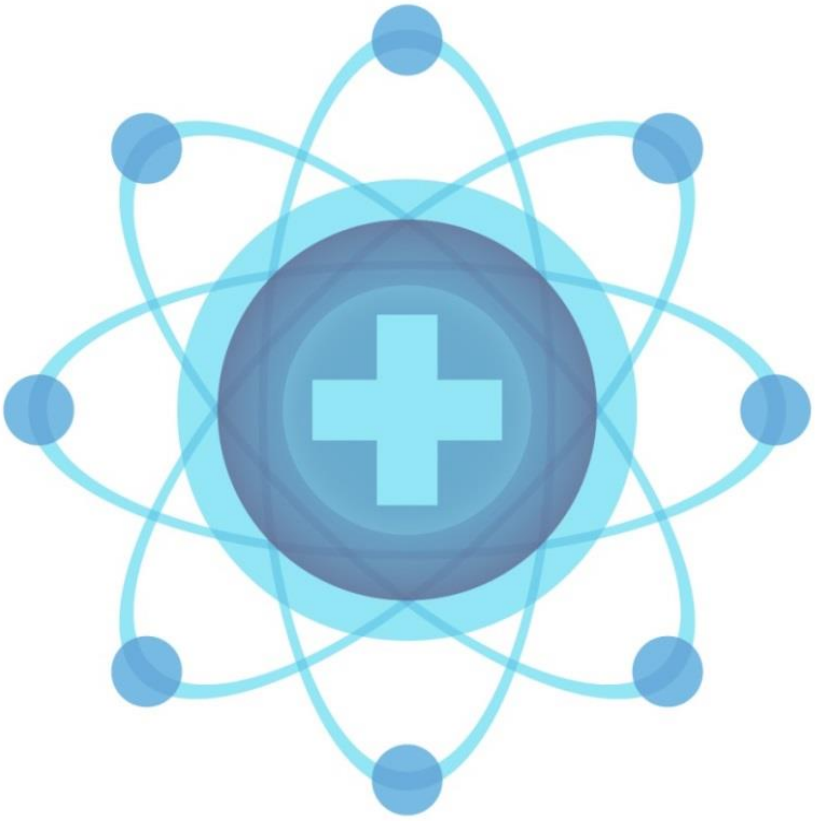

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Reproductive disorders in patients with metabolic syndrome and modern approaches to pharmacological correction.

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Abstract. In recent decades, there has been an active increase in the number of overweight and obese people all over the world, which makes this problem relevant for the medical community. According to some data, 8% of overweight women and 18% of obese women have problems with the exercise of reproductive function. Disorders of glucose, lipids, and arterial hypertension that often develop in patients with polycystic ovary syndrome (PCOS) allow it to be attributed to metabolic diseases. The complex of metabolic disorders, which are based on insulin resistance and hyperinsulinemia, is designated by the term "metabolic syndrome". PCOS can also be considered as one of its manifestations and is considered the most common cause of infertility in overweight and obese women. In the treatment of such patients, it is important to carry out complex therapy aimed not only at restoring reproductive function, but also at correcting metabolic disorders. Lifestyle correction, diet and regular physical activity are not widely used, and therefore there is a need to use and evaluate the effectiveness of pharmacological means of pregravidar preparation for weight loss and improvement of reproductive outcomes in patients with PCOS.

Keywords: polycystic ovary syndrome PCOS obesity metabolic syndrome infertility pre-pregnancy preparation treatment prevention anovulation

Introduction. In recent decades, due to lifestyle changes and significant physical inactivity, there has been a tendency to an increase in diseases associated with metabolic disorders. Cardiovascular morbidity is also increasing, which often accompanies overweight and obesity [1-4]. In the reproductive age, overweight leads to a decrease in fertility. According to a number of authors, 12% of overweight women and 20% of obese women have reproductive disorders that manifest themselves in infertility and miscarriage [1].

