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MODERN ASPECTS OF TREATMENT OF WOMEN WITH POLYCYSTIC OVARY SYNDROME

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UKRAINE

Abstract. *Polycystic ovary syndrome (PCOS) is one of the most common neuroendocrine syndromes of reproductive age, affecting up to 20% of women in this age group. This condition is characterized by hyperandrogenism, ovulatory dysfunction, and polycystic ovary morphology. In the pathophysiology of PCOS, there is a violation of the circadian rhythm of GnRH secretion, which increases the release of LH and decreases FSH. The latter is necessary for the synthesis of aromatases, which convert androgens into estrogens [7].*
Another pathophysiological link in the development of PCOS is insulin resistance.
Androgen hypersecretion increases the level of insulin resistance, and the hyperinsulinemia that develops due to insulin resistance further increases androgen secretion and induces the production of sex hormone-binding globulin (SHBG) in the liver, thereby increasing the concentration of free testosterone in the blood and even more aggravates disorders associated with hyperandrogenism.
In 2003, a consensus of experts at a joint ESHRE/ASRM symposium in Rotterdam adopted diagnostic criteria (remaining relevant to this day), which include a triad of signs: oligoovulation or anovulation; hyperandrogenism (clinical and/or biochemical manifestations); polycystic ovaries detected during ultrasound; diagnosed on the basis of at least two of the following signs [7].
Patients may have different manifestations of this triad depending on the disease phenotype, patient age, and lifestyle. Therefore, treatment strategies are symptomatic and depend on desired goals and clinical preferences.

Introduction

Polycystic ovary syndrome (PCOS) is one of the most common neuroendocrine syndromes of reproductive age, affecting up to 20% of women in this age group. This condition is characterized by hyperandrogenism, ovulatory dysfunction and the morphology of polycystic ovaries [10].

In the pathophysiology of PCOS, there is a violation of the circadian rhythm of GnRH secretion, which increases the release of LH and decreases FSH. The latter is necessary for the synthesis of aromatases, which convert androgens into estrogens [7]. The result is an excessive secretion of androgens, which leads to a delay in the growth of follicles and, as a result, ovulatory dysfunction, thereby causing polycystic changes according to ultrasound [6]. Hyperandrogenism causes excessive secretion of LH[7]. A high concentration of LH leads to an imbalance in the ratio of LH/FSH, which increases the dysregulation of follicle growth, and also causes hypersecretion of androgens from cells of the thecal membrane; these factors and the above interact and reinforce each other. Preantral and primary antral follicles that accumulate in women with PCOS increase anti-Müllerian hormone (AMH) secretion, altering the follicular environment and GnRH secretion, which exacerbates ovarian dysfunction [6]. AMH may serve as a molecular biomarker for PCOS and comparative ovarian size[1].

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Patients may have different manifestations of this triad depending on the disease phenotype, patient age, and lifestyle. Therefore, treatment strategies are symptomatic and depend on desired goals and clinical preferences. PCOS can lead to serious complications such as metabolic syndrome, type 2 diabetes, dyslipidemia, endometrial cancer, and cardiovascular disease[1].

The goal of the work: to conduct an analysis of current medical data on the effectiveness of therapeutic treatment options for women with PCOS, their impact on the normalization of the menstrual cycle, the success of fertility attempts, the reduction of clinical manifestations of hyperandrogenism, the correction of metabolic disorders and the reduction of IR levels.

Materials and methods. 10 articles for the year 2022 were analyzed with keywords: PCOS, Treatment, Life Modifications, Anovulatory, Infertility, Obesity, Hyperandrogenic, for which a review of the available literature was conducted in the National Library of Medicine, PubMed.

Results of current medical data and their discussion.

Lifestyle modification.

One of the first steps in the treatment of PCOS is lifestyle change, especially for women who are overweight and obese. Studies have shown that women with PCOS can improve insulin sensitivity and reduce abnormal androgen levels with vigorous aerobic exercise (over 150 min per week) and strength training (over 90 min) [11]. Regarding dietary changes, studies have shown that the MED (Mediterranean Diet)/LC (Low Carbohydrate Diet) diet model is a good treatment for overweight PCOS patients. MED)/LC promotes menstrual cycle regulation, affects weight, and its overall efficacy is significantly better than the LF (low-fat diet) diet [8].

Treatment of irregular menstrual cycle and hyperandrogenism.

The first line of treatment for PCOS in women who do not have reproductive plans is COCs (they will prevent the development of hyperplastic processes and reduce the increased level of androgens). COCs are a combination of estrogen and progestagen, where estrogen is intended to reduce the level of LH and FSH, and, as a result, decrease ovarian androgen secretion, increase SHBG synthesis, and decrease total and free circulating androgen [9]. A combination of ethinyl estradiol with a progestin that has antiandrogenic properties, such as cyproterone acetate, is effective. An excess of the estrogenic component can worsen insulin resistance, so it should be used with caution in patients with existing metabolic and cardiovascular risk factors/ The recent development of two natural estrogen-containing COCs (17-estradiol and 17-estradiol valerate) may be a therapeutic alternative in PCOS, showing a more favorable effect on the metabolic profile compared to ethinyl estradiol [2].

The most common antiandrogens are spironolactone, finasteride, and flutamide [7]. Spironolactone has a direct blocking effect on the synthesis of androgens in the ovaries and adrenal glands. It has shown excellent results against acne, which regresses in 90% of cases when used for a long period (9 months to a year), unlike pills, which almost always do not maintain the effect after stopping, even if used for a very long time [2]. It has shown excellent results against acne, which regresses in 90% of cases when used for a long period (9 months to a year), unlike pills, which almost always do not maintain the effect after stopping, even if used for a very long time [2]. Finasteride (blocks 5-alpha-reductase) and flutamide (blocks androgen receptors) [7], recently associated with serious disorders, so their use is limited [2].

