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Polycystic ovary syndrome: clinic, diagnosis, treatment principles (part II)

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Abstract. The analysis of modern literature data on the methods of diagnosis and treatment of polycystic ovary syndrome (PCOS) was carried out. The article considers the issues of surgical and medical treatment, with paramount importance given to medical therapy. We emphasize that the treatment of patients with PCOS should be individualized, taking into account the characteristics of the clinical picture, laboratory and instrumental examination methods, as well as reproductive plans. The presented schemes and principles for the treatment of patients with PCOS are based on international clinical guidelines and consensuses adopted by leading experts.

Key words: polycystic ovary syndrome; diagnostic methods; treatment; metformin; hormonal therapy.

Conflict of interest. The authors declare the absence of obvious and potential conflicts of interest associated with the publication of this article.

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The clinical manifestations of polycystic ovary syndrome (PCOS) are extremely diverse. The clinical picture varies largely depending on age, the presence of obesity and metabolic disorders [1,2]. Even with the same body weight, the clinical symptoms of the disease are very individual. On the one hand, the disease may have no obvious clinical symptoms and manifest itself only as anovulatory infertility. On the other hand, the symptoms of PCOS may be so striking as to 'mimic' the picture of a hormone-producing tumour, with patients presenting complaints typical of virile syndrome [2, 3, 4].

Significant difficulties in the clinical diagnosis of PCOS are due to the low diagnostic value of most symptoms, none of which are exclusive to PCOS [3,5,6]. At the same time, despite the variability, it is the clinical picture that is its main diagnostic criterion. Laboratory and instrumental diagnostic methods are of secondary importance [3,5,7].

Diagnosis of PCOS is based on clinical and laboratory findings of hyperandrogenism, assessment of menstrual and ovulatory functions, and evaluation of the morphological structure of the ovaries by echography [8,9].

Signs of polycystic ovaries include irregular menstrual cycle, abnormal uterine bleeding, infertility, symptoms of hyperandrogenism - excess male sex hormones, overweight or obesity (body mass index 25.0 and above), acanthosis nigricans- areas of dark brown color in the skin folds of the neck, armpits, groin (not necessarily a sign of insulin resistance), psychological and psychosexual disorders and eating disorders (overeating) [10,11].

Infertility is observed in 75% of patients with PCOS, hirsutism - in 70%, amenorrhea - in 50%, obesity - in 40%, abnormal uterine bleeding - in 30% of patients [12].

Symptoms of excess male sex hormones include seborrhea - increased sebum formation on the scalp, face, front surface of the chest, back, shoulders; hirsutism - excessive growth of dark, thick hair on the upper lip, chin, chest, back and stomach, inner thighs; acne - a disease of the sebaceous glands of the skin, associated with the blockage of their output ducts; androgen-dependent alopecia-progressive hair loss, starting on the crown or temples and spreads to the parietal and occipital areas [10,13].

Seborrhea is characterized by abnormal sebaceous gland function and quantitative and qualitative changes in sebum. Increased sebum secretion and follicular hyperkeratosis lead to plugging of the sebaceous ducts by horny plugs - comedones. Papular and pustular acne occur because of stagnant sebaceous secretion and the introduction of pyococcal infection [12,14].

Hirsutism (excessive hair growth in androgen-dependent areas of the body) is the most typical clinical manifestation of hyperandrogenism. The Ferriman-Galway scale, a method of quantifying hair growth in women, is used to assess hirsutism. The method was first presented by D. Ferriman and J.D. Gallwey in "The Journal of Clinical Endocrinology"[15,16]. The method originally described eleven body regions to be assessed, but a modification of the method reduced the number to nine (the forearm and lower leg were removed). The evaluation table of each body part examined starts from 0 (no excessive terminal/terminal hair growth) to 4 (extensive growth), all numbers adding up to a maximum of 36.

