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REVIEW
ОБЗОРНАЯ СТАТЬЯ

Polycystic ovary syndrome and obesity: a modern paradigm

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Abstract. Polycystic ovary syndrome is a heterogeneous endocrine disease that affects women of childbearing age. The pathogenesis of polycystic ovary syndrome has not been fully studied to date, its paradigm considers the genetic determinism of the manifestation of hormonal and metabolic disorders, which are considered to be criteria for the verification of the disease (hyperandrogenism, oligo/anovulation and/or polycystic ovarian transformation during ultrasound examination (ultrasound). This review discusses the main ways of interaction between hyperandrogenism, insulin resistance and obesity and their role in the pathogenesis of polycystic ovary syndrome, as well as possible methods of treatment for this category of patients. The review analyzes the role of hyperandrogenism and insulin resistance in the implementation of the genetic scenario of polycystic ovary syndrome and finds out the reasons why women with polycystic ovary syndrome often demonstrate the presence of a «metabolic trio» - hyperinsulinemia, insulin resistance and type 2 diabetes mellitus. It is noted that obesity is not included in the criteria for the diagnosis of polycystic ovary syndrome, but epidemiological data confirm the existence of a relationship between these diseases. Obesity, especially visceral, which is often found in women with polycystic ovary syndrome, enhances and worsens metabolic and reproductive outcomes with polycystic ovary syndrome, as well as increases insulin resistance and compensatory hyperinsulinemia, which, in turn, stimulates adipogenesis and suppresses lipolysis. Obesity increases the sensitivity of tech cells to luteinizing hormone stimulation and enhances functional hyperandrogenism of the ovaries, increasing the production of androgens by the ovaries. Excess body weight is associated with a large number of inflammatory adipokines, which, in turn, contribute to the growth of insulin resistance and adipogenesis. Obesity and insulin resistance exacerbate the symptoms of hyperandrogenism, forming a vicious circle that contributes to the development of polycystic ovary syndrome. These data allow us to conclude that bariatric surgery can become an alternative to drugs (metformin, thiazolidinedione analogs of glucagon-like peptide-1), which has shown positive results in the treatment of patients with polycystic ovary syndrome and obesity.

Key words: polycystic ovary syndrome, obesity, hyperandrogenism, insulin resistance, compensatory hyperinsulinemia

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Introduction

Polycystic ovary syndrome (PCOS) is the most common endocrine disease among women of reproductive age, with an estimated prevalence of 8—13 % [1]. According to the Rotterdam criteria, PCOS is diagnosed when two of the following three criteria are met:

– oligoanovulation;

– hyperandrogenemia (clinical or biochemical);

– polycystic ovarian morphology according to ultrasound [2].

Although the molecular mechanism underlying the pathogenesis of PCOS remains largely undetermined, emerging evidence suggests that hyperandrogenism plays a vital role in the development and complications of PCOS [3, 4].

Obesity is a global pandemic with clinical, social, and economic consequences in both developed and developing countries. Globally, the prevalence of obesity has almost tripled since 1975, and in 2016, more than 1.9 billion adults were overweight, of which more than 650 million were obese [5]. Also during this period, the incidence of comorbidities associated with obesity increased [6]. The development of many conditions such as diabetes, dyslipidemia, and hypertension associated with obesity is due to secondary insulin resistance that occurs with obesity. The capacious term Metabesity, which everyone understands has appeared [7].

Obesity is closely associated with PCOS [8] as supported by epidemiological data showing that, on average, 50 % of women with PCOS are either overweight or obese [9]. Metabolic dysfunction is not included in the criteria for diagnosing PCOS but often accompanies it, significantly reducing the effectiveness of the treatment of the main symptoms and reproductive outcomes [10]. A meta-analysis of relevant studies published in the literature confirmed that women with PCOS had a greater risk of being overweight and obese than women without the condition [11]. In addition, Meri-Maija E Ollila et al. (2016) showed that PCOS was significantly associated with BMI in all age categories [12], and the early manifestation of obesity was associated with the development of PCOS and high BMI in adulthood [13].

