (PD): primary (early) and secondary (late). Primary placental insufficiency develops before 16 weeks of gestation, during implantation, early embryogenesis and placenta formation. Its occurrence is associated with the influence of genetic, endocrine, infectious and other unfavorable factors. The ability of the mother's body to adapt to pregnancy also plays an important role. Quite often, primary PD is accompanied by congenital malformations of the fetus. Secondary (late) placental insufficiency

develops after the 16th week of gestation, when the placenta has already formed, and is caused by exogenous blood supply disorders, as well as dystrophic and inflammatory processes that occur as a result of diseases suffered during pregnancy. The degree of influence of various pathological conditions and diseases of the pregnant woman on the condition of the placenta and fetus is determined not only by the gestational age and duration of exposure, but also by the capabilities of the compensatory-adaptive mechanisms of the fetoplacental complex (FPC) [49, 64]. If the compensatory functions of the placenta are preserved, its insufficiency can be treated, which allows for the normal development of the fetus to be maintained and the pregnancy to be carried to term with the subsequent birth of a healthy child. However, if the adaptive mechanisms are exhausted, the risk of intrauterine growth retardation of the fetus and serious complications increases [1, 33].

The development of placental dysfunction (PD) is caused by the impact of many risk factors, among which the key role is played by late gestosis, the threat of termination of pregnancy, postmaturity, iso-serological incompatibility, as well as somatic diseases of the mother, such as pathologies of the cardiovascular system and kidneys. TORCH group infections are also of significant importance [26, 8].

In addition, predisposing factors for the development of PD are unfavorable socio-economic conditions, low level of education, young age (under 17 years), especially with insufficient body weight before pregnancy and its insufficient increase in the gestational period. Inadequate physical activity, first birth and multiple pregnancy also increase the risk of developing this pathology.

In recent years, the role of TORCH infections in the mechanisms of placental insufficiency development has been actively discussed in scientific research [11]. In particular, the influence of herpes viruses and cytomegalovirus on the formation of PD is confirmed by the high degree of relationship between these infections and placental dysfunction, reaching 92.2%.

Placental dysfunction is one of the leading factors influencing the level of perinatal morbidity and mortality. Despite numerous scientific studies devoted to fetoplacental insufficiency, manifested as intrauterine growth retardation syndrome, all damaging perinatal factors that determine the pathological development of children in the early neonatal period and during the first year of life have not yet been identified [16, 17].

The presence of a significant number of concomitant genital and somatic diseases in the mother creates an unfavorable pregravid background, which contributes to an additional load on the key life support systems. In the early stages of pregnancy, due to the high adaptive capacity of the "mother-placenta-fetus" system, these changes can remain in a compensated state or be accompanied by moderate disturbances in the hormonal regulation of the fetoplacental complex.

Infectious and inflammatory diseases are diagnosed in 28.0%–47.0% of newborns, and in the structure of perinatal losses they make up from 11.0% to 45.0%. Intrauterine infections have a significant negative impact on the perinatal outcome of pregnancy, which necessitates a comprehensive study of this problem in modern scientific research [18].

An analysis of the characteristics of the course of pregnancy and childbirth in women, in a group of which pregnant women with infectious diseases and chronic placental insufficiency complicated by an unfavorable outcome of childbirth were identified, revealed a significant proportion of premature newborns (33.8%) and children with signs of hypotrophy (35.2%). In

addition, among this category of patients, a high level of intrauterine infection of the fetus was recorded, reaching 40.8%, which indicates a significant influence of the infectious factor on the perinatal prognosis. [25].

Many scientists emphasize the significant role of urogenital infections suffered in the first trimester in the development of miscarriage [56,58]. Thus, studies by A.V. Grishchenko and co-authors [22] showed that inflammatory diseases of the reproductive system in the anamnesis occur in 40.2%–51.0% of women who have encountered this pathology.

Persistent viral infections and their combined forms [51], which are detected in 74.0% of patients [43], acquire special etiological significance in miscarriage. In the early stages of gestation, infectious agents have the most pronounced negative impact on the development of the embryo.

Even opportunistic vaginal microflora, which may be asymptomatic in the mother, can provoke intrauterine infection of the fetus and the development of an infectious process.