The most common cause of infertility in such patients is polycystic ovary syndrome (PCOS) [5, 6]. The "metabolic syndrome" combines a symptom complex of metabolic disorders based on insulin resistance (IR) and hyperinsulinemia (GI). PCOS can also be considered as one of the manifestations of MS. In many women, the increase in body weight precedes the clinical manifestations of PCOS. The prevalence of obesity in PCOS varies depending on the study population and reaches 61% in the USA and 76% in Australia, while there is a tendency to increase from 45-51% in the 1990s to 60-76% in subsequent decades. Regardless of body mass index (BMI) in 50-70% of patients with PCOS, there is a redistribution of adipose tissue according to the android type, and an excess of visceral adipose tissue is associated with an increase in IR and the prevalence of MS [7, 8]. According to a study by N.K.

Stepto et al. [9], in PCOS, insulin resistance is determined in 75% of patients with normal body weight and in 95% — overweight.

Pathogenetic aspects of polycystic ovary syndrome and metabolic syndrome. The mechanism of infertility development in such patients is associated with a violation of regulation in the hypothalamic-pituitary-ovarian system, folliculogenesis with the formation of PCOS and endometrial receptivity [3, 10]. These defects are mediated by increased IR, subsequent compensatory hyperinsulinemia, decreased adiponectin concentration, increased androgen production and increased levels of leptin, interleukin (IL) 6 and tumor necrosis factor α (TNF-α) [4, 11].

Due to the significant clinical heterogeneity that generates a number of phenotypes with or without a body weight disorder, the difference and variability of clinical signs that change throughout life, as well as the systemic effect on the body, the treatment of infertility in PCOS, despite active study in the last decade, seems to be an urgent problem that deserves close attention.

The complex pathophysiology and clinical heterogeneity of PCOS do not contribute to a clear understanding of the interaction between PCOS, overweight and fat distribution in the body. Obesity with visceral distribution of adipose tissue increases IR and compensatory hyperinsulinemia. Due to the interaction between IR and gonadotropic, stimulating the production of luteinizing hormone action of insulin, the level of circulating androgens increases. Hyperinsulinemia plays an important role in the pathogenesis of PCOS, causing a decrease in serum globulin binding sex steroids, which leads to an increase in serum free and metabolically active androgens, a decrease in androgen clearance and aromatase activity, and increased steroidogenesis. This aggravates the clinical manifestations of PCOS and accelerates its manifestation, so it is often difficult to say what became the primary pathology: a violation of fat metabolism or PCOS [7, 10]. Obesity affects the phenotypic expression of PCOS, exacerbating metabolic, reproductive and psychological disorders [2, 3].

The frequency of overweight or obesity is higher in women with PCOS compared to the general population, which may be due to a genetic predisposition to obesity in such patients. If the prevalence of MS in the general population is 14-24%, then among patients with PCOS it reaches 43%. In women with a BMI >25 kg/m2, the diagnosis of PCOS is more common by 9%. With an established diagnosis of PCOS, the incidence of obesity increases in the future. Over time, abdominal obesity increases with a progressive increase in the waist-hip ratio between the ages of 20-25 and 40-45 years [1].

These data are consistent with the results of a prospective cohort study conducted by R. Hart et al. [13], which shows that girls with symptoms or an established diagnosis of PCOS in early adulthood later have higher BMI and, as a result, an increased risk of cardiovascular and metabolic disorders.

According to Australian scientists, diseases such as diabetes mellitus, hypertension, coronary heart disease, venous diseases and venous thromboembolic complications, as well as depressive disorders develop more often than in the general population [14]. Hyperandrogenism and low levels of sex hormone binding globulins are associated with an increased risk of cardiometabolic complications in women of

all ages [1, 14]. The frequency of disorders in the coagulation system and blood lipid profile increases with PCOS and is aggravated by overweight, which also adversely affects reproductive function [1, 15]. Due to IR and obesity, the risk of developing endothelial dysfunction, loss of elasticity of arterial walls, atherosclerosis and calcification of coronary vessels increases.

Among the pathomorphological mechanisms characteristic of obesity, the hemostasis system acquires pronounced procoagulant activity due to a chronic inflammatory reaction and the direct effect of circulating proinflammatory cytokines (TNF-α, IL-6, IL-1β) on the endothelium [16, 17]. Stimulation of the vascular wall endothelium and platelet activation lead to the realization of the prothrombotic potential of the blood, while anticoagulant activity decreases and thrombin formation increases.