Treatment of metabolic diseases and reduction of IR.

Insulin resistance is not one of the diagnostic criteria, but it is one of the main goals of PCOS therapy. An effective and safe insulin-sensitizing drug is metformin (MET) [2], which is used in PCOS even without diabetes and affects tissues affected by insulin resistance. It is indicated in combination with COCs, especially for overweight or obese patients [9]. Metformin is also a second-line therapy for menstrual cycle disorders in patients with contraindications to hormonal contraceptives [5]. Long-term use of metformin in the treatment of PCOS can increase the rate of ovulation, regulate the menstrual cycle, and reduce androgen secretion [9].

Canafliglosin (CANA) may be a new treatment option for PCOS, according to a randomized controlled trial. The study compared the efficacy and safety of CANA/MET combination therapy and MET monotherapy in the endocrine and metabolic profiles of overweight and obese women with PCOS.

Sodium-glucose cotransporter-2 (SGLT-2) inhibitors, new oral hypoglycemic drugs that promote renal glucose loss. Studies have shown that SGLT-2 can promote weight loss in overweight or obese non-diabetic individuals. Compared with MET monotherapy, CANA/MET may have greater benefits in reducing total testosterone, AUC for glucose, and AUC for insulin over three months. However, more studies are needed to evaluate the long-term effects of SGLT-2 inhibitors in patients with PCOS [3].

In particular, recent studies have shown the possibility of using glucagon-like peptide-1 receptor agonists (GLP-1 RA) alone or in combination with metformin in women with PCOS, improving body weight and insulin resistance. Recent years of research have shown the positive effects of inositol supplementation, the most common forms being Myo-inositol (MYO) and D-chiro-inositol (DCI) in a ratio of 40:1,

which is effective in improving ovarian function and metabolic profile in female patients [2]. Regular use of MI-DCI tablets had a positive effect on the LH/FSH ratio and the levels of free testosterone and DHEA in the blood, contributed to the restoration of menstruation and spontaneous ovulation. MYO has been shown to improve acne by reducing hyperandrogenism in PCOS patients over 8 weeks along with improving hirsutism[4].

Treatment of infertility.

In order to induce ovulation in patients with PCOS, indirect stimulants are used, in particular clomiphene citrate and letrazol. Clomiphene citrate competitively antagonizes the estrogen receptor in the hypothalamus to increase GnRH release. Clomiphene citrate competitively antagonizes the estrogen receptor in the hypothalamus to increase GnRH release. A high level of GnRH leads to higher production and secretion of FSH by the pituitary gland, which stimulates the growth and development of follicles[5].

The effects of clomiphene citrate were compared with placebo in three randomized clinical trials in non-ovulatory women, and the results were summarized in a meta-analysis. This meta-analysis showed a higher clinical pregnancy rate in all treatment groups compared to placebo. 80-85% of women with PCOS ovulate after treatment with clomiphene citrate, and 15-20% are resistant to it and do not respond to doses up to 150 mg/day for 5 days for at least three courses of treatment[1].

A combination regimen of clomiphene and metformin is considered to be more beneficial than single therapy with clomiphene or metformin for ovulation and pregnancy in women with PCOS[9]. Letrozole is currently preferred over clomiphene citrate for ovulation induction. Letrazole inhibits the aromatase enzyme involved in the aromatization of androgens into estrogens, and this increases pituitary FSH secretion by inhibiting the estrogen negative feedback loop in the hypothalamus. Its more widespread use is due to the fact that it has fewer side effects due to its high elimination rate and half-life. Another reason is the higher frequency of ovulation and live birth in infertile women with PCOS.

The next stage is the use of direct stimulators of ovulation - gonadotropins. Gonadotropins are hormones that are endogenously produced by the pituitary gland and are used when there is no response to indirect stimulation. There are human (highly purified urinary FSH), recombinant FSH, and highly purified human menopausal gonadotropin.

The disadvantage is the increased risk of ovarian hyperstimulation syndrome and multiple pregnancy [1].

Prospects for further scientific research

Treatment of this syndrome remains difficult, and, of course, the relationship between genetic predisposition and insulin resistance should be the subject of new studies. Further studies are needed to evaluate the effectiveness of new therapeutic approaches, taking into account that therapy must be individualized, as the syndrome has different phenotypes.

Conclusions

1. Polycystic ovary syndrome is a common neuroendocrine disease. Women with PCOS should be diagnosed early, properly treated, and closely monitored to avoid harmful outcomes.

2. Treatment strategies depend on desired goals and clinical preferences. Many successful non-drug and pharmacological treatments have been developed to address this problem.

3. Lifestyle modification is the main initial stage of treatment of this disease. However, this is often not enough.

4. Women who do not plan to become pregnant are primary prescribed COCs in order to regulate the menstrual cycle, prevent endometrial hyperplasia and reduce the clinical manifestations of hyperandrogenism.

5. Overweight and obese women with PCOS are prescribed insulin-sensitizing drugs such as MET. CANA/MET combination may have greater benefits in improving menstrual cycle frequency, weight control, and reducing IR. However, further trials are needed to evaluate the long-term effects of SGLT-2 inhibitors in patients with PCOS.

6. To treat infertility in women with PCOS, indirect ovulation inducers (clomiphene citrate and letrazol) are primarily used.

7. For patients who have not responded to first-line drugs, gonadotropine are the next step.

8. Finally, assisted reproductive techniques are alternative options for those who have failed ovulation induction therapy or have additional infertility factors.

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