Cytomegalovirus infection (CMV) is recognized as one of the most common intrauterine infections. According to statistics, about 1.0% of newborns are infected with CMV, but only 10.0% of them have clinical manifestations at birth confirming intrauterine infection.

Natural origin, physical and chemical properties and medical and biological effects of medical ozone.

Ozone was first reported by the Dutch physicist Mac van Marum in 1785, during experiments with a powerful installation for electrification, he observed how, when passing an electric spark through the air, a gaseous substance with a peculiar smell and strong oxidizing properties appeared. In 1801, Krunschenk discovered a similar smell during the electrolysis of water, and in 1840, Professor K. F. Schonbein of the University of Basel associated these changes in the properties of oxygen with the formation of a special gas, which he named ozone (from the Greek word "smell"). A hundred years later, Hansler created the first medical ozone generator, which expanded the boundaries of its use, thanks to the ability to accurately dose the ozone-oxygen mixture. [66]

It is known that ozone is formed in all processes accompanied by the appearance of atomic oxygen. In laboratory conditions and industry, ozone is obtained in ozonizers by the action of an electric discharge on oxygen. The main types of industrial ozonizers have a flat or tubular discharge chamber, glass or ceramics are used as a dielectric, and the electrodes are made of aluminum or copper. The power of the ozonizer is proportional to the frequency of the current.

The main physical characteristics of ozone have been studied in detail and described by S.D. Razumovsky and G.E. Zaykov [47]. Ozone (03) is an allotropic modification of oxygen; its molecule consists of three oxygen atoms and can exist in all three aggregate states. [48]. Medical ozone is an ozone-oxygen mixture (OOM) obtained from medical oxygen by its decomposition in an electric discharge and consisting of 5% O3 and 95% O2. Ozone-oxygen mixtures are produced using special devices - medical ozonizers. In order to minimize the toxic effect of ozone on the body and increase its therapeutic effectiveness when using OOM, it is necessary to know the exact concentration of ozone, the total dose and the time of exposure [63]. Despite the fact that ozone has been actively used for medical purposes for several decades, the mechanisms of its action were established not so long ago and their study continues.

The use of ozone in medicine is based on two fundamental approaches determined by its properties: 1) direct action of ozone, detected during external application in the form of disinfection activity (bactericidal, fungicidal, viricidal properties used to clean wounds, enhance the body's antimicrobial defense and activate local immunity); 2) systemic effect due to low concentrations of ROS induced by ozone (regulation of vasodilation and vasoconstriction, activation of energy metabolism, modulation of oxidation-reduction homeostasis, immunomodulation). Based on the mechanisms of ozone action, methods of using OOM have been developed: 1) external, providing a direct effect of ozone; 2) parenteral, leading to a systemic effect of ozone. External methods of OOM administration include ozone irrigation in a plastic chamber, balneotherapy, various options for using ozonized distilled water and olive oil, intra-articular and para-articular ozone injections, regional lymphotropic administration of OOM. Parenteral methods of administration include major autohemotherapy with OOM (MAHT), minor autohemotherapy with OOM (MAHT), intravenous and lymphotropic drip administration of ozone-saturated saline, intravenous and intra-arterial administration, intramuscular and subcutaneous injections, rectal insufflation of OOM[63].