In L. Carvalho et al. [12] it is noted that in PCOS, the main pathogenetic link affecting the hemostasis system is a systemic inflammatory reaction. An increase in the concentration of proinflammatory biomarkers in blood plasma in patients with PCOS activates hemostasis factors and reduces fibrinolytic activity. According to a number of authors, when assessing the parameters of the vascular-platelet link, a significant increase in the level of platelets in patients with PCOS in comparison with healthy women of the same age and with the same body weight attracts attention. In addition, there was a significant increase in platelet volume, which is a marker of platelet activity, as well as a correlation between this indicator and the level of androgens [18, 19].

The results of studies on the role of plasminogen activator inhibitor (IAP) in general hemostasiological distress in PCOS patients show that the level and activity of IAP-1 is significantly higher in patients with this syndrome compared to healthy women of similar age [20, 21]. Several studies with a small number of observations [22, 23] concerned the level of antiplasmin and thrombin-activated fibrinolysis inhibitor (TAFI). At the same time, there was no statistical difference in the level of antiplasmin. In turn, the thrombin-activated fibrinolysis inhibitor of blood plasma was higher in patients with PCOS than in the control group, and positively correlated with the markers of IR. The study of the hemostasis system in obese patients is relevant in terms of the increase in the number of unfavorable reproductive outcomes, one of the reasons for which may be an increase in procoagulant potential.

According to C. Bañuls et al. [17], oxidative stress and endothelial dysfunction are associated with PCOS and MS. The authors found that there is a link between altered metabolic status, increased production of reactive oxygen species, markers of oxidative stress and endothelial dysfunction, which can negatively affect reproductive outcomes. L.J. Moran et al. in 2009 a number of studies were conducted, as a result of which a positive correlation was revealed between an increased level of asymmetric dimethylarginine, IR markers, as well as reduced NO production, which confirms the negative impact of PCOS on the balance of mediators that contribute to the normal functioning of the endothelium and increases the risk of cardiometabolic complications.

According to a study by R. Hart et al. [11] compared to the general population, women with PCOS were more often hospitalized in hospital due to uterine bleeding

and habitual miscarriage for infertility treatment, and also more often resorted to in vitro fertilization (IVF).

Metabolic syndrome in combination with PCOS exacerbates ovulatory dysfunction with menstrual cycle disorders, reduces the effectiveness of infertility treatment and ovulation induction and, according to some authors, is associated with an increased frequency of spontaneous termination of pregnancy, preeclampsia, fetal macrosomia and perinatal morbidity. In combination with IR and type 2 diabetes mellitus, adverse outcomes may be more pronounced [11, 13].

Many researchers point to genetically determined metabolic disorders on the background of PCOS, the manifestation of which is aggravated by overweight. The results of recent studies of genomic associations have shown that PCOS is associated with genes associated with the development of obesity, IR and various variations of follicle-stimulating hormone [25].

BMI also affects the results of IVF in patients with PCOS. According to the Frefro-PCOS 2019 multicenter randomized trial, infertility treatment was longer in MS patients, significantly higher doses of gonadotropin were required when ovulation was stimulated, and the frequency of ovarian hyperstimulation syndrome was higher than in the general population. However, despite the smaller number of oocytes obtained and the lower quality of embryos, the cumulative fertility rate after treatment did not show a significant difference between the groups (57.8% vs. 62.2%) [26].

According to A.P. Bailey et al. [20], with PCOS, obese women have 69% lower chances of spontaneous pregnancy, and the frequency of pregnancy after IVF is 77% lower compared to women with PCOS and normal body weight. In this regard, in order to improve reproductive outcomes, it is advisable to correct body weight before the patient enters the IVF program. This approach increases the chance of pregnancy and reduces the number of unsuccessful ovarian stimulation during IVF, which reduces the risk of ovarian hyperstimulation syndrome. However, it is noteworthy that during this study there was a tendency to decrease the frequency of ovarian hyperstimulation syndrome with an increase in BMI among women with PCOS: 19.6% in women with normal body weight, 10.5% — overweight and 3.2% — obese [27, 28].

Metabolic syndrome and obesity are negative factors in the treatment of infertility in patients with PCOS and negatively affect fertility, as evidenced by the worse characteristics of ovulation stimulation, lower pregnancy rate and less favorable clinical outcomes shown in numerous studies [15, 16, 25, 26, 28].