Androgen synthesis and possible mechanisms of hyperandrogenism in a woman with PCOS

Androgens are part of the family of steroid hormones, and manifestations of their excess are recognized as one of the main clinical manifestations of PCOS [14]. This group includes testosterone (T), dihydrotestosterone (DHT),

androstenedione (A4), dehydroepiandrosterone (DHEA), and dehydroepiandrosterone sulfate (DHEA-S). A4, DHEA, and DHEA-S serve as precursors for DHT and T. Only T and DHT can directly interact with the androgen receptor.

The ovaries and adrenal glands are the two main sources of androgens in women [15], and steroidogenic enzymes regulate their production. The entire synthesis of steroid hormones begins with the conversion of cholesterol to pregnenolone by the cholesterol side chain cleavage enzyme, cytochrome P450 (P450scc), which is encoded by CYP11A1 [16]. In a study by S. Bakhshalizadeh et al. (2018) noted that the expression of CYP11A1 in granulosa cells in rats with PCOS was increased [17]. Cytochrome P450 17α-hydroxylase (CYP17A1) is another major enzyme involved in androgen production in the ovaries and adrenal cortex and is also overexpressed in PCOS [18, 19].

In the ovaries, androgen synthesis occurs in theca cells under the action of luteinizing hormone (LH). Several downstream LH signaling pathways, such as cAMP-PKA-CREB [20], Ras-Raf-MEK-ERK [21], and PI3K-Akt [22], have been reported to promote the expression of steroidogenic enzymes to increase androgen biosynthesis. The cAMP/PKA pathway increases LH levels by maintaining the expression of genes responsible for the synthesis of enzymes such as CYP17A1, CYP11A1, and 3β-HSD [23].

The final stage of steroid genesis is the conversion of androgens to estrogens using a three-step aromatization reaction involving the specific aromatase enzyme (P450arom) [24]. In women with PCOS, the hyperandrogenic follicular environment significantly downregulates P450arom expression in granulosa cells [25]. Thus, insufficient levels of P450arom reduce the conversion of androgen to estrogen, which leads to an increase in androgen levels.

Hyperandrogenism causes a number of pathophysiological changes, including insulin resistance [26], hyperinsulinemia, dyslipidemia [27] and an imbalance in the LH/FSH ratio [28]. These changes, not only individually, but also interacting with each other and forming a vicious circle, contribute to the development and progressive course of PCOS from a metabolic point of view.

Insulin resistance and hyperandrogenism: pathways of interaction in the pathogenesis of PCOS

The relationship between insulin resistance and androgen excess determines the main mechanism for the formation of PCOS in women. Insulin mediates two major molecular signaling pathways, including the phosphatidylinositol 3-kinase (PI-3K)/Akt pathway [29], which is more involved in cellular metabolism, and the mitogen-activated protein kinase (MAPK) pathway, which is primarily involved in stimulation growth, proliferation and differentiation of cells [30, 31].

Iqbal Munir et al. (2004) in their study showed that insulin is able to stimulate 17α-hydroxylase through the PI3K signaling pathway, promoting excessive androgen synthesis in theca cells [29]. Also, several studies demonstrate that the interaction between insulin and LH increases the expression of the steroidogenic acute regulatory protein (StAR) and CYP17A1 mRNA, thereby increasing androgen levels [32, 33]. In addition, high insulin levels can reduce the synthesis of sex hormone-binding globulin (SHBG), which, in turn, increases the pool of free androgens in the body [28].

Insulin resistance appears to be the central etiological characteristic in most women with PCOS. Although the mechanism of insulin resistance in PCOS is not fully understood, the main defect, as we reported above, occurs in the PI3K post-receptor pathway, which mediates the metabolic effects of insulin [34]. Hyperinsulinemia plays an important role in the development of some of the phenotypic features of PCOS and, together with β-cell dysfunction, increases the risk of developing other metabolic disorders such as type 2 diabetes mellitus (DM2), hypertension, dyslipidemia, and cardiovascular disease, collectively referred to as the metabolic syndrome [35]. By increasing body weight, the post-receptor insulin PI3K pathway becomes resistant to its effects due to the formation of selective dysfunction of this pathway, which leads to compensatory hyperinsulinemia [36].