A score of 6-8 corresponds to moderate hirsutism; 8-15 corresponds to severe hirsutism; a score over 15 corresponds to severe hirsutism. In the development of acne (*acnevulgaris*, acne), the main key factors are impaired sebum produc-

tion and composition, increased pathogenicity of skin microflora, follicular hyperkeratosis and impaired keratinisation processes due to excessive androgen production. Androgens interact with the sebaceous glands to stimulate sebum secretion. Staphylococci, corynebacteria, propionibacteria cause inflammation of the sebaceous gland duct.

If the follicle mouth is closed or narrowed, a closed comedon (white) is formed; if the follicle mouth is open, horny masses move into the follicle mouth like a plug and an open comedon (black) is formed [14,17].

Alopecia is progressive baldness caused by the action of androgens on the hair follicles. Female pattern baldness is slower, the frontal hairline usually remains the same, there is diffuse hair thinning in the frontoparietal area, and the central partition is widened. Under conditions of increased androgen production or changes in androgen metabolism, the terminal hair follicles on the head rebuild and begin to produce shorter, thinner, fuzz-like hair. Under certain circumstances, scalp hair follicles regress under the influence of androgens, while in other parts of the body they grow intensively under the same exposure. This phenomenon is since the capillary blood vessels in the scalp of predisposed individuals show an increased sensitivity to androgens, in particular dihydrotestosterone, as well as to the enzyme 5α-reductase. The result is vasospasm, the hair follicle's nutrition is impaired and, as a result, baldness occurs. Female androgenic alopecia is classified according to the Ludwig scale and is divided into three types [18, 19].

Type I: Marked thinning of hair within the frontoparietal area, widening of the parting, but the hair growth margin remains intact.

Type II: Distinct hair thinning within the frontoparietal area.

Type III: Within the frontoparietal area, hair is completely lost.

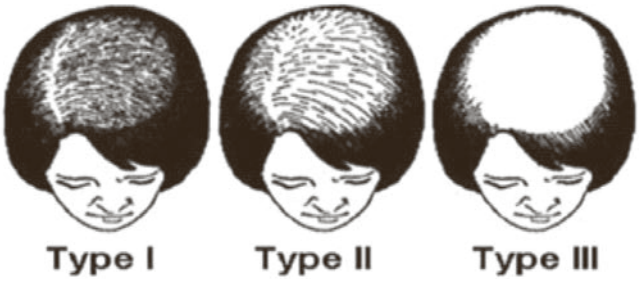

Figure 1. Classification of female androgenic alopecia on the Ludwig scale.

Currently, the Rotterdam (2003) agreed criteria of the European Society of Human Reproduction and Embryology and the American Society of Reproductive Medicine (ASRM/ESHRE) are used to diagnose PCOS. The agreed ASRM/ESHRE criteria expand the range of patients who can be diagnosed with PCOS, as they suggest the presence of any two of the following signs: Oligo-anovulation, hyperandrogenemia, and/or hirsutism, polycystic ovarian morphology on ultrasound [20,21].

The AES criteria (AE-PCOS Society, 2006) require the presence of 2 out of 2 features: hirsutism and/or hyperandrogenemia; oligo-anovulation and/or polycystic morphology [22, 23]. Applying the AE PCOS Society criteria (2006) requires the use of accurate methods for determining the level of androgens, which is not always possible.

It is common to distinguish several types (phenotypes) in PCOS (Table 1).

Phenotype A is "classical". Symptomatology - androgen excess (clinically and/or biochemically) + ovulation dysfunction + polycystic ovarian morphology (ultrasound)

Phenotype B is "anovulatory". Symptomatology - androgen excess (clinically and/or biochemically) + ovulation dysfunction

Phenotype C is "ovulatory". Symptomatology - androgen excess (clinically and/or biochemically) + polycystic ovarian morphology (ultrasound)

Phenotype D is "nonandrogenic". Symptomatology - ovulatory dysfunction + polycystic ovarian morphology (ultrasound).