Methods of treatment of PCOS in women with obesity and metabolic syndrome.

The key task of treating patients with a combination of MS and PCOS is indisputably weight loss, but uniform schemes and standards of such treatment have not yet been optimized.

In the past, the treatment of PCOS patients was aimed at eliminating chronic anovulation and clinical manifestations of hyperandrogenism, while remaining symptomatic. However, a change in ideas about pathogenetic mechanisms and frequent combination with metabolic disorders led to a change in the tactics of

examination and treatment of such patients. In addition to correction of reproductive disorders, it is necessary to monitor anthropometric parameters, indicators of the hemostasis system, lipid and carbohydrate profile, as well as blood pressure [29, 31].

Weight loss reduces the amount of abdominal adipose tissue, reduces IR and compensatory hyperinsulinemia, which improves the clinical course of PCOS. Measures aimed at normalizing body weight can not only restore impaired ovarian function, but also reduce the risk of cardiovascular complications and have a positive effect on lipid and carbohydrate metabolism and hemostasis system indicators.

Lifestyle modification, physical activity, and a balanced diet are recommended to all women with PCOS in order to reduce weight or prevent overweight as the first line of treatment. To improve reproductive outcomes, it is necessary to postpone active infertility therapy in patients planning pregnancy until the normalization of body weight [4, 7].

A systematic review and meta-analysis in 2018 [22] showed that lifestyle modification that promotes weight loss increases the frequency of pregnancy naturally, but there is no data on pregnancy outcomes in the work. In every second patient, against the background of a moderate decrease in body weight (by 2-5%), the menstrual cycle was restored, and 2 out of 18 became pregnant. According to an American study of women with infertility and PCOS on the background of obesity, weight loss before using ovulation stimulants led to higher rates of ovulation and live birth [31].

Recently, metformin has been actively used to reduce IR. Improvement of insulin sensitivity against the background of the use of this drug in patients with PCOS has been confirmed in several studies [1, 3, 18, 20]. According to P. Moghetti et al. [20], the use of metformin leads to a decrease in IR regardless of changes in body weight. A decrease in IR against the background of taking this drug is accompanied not only by a decrease in hyperandrogenism, an improvement in ovarian function and menstrual cycle, but also an improvement in the metabolic profile. According to some authors, metformin, compared with placebo, increases the frequency of ovulation in women with PCOS [1, 32, 33]. However, there is insufficient evidence that metformin in combination with other agents used to stimulate ovulation increases fertility. To date, in the treatment of PCOS in combination with metabolic disorders, this drug is used by gynecologists outside of the registered indications (off-label), and in the instructions for use, the only indication for the use of metformin is type 2 diabetes mellitus and its prevention in patients with prediabetes with additional risk factors.

Nevertheless, the use of metformin leads to an improvement in the menstrual cycle and a decrease in androgen levels [34]. In a number of studies, metformin has demonstrated a positive effect in reducing the level of anti-muller hormone elevated in women with anovulatory infertility in PCOS, which casts doubt on hyperandrogenism as the primary link in the occurrence of infertility.

Thus, metformin in combination with lifestyle modification can be recommended for women with PCOS to reduce body weight and treat hormonal and metabolic disorders, but should not be used as a first-line therapy for the treatment of oligoanovulation, since normalization of body weight followed by the use of oral

ovulation inducers such as clomiphene citrate or letrozole is much more they are effective for increasing the frequency of ovulation, pregnancy and fertility in such patients [1, 32].

Adherence to lifestyle correction, diet and regular exercise remains low, and therefore there is a need to apply and evaluate the effectiveness of pharmacological agents as a pre-gravidar preparation for weight loss and improvement of reproductive outcomes in patients with PCOS. For this purpose, drugs with various mechanisms of action are used. However, almost all of them have a fairly high frequency of side effects.

New drugs for pharmacological correction of body weight of interest are analogues of the glucagon-like peptide-1 receptor (GLP-1), which stimulates a feeling of satiety through its action on the neurons of the brain that control food intake. GPP-1 receptors are found in various organs, including the brain, pancreas, gastrointestinal tract, heart, vascular system and kidneys. GPP-1 is rapidly cleaved by the enzyme dipeptidyl peptidase-4, and its period of action is less than 2 minutes. Once in the bloodstream, analogues of GPP-1 bind to albumin, which prevents them from breaking down and prolongs its action time, therefore, the half-life in the human body is 13 hours, which stimulates a feeling of satiety during the day and leads to a decrease in food intake and a decrease in body weight [3, 4, 22].