When high concentrations of gaseous ozone and ozonized solutions are used externally, its powerful oxidizing potential against the bioorganic substrate of microorganisms is manifested. It is believed that the immediate cause of bacterial death under the influence of ozone is local damage to the plasma membrane, leading to the loss of viability of the bacterial cell and (or) its ability to reproduce; in yeast, the main reason is the disruption of intracellular homeostasis. It is important that ozone molecules interact not only with the components of the surface membrane, but, by changing its permeability, lead to the destruction of intracellular organelles. It is also impossible to exclude the mechanism consisting in the action of free oxygen radicals formed during the decomposition of ozone in an aqueous environment, i.e. the one that living organisms use to eliminate foreign antigens. The presence of a highly reactive hydroxyl radical is destructive for most microorganisms [20, 39]. Thus, in vitro experiments have shown that gaseous ozone kills virtually all types of gram-positive and gram-negative bacteria, viruses, fungi and protozoa [9]. According to a number of authors, ozone in concentrations from 1 to 5 mg/l leads to the death of 99.9% of E. coli, Streptococcus faecalis, Mycobacterium tuberculosum, Cryptosporidium parvum, Varavium and others within 4-20 minutes [54]. Ozone therapy for anaerobic infections is considered pathogenetically justified, a significant number of works are devoted to the use of ozone for the purpose of sanitizing the abdominal cavity in the complex treatment of peritonitis. Thus, O.E. Kolesova [41] notes not only a pronounced clinical, but also a noticeable biochemical effect of abdominal cavity sanitation and intravenous administration of ozonated saline (correction of LPO, AOSZ, increased activity of glucose-6-diphosphoglycerate (G-6-DPG). Significant effects on the phagocytic activity of neutrophils, activation of humoral immunity and a pronounced detoxifying effect of ozone therapy in this group of patients were revealed by B.P. Kudryavtsev [30], S.V. Semenov et al. [50], V.S. Zui et al. [23]. All authors emphasize, along with the clinical, and economic aspects of the use of ozone in purulent surgery - a decrease in bed-day, consumption of expensive antibacterial drugs, antiseptics. According to the unanimous opinion of the authors, the high efficiency of systemic ozone therapy methods, even in the case of a decompensated process, is explained by the normalization of the acid-base balance and lipid peroxidation, elimination of hypoxemia, improvement of tissue oxygenation, and reduction of hyperglycemia that occurs during

treatment. Along with the antibacterial effect, the viricidal effect of ozone has been widely used, which is realized through the oxidation of the surface receptors of the virion, as well as the disruption of the synthesis of viral proteins due to a change in the activity of the reverse transcriptase enzyme [4, 12]. It has also been established that encapsulated viruses are more sensitive to the action of ozone than non-encapsulated ones, which is explained by the large amount of lipids in their capsule (for example, in the herpes virus there are up to 22%), which easily interact with ozone [9]. This circumstance underlies the pronounced therapeutic effects of ozone therapy in recurrent herpes. The most important discovery was the detection of the antiviral effect of ozone on a lymphocyte culture infected with HIV-1 [6]. Researchers explain the mechanism of HIV virus inactivation by the following points: 1) partial destruction of the viral membrane and the loss of its properties; 2) inactivation of the reverse transcriptase enzyme, as a result of which the process of transcription and translation of proteins is inhibited and, accordingly, the formation of new viral cells; 3) disruption of the ability of viruses to bind to receptors of target cells.

Ozone therapy provides increased oxygen delivery to tissues with insufficient blood supply, which has been confirmed by analysis of the gas composition of the blood: the partial pressure of oxygen in venous blood after a course of ozone therapy decreases from 40 to 20 mm Hg [13]. This means that more oxygen is released in tissues suffering from insufficient blood supply - an effect that cannot be achieved with medication. In the mechanisms of antihypoxic action, a certain role is played by vasodilation, which concerns primarily capillaries, arterioles and postcapillary venules. The vasodilating effect of ozone is associated with the release by endothelial cells of the so-called "endothelial vascular relaxation factors", which include nitric oxide. S.P. Peretyagin [42] confirm the positive effect of parenteral ozone on blood circulation and, especially, microcirculation, leading to an increase in the release of oxygen to the tissues. According to their data, after the cessation of treatment, the increased time point of oxyhemoglobin reduction decreases very slowly, over several weeks and even months. Thus, the increased oxygen content in the blood can have a therapeutic effect even when ozone treatment has already been completed.

Improvement of blood rheological properties under the influence of ozone is largely associated with changes in the hemostasis system. It is believed that at the stage of primary (vascular-platelet) hemostasis, a decrease in the aggregation capacity of platelets may be associated with the effect of ozone on the metabolism of arachidonic acid contained in their cell membrane, which, on the one hand, is a source of formation of a powerful activator of platelet aggregation - thromboxane, and on the other - an important inhibitor of thromboxane - prostacyclin in the vascular wall [14]. Ozone is able to activate the platelet enzyme phospholipase A2, which, by breaking down phospholipids of cell membranes, leads to the release of fatty acids, mainly arachidonic. This acid is a substrate for a number of enzymes, one of which is cyclooxygenase, which converts arachidonic acid into endoperoxide. The further transformation of endoperoxide depends on its localization: in an intact vascular wall it is converted into prostacyclin and prevents the spread of platelet aggregates, and at the site of damage - into thromboxane, which ensures the immediate release of a number of highly active agents that initiate the blood clotting process .