Metabolic dysfunction in PCOS: the role of androgen excess

Abdominal obesity and insulin resistance synergistically stimulate androgen synthesis in the ovaries and adrenal glands, which subsequently leads to even more fat deposition in the trunk and around the internal organs, thus creating a vicious exchange cycle [37—39]. Hyperandrogenism plays an important role in the development of metabolic disorders associated with PCOS, affecting both peripheral tissues and the central level.

The effect of hyperandrogenism on adipose tissue

There is a differential pattern of fat distribution between men and women. Women accumulate fat predominantly in subcutaneous fat depots (SAD) and especially in the gluteal and femoral areas, while men accumulate fat in the visceral depot [40].

In women with PCOS, the visceral form of obesity often predominates [37], which is mainly due to androgen excess [41]. Testosterone contributes to the accumulation of visceral fat and the development of insulin resistance by inhibiting lipolysis and stimulating lipogenesis [42]. However, the molecular mechanisms involved in chronic androgen-induced abdominal obesity remain largely unknown. Nohara K. et al. (2014) in a preclinical study of female mice showed that an excess of androgens can impair the ability of leptin to stimulate energy expenditure, which, in turn, contributes to the accumulation of visceral fat [43]. Such a change in regional fat distribution induced by androgens may have particularly detrimental metabolic consequences for patients with PCOS since the formation of visceral obesity is recognized as a risk factor for the development of the metabolic syndrome and contribute to the progression of metabolic disorders associated with this endocrinopathy [44]. A large study showed that the formation of visceral obesity in women with PCOS is due to the inability of the adipose tissue of the gluteofemoral region to properly accumulate lipids, confirming this by a decrease in the expression of genes associated with lipid metabolism (LPL, CD36, SNAIL and ADIPOQ), angiogenesis (VEGFa, RSPO3) and genes involved in the remodeling of the extracellular matrix (FN1, COL6A1, and MMP3), as well as a decrease in lipolysis in the adipose tissue of the same area [45].

A growing body of evidence suggests that androgen excess increases the size of adipocytes in subcutaneous adipose tissue in women with PCOS [46, 47]. This hypertrophy can lead to their dysfunction, as it has been suggested that enlarged adipocytes are more susceptible to inflammation, macrophage infiltration, and apoptotic processes [48]. Interestingly, the adipose tissue in women with PCOS has a greater potential for inflammation and fibrosis, as well as a lower angiogenic capacity compared to the adipose tissue of women without PCOS.

The expression ratio of TIMP4/MMP3 in the study by Divoux A. et al. (2022) was significantly lower in women with PCOS than in controls [45]. TIMP4 is an adipogenesis activator [49], and the TIMP4/MMP3 ratio reflects the body's ability to adipogenesis [50]. Since PCOS is associated with higher levels of circulating testosterone, which is believed to contribute to the corresponding disease phenotype, the correlation between TIMP4 gene expression and circulating testosterone levels was evaluated and found to be negative [45].

Recent studies have also looked at the effect of androgens on adipocyte size and differentiation. So Echiburu B. et al. (2018) showed in their work that androgen excess increases the size of adipocytes in women with PCOS [47]. These data were confirmed in an experimental rodent study in which excessive exposure to androgens was associated with an increase in the size of adipocytes in the subcutaneous and visceral fat depot and the development of insulin resistance [51].

There is also information that androgens affect the differentiation of adipocytes, disrupting the transition of preadipocytes to mature adipocytes [52]. So Chazenbalk G. et al. (2013), examining subcutaneous adipocytes isolated from non-obese women, showed that androgens impair the differentiation of human adipocyte-derived stem cells into preadipocytes by altering the activity of bone morphogenic protein 4 (BMP4), the

effect of which was blocked after administration of an antiandrogen drug [53]. Failure to properly differentiate can lead to IR, the formation of large adipocytes filled with excess lipids and inflammatory markers [54].