Diagnosis of PCOS includes laboratory diagnosis of androgen excess and other laboratory abnormalities that occur in PCOS (but are not criteria for this diagnosis); confirmation of polycystic ovaries by ultrasound; diagnosis of metabolic syndrome; diagnostic laparoscopy and endometrial biopsy may be used.

Ultrasound is advisable to carry out on the 3-5th day from the onset of menstruation, preferably with a vaginal probe. In amenorrhea, ultrasound is performed either at any time or 3-5 days after menstruation caused by progesterone preparations.

At least one of the following criteria supports the diagnosis of PCOS: more than ≥ 20 follicles 2–9 mm in diameter in any ovary; ≥ 10 cm3 enlargement of any ovary (in the absence of a corpus luteum, cysts, or dominant follicles) [6,14].

Table 1

Main types (phenotypes) of PCOS

	Anovulation	Hyperandrogenism (clinical and/or biochemical)	Polycystic ovarian structure according to ultrasound
Type (phenotype) A ("classic")	+	+	+
Type (phenotype) B ("anovulatory")	+	+	
Type (phenotype) C ("ovulatory")		+	+
Type (phenotype) D ("nonandrogenic")	+		+

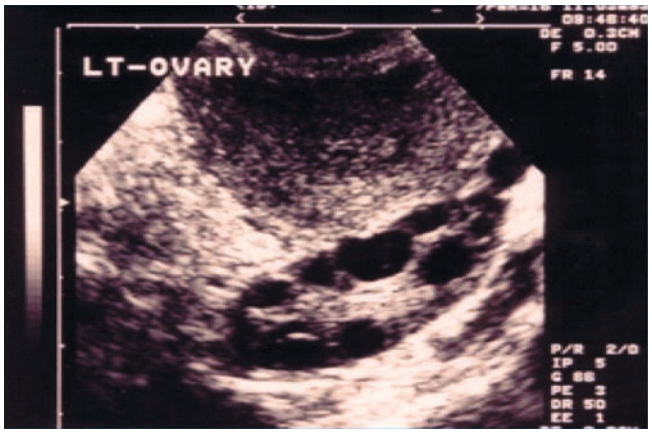

Figure 2. Echogram. The necklace is an ultrasound sign of PCOS.

The absence of polycystic ovaries on ultrasound does not rule out PCOS.

- If testosterone is elevated ≥200 ng/dl, an ultrasound, MRI or CT scan should be performed to detect an ovarian or adrenal tumor;

- If dehydroepiandrosterone (DHEA) rises >700 mug/dl, consider adrenal hyperfunction.

- With an increase in dehydroepiandrosterone (DHEA) ≥500-700 mug / dl, an increase in the level of 17-OH progesterone, which may be a manifestation of late onset congenital adrenal hyperplasia.

To diagnose PCOS, the following indicators should also be determined: TSH and prolactin; FBS, fasting insulin and calculation (not in the guidelines).

An oral glucose tolerance test (OGTT), fasting plasma glucose or HbA1c should be performed to assess glycaemic status. Testing should be done in women at high risk of developing PCOS (BMI > 25 kg/m2 or in Asians > 23 kg/m2, with a history of impaired fasting glucose, impaired glucose tolerance, or gestational diabetes, a family history of type 2 diabetes mellitus, hypertension, or ethnic high-risk items).

To diagnose metabolic syndrome, the following should be done: measurement of body mass index (BMI) or waist circumference; measurement of blood pressure; fasting plasma glucose test, oral glucose tolerance test, glycated hemoglobin (HbA1c) - these indicators are recommended in all women with already diagnosed polycystic ovaries, and then every 1-3 years, depending on the presence of other risk factors for type 2 diabetes; assessment of lipid grams - blood tests for cholesterol, triglycerides, low-density lipoproteins and high-density lipoproteins [7,10].