In therapeutic concentrations, ozone is capable of selectively reacting at the site of the double bond in arachidonic acid, triggering its metabolism along the path of prostacyclin

formation, thereby preventing the formation of platelet aggregates [21]. L. V. Shatalina [60] puts forward a hypothesis about free-radical regulation of platelet aggregation activity, and also cites data that diene conjugates can directly activate platelets, leading to their increased aggregation. Thus, ozone administered parenterally, by reducing the level of DC, can contribute to the normalization of the aggregation activity of blood platelets.

A number of studies [52, 53] have established that after a course of ozone therapy, the indices of the first phase of plasma hemostasis - activated recalcification time (ART) and activated partial platelet time (APTT) - increase reliably (within normal values), which indicates a moderate decrease in prothrombinase formation. The above-mentioned shifts, occurring under the influence of ozone therapy, may indicate a decrease in the functional activity of XII, XI, IX and VIII plasma blood coagulation factors. Normalization of the elevated level of fibrinogen, which plays an important role in the aggregation of erythrocytes and platelets, is also noted [24]. E.O. Obukhova et al. [37] describe an increase in fibrinolytic activity, normalization of soluble fibrin-monomer complexes, a decrease in intravascular blood coagulation, and a decrease in total peripheral vascular resistance when using ozone. Some authors presumably associate the vasodilating effect of ozone therapy with the activation of NO synthase and the action of nitric oxide [45]. Thus, by reducing the concentration of fibrinogen, ozone reduces the aggregation of formed elements of the blood and improves its rheological properties, which is essential for the normalization of microhemocirculation. Ozone therapy also affects lipid metabolism: it has been established that ozone oxidizes lipoic acid, which reacts with the activated form of acetaldehyde, resulting [28, 45] in a decrease in the level of lipids in the blood plasma (especially cholesterol and atherogenic fractions of lipoproteins), as well as carbohydrates and a number of under-oxidized products. In many pathological conditions, and especially in the presence of inflammatory processes, the analgesic effect of ozone is clearly expressed, caused, in all likelihood, by the gradual supply of oxygen to the area of inflammation and the oxidation of mediators formed at the site of tissue damage and involved in the transmission of the nociceptive signal to the central nervous system. In the relief of chronic pain syndromes, a major role is also given to the restoration of the balance between the processes of lipid peroxidation and the antioxidant defense system.

Metabolic effects of ozone therapy also occur in the kidneys - it has been established that in nephrocytes ozone intensifies the processes of utilization of glucose, glucose-6-phosphate, lactate, pyruvate with high activity of gluconeogenesis, accumulation of ATP, increase in stability of cell membranes have also been noted [35]. This aspect is of great clinical significance.

The authors emphasize not only the effectiveness of the sanitizing effect of intra-abdominal irrigation with ozonized solutions in inflammatory pathology, but also the advisability of the prophylactic use of ozone. Due to the combined use of local and systemic exposure to ozone, the risk of developing postoperative purulent-inflammatory complications during laparoscopic operations for common forms of genital endometriosis [40] and uterine fibroids [59] is significantly reduced.

Intravaginal and intrauterine methods of introducing ozonized solutions have been described. Thus, intrauterine introduction of ozonized antiseptic solutions, according to L.I. Tsygankova et al. [59], led to a more rapid relief of postpartum endometritis than in the control, normalization of laboratory parameters (ESR, leukocytes, NBT test, levels of lipid peroxidation

products and AOS3, G-6-PDH) in combination with significantly lower consumption of medications, especially antibiotics. The use of ozonized physiological solution in the treatment of patients with inflammatory diseases of the internal genital organs in women is the subject of the work of N.M. Shakhova [61].

Conclusion. Thus, by now many mechanisms of the therapeutic effect of medical ozone have been revealed, its bactericidal, viricidal, fungicidal action, antihypoxic, vasodilating, immunomodulatory, sedative, detoxifying, analgesic effects, the ability to normalize antiradical protection and lipid peroxidation, the structure and functions of cell membranes, etc. have been established. Modern ozone synthesizers and auxiliary means have become widespread, allowing for the implementation of various ozone therapy methods.

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