It should be noted that under the action of androgens the function of adipose tissue suffers. A recent study showed that androgen production within adipose tissue, mediated by the AKR 1C 3 enzyme in PCOS, leads to adipose tissue dysfunction. This enzyme promotes the synthesis of testosterone from androstenedione, and in patients with PCOS, its increased expression was noted, thereby increasing local production of androgens. This condition led to a decrease in the processes of lipolysis and the formation of lipotoxicity, insulin resistance and compensatory hyperinsulinemia. Interestingly, in vitro experiments have shown that insulin increases the expression of the AKR 1C 3 enzyme, which can exacerbate androgen production within adipose tissue and create a vicious circle, thereby increasing the severity of metabolic complications in patients with PCOS [55].

It should be added that adipose tissue is defined as an endocrine organ that produces adipokines (leptin, adiponectin, resistin, chemerin, omentin, visfatin, etc.) [56].

Adiponectin is a hormone synthesized by adipocytes that has a positive effect on the sensitivity of the whole body to insulin [57], as well as on the functional activity of pancreatic β-cells. Research by van Houten E.L. et al. (2012) confirmed the ability of androgens to reduce the level of circulating adiponectin, contributing to the development of insulin resistance in women with PCOS [58]. In an experimental study in mice, it was shown that its increased expression in adipose tissue prevents metabolic disorders associated with continuous exposure to androgens [59].

In addition to the fact that adiponectin levels are affected, it should be emphasized that androgens also decrease circulating levels of another adipokine, omentin-1. The latter has insulin-sensitizing properties and its circulating levels are negatively correlated with free testosterone levels in obese patients with PCOS [60]. Taken together, these results demonstrated that hyperandrogenism reduces the level of adipokines with insulin-sensing properties, which may be an additional source of insulin resistance in women with PCOS.

A number of studies show that visfatin plays a role in pathways that include metabolism, inflammation, and insulin sensitivity [61, 62]. Serum levels of visfatin are higher in women with PCOS than in control women [62—64]. Thus, an increase in serum visfatin in PCOS may contribute to insulin resistance and metabolic dysfunction, which requires further study.

Folliculogenesis in PCOS: the impact of hyperandrogenism, hyperinsulinemia and obesity

In the developmental cycle of the follicles in PCOS, most of them gradually stop at an early stage of development. This disruption of folliculogenesis is the result of hyperandrogenism, hyperinsulinemia with insulin resistance, and exposure to abnormal reactive oxygen species (ROS) and inflammatory cytokines, which are present in excess in obesity. Folliculogenesis is a very complex and carefully organized process with many developmental stages that differ in terms of morphology, physiology, and molecular composition. Follicular development is regulated by endocrine signals from the pituitary gland and locally produced intraovarian factors that act in a paracrine and autocrine manner. Optimal androgen levels are required to maintain normal ovarian function [65]. Aberrant androgen levels disrupt the balance required for normal growth and maturation of follicles in various animal models, leading to a negative effect of androgens on ovarian function [66]. There is evidence that the features of the regulation of growth and differentiation of ovarian follicles by androgens depend on the stage of follicle development [3]. Androgens can inhibit the growth of antral follicles during folliculogenesis. In contrast, preantral follicles respond to androgens by stimulating follicular growth [67]. In addition, androgens inhibit FSH-induced aromatase activity in large follicle granulosa cells, thereby inhibiting follicle development. The growth and differentiation of follicles are determined by the dose of androgens. Low doses can

promote recruitment and growth of follicles, while high doses promote excessive secretion of anti-Müllerian hormone (AMH) by granulosa cells, which in turn inhibits folliculogenesis [68].

Hyperinsulinemia can also interfere with the growth and development of follicles. In the preovulatory stage of development, an increase in insulin helps to reduce the growth of large follicles, and thus reduces the likelihood of ovulation and conception. The effect becomes more evident when hyperinsulinemia is combined with an increase in LH levels [24]. In addition, the regulation of growth and differentiation of follicles by insulin is possible through the insulin-like growth factor (IGF) system. An excess of insulin can reduce the synthesis of IGF-binding proteins (IGFBP), increasing the content of free IGF-1 [69], which is a direct target of miR-323-3p [70]. Androgen stimulation results in the downregulation of miRNA-323-3p while IGF-1 is elevated. This can accelerate the apoptosis of granulosa cells and, as a result, significantly impair folliculogenesis [70]. In addition, insulin or IGF can increase vascular endothelial growth factor (VEGF) levels in luteinized granulosa cells [69]. VEGF is the main regulator of physiological angiogenesis. VEGF levels and vascular flow index are elevated in women with PCOS [71]. Increased vascularization can lead to increased androgenic steroidogenesis and lead hyperandrogenism. These results suggest that an increase in VEGF levels may be one of the mechanisms relevant to the pathogenesis of PCOS.