Since PCOS is a chronic disease, it is important to assess the development of possible long-term complications and diseases, the main of which are: obesity: waist circumference > 78 cm; low quality of life; depression; diabetes - 20%; hypertension - 40%; higher TAH rate; cardiovascular diseases; endometrial and ovarian cancer - 2-3 times more often; PCOS and pregnancy; hirsutism; infertility; sleep apnea; irritable bowel syndrome (IBS).

The formation of PCOS and its clinical manifestations often begin in adolescence [25,26]. Clinical manifestations of PCOS in adolescents are: the presence of hair on the back, acne, thinning hair, the presence of hair on the lips / chin / neck, the presence of hair on the chest, the presence of hair on the abdomen, excess weight around the waist, dark/discolored patches on the skin, hidradenitis, delayed menstruation and ovarian cysts.

Diagnostic criteria for PCOS in adolescents are clinical hyperandrogenemia, biochemical hyperandrogenemia, insulin resistance and hyperinsulinemia, acanthosis nigricans, visceral obesity and impaired glucose tolerance; oligomenorrhea persists for 2 years after menarche, morphology of polycystic ovaries on ultrasound (ovarian volume and morphology may be of limited use in adolescence). Differential diagnosis of polycystic ovary syndrome is carried out with the following diseases: non-classical adrenal hyperplasia of the adult type; Cushing's syndrome; androgen-producing tumor (adrenal gland, ovary); thyroid disease; hyperprolactinemia; ovarian insufficiency; drug exposure [26,27].

The treatment of patients with PCOS is done on a case-by-case basis. The choice of treatment depends on age, complaints, severity and combination of symptoms, presence or absence of insulin resistance, women's reproductive plans, cardiovascular risk [13].

Anxiety and depressive symptoms should be routinely screened in all adolescents and women with PCOS at diagnosis. If the screen for these symptoms and/or other aspects of emotional wellbeing is positive, further assessment and/or referral for assessment and treatment should be completed by suitably qualified health professionals, informed by regional guidelines.

The success of treatment depends on many factors: the needs of the patient and the prevention of long-term health problems. Weight loss leads to an improvement in all symptoms of PCOS. Lifestyle changes in women with PCOS improve hyperandrogenism and insulin resistance (Cochrane review, Moran LJ, 2011). A loss of only 7 to 10% of body weight can lead to improved insulin resistance, a significant decrease in testosterone levels, a reduction in abdominal fat and a resumption of menstruation. Lifestyle intervention (diet and exercise) normalizes FSH, SHBG, total testosterone, and androstenedione, FAI, and FG in women with PCOS.

As a first-line drug for impaired glucose tolerance, type 2 diabetes, metformin is recommended. It is a tableted antidiabetic drug of the biguanide class for oral administration [28,29].

Metformin is the only anti-diabetic drug that has been convincingly shown to prevent cardiovascular complications of diabetes. It helps lower LDL and tri-

glyceride levels and is not associated with weight gain. The most serious potential side effect of biguanide use is lactic acidosis, with an incidence of 9 per 100,000 persons/year.

Metformin is an insulin sensitizer. Therapy with metformin leads to a decrease in the concentration of leptin in the blood in women with PCOS and overweight. It reduces the rate of glucose absorption in the small intestine and suppresses appetite, has a positive effect on carbohydrate metabolism, leads to a decrease in the incidence of IGT and a decrease in hyperinsulinemia, as well as ovarian hyperandrogenemia.

Other benefits of metformin: short-term metformin therapy improves arterial stiffness and endothelial function in young women with PCOS; the combination of metformin and simvastatin may lead to a better reduction in T and LH levels and thus reverse the LH:FSH ratio, lipid profile and insulin resistance. Metformin may also prevent endometrial cancer in PCOS [30].

In women with PCOS and anovulatory infertility and without any other infertility factors, letrozole should be considered as first-line pharmacological treatment for ovulation induction to improve ovulation, pregnancy, and increase live births (ESHRE 2018) [31].