In the SCALE study, GPP-1 analogues significantly outperformed placebo in the treatment of obesity. In the 1st group after 56 weeks. applications approximately 2/3 of patients lost weight by more than 5%, while about 1/3 lost more than 10% of body weight. A 5-10% decrease in body weight is associated with a decrease in the volume of visceral tissue and an improvement in insulin sensitivity. Treatment also contributed to an increase in the amount of adiponectin, a decrease in the levels of androgens, leptin, proinflammatory cytokines and IAP-1, followed by an improvement in reproductive outcomes [4].

As a complex therapy, the use of inositol in the form of its bioavailable isoforms — myo-inositol (MI) and D-chiro-inositol (D-CHI) seems promising in this group of patients. Both forms are able to counteract IR. While D-CHI is involved in the mediated activation of insulin outside the ovarian tissue, MI has a specific effect on the ovary, mainly by modulating glucose metabolism and signaling follicle-stimulating hormone. MI reduces the concentration of insulin and restores sensitivity to it, reduces the concentration of leptin, the NOME index and body weight, and also has an antioxidant and anti-anxiety effect. D-CHI is involved in glycogen synthesis and affects steroidogenesis, reduces the expression of the aromatase gene (CYP19A1) and, consequently, the conversion of testosterone into estrogen. The insufficiency of these secondary insulin messengers may be an independent mechanism of IR. The ovaries, unlike other organs and tissues (muscles, liver, adipose tissue), cannot be insulin resistant and always retain normal insulin sensitivity even in the presence of systemic IR. Hyperinsulinemia, which occurs against the background of MS, increases the activity of epimerase in teka cells, which is responsible for the conversion of MI into D-CHI, causing an increase in the concentration of D-CHI and a corresponding decrease in MI. In the blood plasma of healthy women, the ratio of MI / D-CHI is 40:1, in the follicular fluid — 100:1. In PCOS, an imbalance of

inositols is formed in the follicular fluid, a specific depletion of MI occurs with an overload of D-CHI, while the ratio of MI/D-CHI decreases to 0.2:1. This condition is called the "ovarian paradox" and is currently considered as the main cause of changes in the ratio of teka cells/granulosis and ovarian dysfunction in women with PCOS. For the normal functioning and restoration of the ovarian structure in women with PCOS, it is necessary to restore the physiological levels of both stereoisomers of inositol [31].

The best laboratory and clinical effects are observed when using a combination of MI and D-CHI in a ratio of 40:1. One of the means with such an optimal composition is Actifet-Gino, containing in 1 tablet a combination of MI and D-CHI in a ratio of 40:1, which corresponds to the physiological ratio of stereoisomers of inositol. According to a number of studies, it has been revealed that this ratio of inositol isoforms is most favorable for PCOS therapy aimed at restoring ovulation and normalizing important hormonal and metabolic parameters in these patients. Other combinations of inositol fractions were less effective [31, 32].

Such therapy deserves attention and requires further research to prove its effectiveness.

Despite the fact that currently inositol should be considered an experimental therapy for PCOS, systematic reviews of recent years show that its use as part of the complex therapy of PCOS increases the frequency of ovulation and reduces insulin resistance, which further leads to an improvement in reproductive function and an increase in the number of spontaneous pregnancies [33]. According to some authors, the use of inositol reduces the frequency of gestational diabetes mellitus in pregnant women with PCOS and MS, which also requires in-depth study of this problem, given the increased risk of gestational diabetes mellitus in these patients.

Conclusion. Thus, it is extremely important to carry out comprehensive treatment of women with PCOS, aimed not only at restoring fertility, but also at correcting metabolic disorders, parameters of the hemostasis system. Due to the significant clinical heterogeneity, the lack of uniform schemes and standards for the management of such patients, it is necessary to implement an individual approach in each case. Considering that adipose tissue is a key factor in the development and progression of IR and other complications, weight loss is recognized as the main mechanism for their correction and a means of pre-gravidar preparation for improving reproductive function in patients with PCOS.

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