Dysfunction of adipose tissue in obesity is characterized by increased synthesis and accumulation of pro-inflammatory cytokines, and infiltration by macrophages and other immune cells [56, 72]. Such infiltration leads to the formation of a pro-inflammatory profile (latent inflammation) in obese women, which causes disturbances in tissues throughout the body. As the study by Macarena B Gonzalez et al. (2018) intrafollicular cytokine levels (IL6, TNFα, and IL10) correlate more strongly with lipid levels than with BMI. They suggest that dyslipidemia and saturated lipotoxic fatty acids, which are elevated in the follicular fluid of obese women, are responsible for increased inflammation in ovarian tissue, which exacerbates folliculogenesis [73]. It was previously mentioned that adipose tissue produces a number of adipokines. Leptin is a peptide hormone of adipose tissue that regulates energy metabolism. Serum leptin can be elevated in patients with PCOS, and high concentrations of leptin inhibit the expression of aromatase mRNA in granulosa cells, thereby preventing the conversion of androgens to estrogens, which leads to an increase in serum androgen levels and, ultimately, contributes to follicular atresia [14]. In recent years, adiponectin has attracted increasing attention from researchers. Adiponectin receptors, including AdipoR 1 and AdipoR 2, are expressed in female granulosa cells [74]. Adiponectin can increase IGF-1-induced progesterone and estrogen production [74]. In porcine ovarian granulosa cells, adiponectin can induce the expression of ovulation-associated proteins such as cyclooxygenase (COX)-2 and prostaglandin [75]. Therefore, a decrease in adiponectin leads to suppression of the ovulatory mechanism [76]. Moreover, adiponectin significantly reduces the secretion of gonadotropin-releasing hormone (GnRH) from hypothalamic neuronal cells, which reduces LH secretion. Thus, a decrease in its concentration in the body in patients with obesity, in combination with other factors, contributes to the development of PCOS [77].

PCOS and obesity: genetic aspects

The commonality of obesity with PCOS was also considered at the genetic level. Day F.R. et al. (2015) found an association between high BMI and PCOS based on a Mendelian randomized study of 32 single nucleotide polymorphisms (SNPs) [78]. Conclusions opposite to this opinion were made by Batarfi A.A. et al. (2019) in a randomized controlled trial that refuted the data for a single genetic component of obesity and PCOS [79]. However, Xu L. et al. (2014) identified SNP-501 A/C (rs26802) of the ghrelin gene, which has been associated with some metabolic changes in PCOS. BMI and waist-to-hip ratio were higher in PCOS patients with SNP-501 A/CA than in PCOS patients with SNP-501 A/CC. In addition, the frequency of

occurrence of the –501 A/CA allele was higher in the group of patients with PCOS [80].

The latest large-scale study of the genomic correlation and causation between obesity and PCOS was carried out by Qianwen Liu et al. (2022). Using genome-wide association studies (GWAS); they identified 15 common loci underlying PCOS and associated with obesity (9 loci between BMI and PCOS, 6 loci between waist to hip circumference and PCOS). Mendelian randomization (MR) has supported causal roles for both adult BMI and childhood BMI in PCOS. This study suggests a common genetic basis for obesity and PCOS [81].