Ten years ago, Clomiphene citrate was recommended for the treatment of anovulatory infertility. The duration of ovulation induction with clomiphene citrate should be limited to six cycles. The combination of metformin with clomiphene citrate increased the chance of ovulation by a factor of 3.5 compared to clomiphene citrate alone. CC works by blocking estrogen receptors, which causes the release of FSH. Clomiphene citrate restores ovulation in about 75% and induces pregnancy in 35-40% of anovulatory women with PCOS. It is thought that the reasons for the differences in the frequency of ovulation and pregnancy are mainly due to the anti-estrogenic effect of clomiphene citrate on endometrial development and cervical mucus [32,33]. However, recent updated guidelines of ESHRE recommended that Letrozole (aromatase inhibitor) should be considered first line pharmacological treatment for ovulation induction in women with PCOS with anovulatory infertility and no other infertility factors to improve ovulation, pregnancy, and live birth rates. Health professionals and women need to be aware that the risk of multiple pregnancy appears to be less with letrozole, compared to clomiphene citrate (Reference: International evidence-based guideline for the assessment and management of polycystic ovary syndrome. ESHRE, 2018).

Gonadotropins are used as second-line drugs when clomiphene citrate or letrozole are ineffective. Induction of ovulation by gonadotropins ensures that more follicles enter the gonadotropin-dependent growth phase.

Two schemes are used:

1. Step-up protocol, low-dose gonadotropin:

14 days: 50-75 IU -7 days: 75-112,5 IU - 7 days: 100-150 IU.

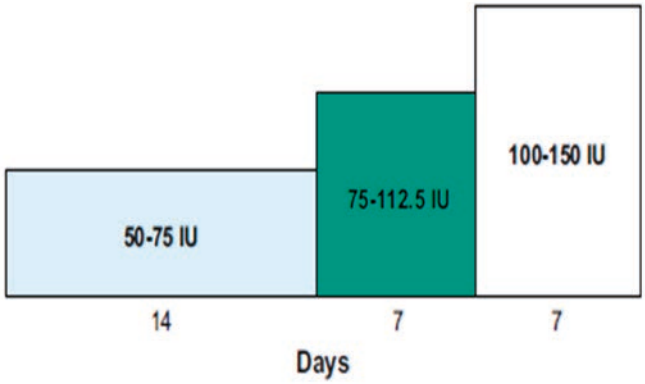

Figure 3. Scheme of the protocol for increasing the level of gonadotropins during the stimulation period.

2. Protocol for lowering the dose of gonadotropin (Great to prevent OHSS in PCOS): 5 days: 150 IU > follicle 10 mm - 5 days: 112.5 IU - 75 IU.

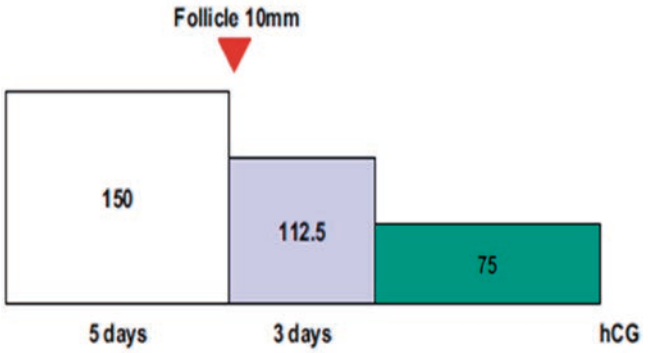

Figure 4. Scheme of the protocol for lowering the level of gonadotropins during the stimulation period.