Treatment of PCOS in patients with metabolic dysfunction

Considering the fact that today there is no specific method for treating metabolic dysregulation in PCOS, and most women with PCOS are overweight and obese, and also show insulin resistance associated with compensatory hyperinsulinemia, which ultimately forms a risk group for the development of DM2, the initial stage of therapy is recommended diet and exercise in order to reduce body weight. To date, data from a meta-analysis including 15 studies have shown that lifestyle modification, namely diet, and exercise, contributed to the reduction of free androgen index and body weight in women with PCOS [82]. Nybacka et al. (2011) conducted a randomized comparison of the effects of diet and/or exercise on ovarian function and metabolic parameters in overweight women with PCOS. After four months, the authors noted a decrease in BMI, serum testosterone levels, and an increase in SHBG levels. At the same time, more than every second of the patients restored the menstrual cycle. These results suggest that diet and exercise alone or in combination are equally effective in improving fertility in overweight or obese women with PCOS [83]. Chan Hee Kim et al. (2022), reviewing 25 studies, noted that a combination of diet and exercise can reduce BMI and fasting blood glucose and improve tissue sensitivity to insulin. Subgroup analyzes showed that the lifestyle modification group had significantly more patients who had normalized menstrual cycles compared to control groups [84]. However, most obese women with PCOS cannot achieve significant weight loss through lifestyle modification. For these women, the use of insulin-sensitizing drugs such as metformin is the preferred treatment. Improving insulin sensitivity while taking this group of drugs helps to reduce the level of circulating insulin and weaken the insulin-mediated stimulation of androgen production in the ovaries [1, 85].

However, the use of metformin has had conflicting results. Chan Hee Kim et al. (2020) conducted a meta-analysis including studies comparing the efficacy of metformin and lifestyle modification. The authors demonstrate no difference in the number of patients who recovered their menstrual cycle between lifestyle modification in conjunction with metformin and lifestyle modification alone. Pregnancy rates and BMI were not significantly different between the lifestyle modification group and the metformin group. Diet and exercise reduced insulin resistance and increased serum SHBG levels compared with metformin [86].

Thiazolidinediones (TZDs) are an alternative treatment for metabolic and reproductive disorders associated with PCOS. TZDs are a group of drugs that activate PPAR-γ, a nuclear receptor, resulting in increased insulin sensitivity, mainly in adipose tissue and skeletal muscle [87]. Treatment with this group of drugs has been shown to improve insulin sensitivity, lower insulin levels, and improve reproductive parameters in women with PCOS [88]. However, like metformin, TZDs have little effect on body weight or may even contribute to weight gain [89].

Glucagon-like peptide-1 (GLP-1) analogs have recently emerged as novel antidiabetic drugs that have hypoglycemic effects and reduce insulin resistance and promote weight loss [90]. Given the importance of weight loss and increased insulin sensitivity in obese/overweight women with PCOS, several studies have evaluated the metabolic and reproductive effects of this group of drugs in the above cohort of patients. Studies have shown that GLP1 treatment reduces body weight and serum androgen levels normalize the

menstrual cycle in obese women with PCOS [91, 92]. Interestingly, a recent meta-analysis reported that the use of GLP-1 drugs may be more effective than metformin monotherapy in improving insulin sensitivity and other metabolic parameters [93]. Thus, drugs of the GLP-1 group can be considered as clinically beneficial drugs in the choice of tactics for managing patients with obesity and PCOS. Of note, the combined action of GLP-1 and metformin may be more effective than either drug alone for the treatment of metabolic and reproductive disorders associated with PCOS [94] and may even improve metabolic outcomes in women who previously showed poor response to the action. metformin [95]. However, despite the study results, further studies are needed to evaluate the reproductive and metabolic efficacy and safety of this drug combination in obese women with PCOS.

Bariatric surgery is widely used to treat obesity and related diseases such as type 2 diabetes, hypertension, and sleep apnea. Currently, there are few studies looking at the effectiveness of bariatric surgery for PCOS. A recent meta-analysis of nine different studies covering 234 obese patients with PCOS found that bariatric surgery reduced BMI, circulating serum glucose, and IR in patients with PCOS. The operation also helped to reduce the level of androgens in the blood, and restore the menstrual and ovulatory cycles [96]. A significant decrease in androgen levels and ovarian volume in women with PCOS was also noted by Christ J.P. et al. (2018) in their study using bariatric surgery [97]. Singh D. et al. (2020) in a prospective study that included 50 women with PCOS and obesity who underwent bariatric surgery, observed the normalization of the menstrual cycle, a decrease in the hirsute number to the minimum values, and a decrease in the level of free testosterone in the blood serum. Complete resolution of polycystic disease according to ultrasound was observed in 70 % of patients in the studied cohort [98]. The specific mechanisms by which bariatric surgery improves metabolic and reproductive dysfunction in patients with obesity and PCOS remain unclear and require further study.

Conclusion

PCOS is a heterogeneous disease and its pathogenic mechanisms remain unclear.

Analysis of the literature of the last decade shows that androgen excess not only contributes to the development of PCOS, but may also interact with several factors that exacerbate it, such as insulin resistance, hyperinsulinemia, and obesity. Interestingly, there is a genetic correlation between obesity and PCOS. A detailed study of the specific mechanisms of the relationship between androgens, insulin resistance and obesity that regulate the functioning of the female reproductive system will help identify and develop targeted treatments for women with PCOS. At the same time, priority areas are associated with risk prediction, the reduction of which is based on the normalization of body weight. To date, there are several groups of drugs for the treatment of metabolic dysfunction in women with PCOS, these include metformin, thiazolidinediones, and GLP-1 analogs. In the near future, experimental and clinical studies will focus on the potential therapeutic utility of new GLP-1-based unimolecular poly-agonists for the treatment of metabolic and reproductive disorders associated with PCOS. The metabolic efficacy and safety of these unimolecular multi-agonists compared to GLP-1 receptor agonists have recently been demonstrated in various preclinical models of obesity [99] and several of these drugs are currently being clinically evaluated for the treatment of T2DM.

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Синдром поликистозных яичников и ожирение: современная парадигма

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Аннотация. Синдром поликистозных яичников представляет собой гетерогенное эндокринное заболевание, которым страдают женщины детородного возраста. Патогенез синдрома поликистозных яичников на сегодняшний день до конца не изучен, его парадигма рассматривает генетическую детерминированность манифестации гормональных и метаболических нарушений, которые принято считать критериями верификации заболевания (гиперандрогения, олиго/ановуляция и/или поликистозная трансформация яичников при ультразвуковом исследовании. В данном обзоре рассмотрены основные пути взаимодействия гиперандрогении, инсулинорезистентности и ожирения и их роль в патогенезе синдрома поликистозных яичников, а также возможные методы лечения данной категории пациенток. В обзоре анализируется роль гиперандрогении, и инсулинорезистентности в реализации генетического сценария синдрома поликистозных яичников и выясняются причины, почему женщины с синдромом поликистозных яичников часто демонстрируют наличие «метаболического трио» - гиперинсулинемии, резистентности к инсулину и сахарного диабета 2 типа. Отмечается, что ожирение не входит в критерии постановки диагноза синдрома поликистозных яичников, но эпидемиологические данные подтверждают наличие взаимосвязи между этими заболеваниями. Ожирение, особенно висцеральное, которое часто встречается у женщин с синдромом поликистозных яичников, усиливает и ухудшает метаболические и репродуктивные исходы при синдроме поликистозных яичников, а также увеличивает резистентность к инсулину и компенсаторную гиперинсулинемию, что, в свою очередь, стимулирует адипогенез и подавляет липолиз. Ожирение повышает чувствительность тека-клеток к стимуляции лютеонизирующим гормоном и усиливает функциональную гиперандрогению яичников, повышая выработку андрогенов яичниками. Избыток массы тела ассоциирован с большим количеством воспалительных адипокинов, которые, в свою очередь, способствуют росту резистентности к инсулину и адипогенез. Ожирение и инсулинорезистентность усугубляют симптомы гиперандрогении, образуя порочный круг, способствующий развитию синдрома поликистозных яичников. Приведенные данные позволяют сделать вывод, что альтернативой лекарственным средствам (метформин, тиазолидиндионы аналоги глюкагоноподобного пептида-1) может стать бариатрическая хирургия, показавшая положительные результаты лечения пациенток с синдромом поликистозных яичников и ожирением.

Ключевые слова: синдром поликистозных яичников, ожирение, гиперандрогения, инсулинорезистентность, компенсаторная гиперинсулинемия

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