Surgical treatment for PCOS. The efficacy of surgery for PCOS has been established empirically: spontaneous recovery of menstrual function has been observed in patients with PCOS who underwent surgery for morphological examination of ovarian tissue. Laparoscopic ovarian surgery could potentially be offered as first line treatment if laparoscopy is indicated for another reason in women with PCOS with anovulatory infertility and no other infertility factors. In women with PCOS and infertility with resistance to clomiphene citrate, high LH levels, other indications for laparoscopic surgery (endometriosis, tubal-peritoneal factor infertility), inability to monitor when using gonadotropins, laparoscopy is recommended [34]. Laparoscopic ovarian drilling is only indicated if laparoscopy is performed for other causes of infertility [35,36]. The effectiveness of laparoscopic drilling and the use of gonadotropins are comparable. Monopolar electrocautery

and laser are used with the same efficiency. To achieve an effect in PCOS, rule of 4 is recommended in one ovary: 4 punctures, 4 seconds and 4 mm depth are sufficient, with many of them may cause an increase in premature ovarian insufficiency [37]. Ovulation induction is required in 50% of patients after laparoscopy. If there is no ovulation for 12 weeks after laparoscopy, CC stimulation should be used, and after 6 months of using clomiphene citrate, gonadotropins may be used.

If pregnancy is currently undesirable for the patient, the treatment has two main aims: first, to treat hirsutism, acne, and menstrual disorders, and second, to assess and reduce risk factors for associated diseases (type 2 diabetes, cardiovascular disease, etc.). Lifestyle modification and weight loss is the first step in treatment. In the presence of excess weight, the first step in treatment will be the settlement of the diet and weight loss, regardless of whether the woman is planning a pregnancy or not. Adipose tissue, especially in the abdomen and thighs, is a reservoir of male sex hormones, so getting rid of these reservoirs leads to a decrease in androgen levels in the blood, as well as a decrease in insulin levels. However, weight loss should be gradual and moderate because drastic weight loss can worsen menstrual disorders. With moderate weight loss, improvement is seen after 4-12 weeks. In the history of polycystic ovarian syndrome, there is an insufficient number of publications on the effects of different types of diet on PCOS and the restoration of menstrual cycle regularity and fertility in women. Of all the most popular diets, the effects of energy-restricted diets (1000 to 1400 kcal/day) and protein have been studied. Low glycaemic index diets are worth considering. Combinations of diet and exercise are becoming popular in the treatment of PCOS, as well as supplementation with metformin.

Antiandrogens are used to treat hirsutism [38]. Aldactone (*spironolactone*) is an aldosterone antagonist used for the treatment of hirsutism at a dose of 100-200 mg per day from the 5th to the 25th day of the menstrual cycle. The course of treatment takes from 6 to 24 months or more. Veroshpiron suppresses the production of androgens in the ovaries and thereby has an antiandrogenic effect, and prevents the conversion of testosterone into dihydrotestosterone.

Combined oral contraceptives (COCs). The mechanism of action of COCs is based on the suppression of LH synthesis, as well as an increase in the level of Sex Hormone Binding Globulin (SHBG), which reduces the concentration of free androgens. COCs and antiandrogens are more effective than metformin for hyperandrogenic symptoms and endometrial protection. Their combination with metformin has a positive effect on BMI and glucose tolerance. [39, 40].

Data on the effects of combined hormonal oral contraceptives (OCs) on metabolic changes in women with polycystic ovarian syndrome (PCOS) have been inconsistent and based predominantly on OCs with cyproterone acetate (not available in the United States). Most studies did not include normal women as controls.

In recent years, there have been many studies comparing clinical, hormonal, and metabolic parameters in women with PCOS treated with various combined oral contraceptives (containing chlormadinone acetate versus drospirinone). The use of both drospirinone-containing and CMA-containing COCs provided similar positive therapeutic effects in relation to clinical, metabolic, and hormonal parameters. Among clinical parameters such as hirsutism, after 6 months of continuous COC treatment, a statistically significant improvement was observed in both groups. In addition, significant improvement has been shown according to acne lesions, both after COC use with drospirinone and after CFU treatment with chlormadinone acetate [41].

The treatment of patients with polycystic ovary syndrome should therefore be individualized, considering the clinical picture, laboratory and instrumental examinations, and reproductive plans. Currently, the doctor in the treatment of patients with PCOS should consider international and regional clinical recommendations and consensuses adopted by leading experts in this field of medicine.

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