

Assessment of Clinical, Biochemical and Hormonal Aspects of Women of Fertile Age with Polycystic Ovary Syndrome

Abdusattarov A.A.

Department of Internal Medicine

Ibragimova D. D.

Department of Hospital therapy and Endocrinology 1 stage magistracy

Kholmatova G.A. (PhD) assistant

Department of hospital therapy and Endocrinology

Andijan State Medical Institute

Andijan, Uzbekistan

Resume. Assessment of patient management tactics and the effectiveness of polycystic ovary syndrome (PCOS) therapy, taking into account modern international recommendations. Inadequate assessment of the menstrual cycle without taking into account modern characteristics of the normal menstrual cycle leads to overdiagnosis and, as a result, the appointment of unnecessary therapy. The incidence of PCOS among women of young fertile age with menstrual disorders was 49.5%. Clinical hyperandrogenism of varying severity was detected in all patients with PCOS. The use of microdosed COCs containing drospirenone in the treatment of PCOS in 93% of cases reduces the severity of clinical hyperandrogenism, normalizes the menstrual cycle and improves anxiety indicators by 16.5%.

Keywords: polycystic ovary syndrome, hyperandrogenism, acne, depression, AS, drospirenone.

Introduction. Polycystic ovary syndrome (PCOS) is a polyendocrine syndrome with a frequency of 5-20% in the general population [1]. The frequency of detection of PCOS in women with menstrual cycle disorders (NMC) is 17-46%, clinical hyperandrogenism is 70-80%, and anovulatory infertility is 55-91% [2]. In recent years, PCOS has been considered not only as a gynecological disease, but also as a condition leading to endocrine and metabolic disorders (impaired carbohydrate tolerance, insulin resistance (IR)), dyslipidemia and, as a result, atherosclerosis, arterial hypertension and changes in the psychological status of a woman. The classification of PCOS phenotypes varies in domestic and foreign sources.

Risk factors for PCOS are childhood infectious diseases, traumatic brain injuries, smoking, psychoemotional stress and stress, obesity during the adrenarcho period, pathology of pregnancy and childbirth in the patient's mother, low birth weight of the girl, genetic predisposition. The risk of developing the disease is higher if there is a family history of PCOS [2, 3].

The disease manifests itself in adolescence or early reproductive age. The main clinical manifestations are hyperandrogenism (clinical, biochemical), ovulatory dysfunction, NMC and multifollicular morphology of the ovaries, detected by ultrasound of the pelvic organs [1-3].

IR is detected in 30-70% of patients with PCOS who are obese, and in 20-25% with normal body weight. In the presence of IR, hyperinsulinemia subsequently occurs [2, 3]. The International Protocol (2018) [3] recommends testing for prediabetes, type 2 diabetes mellitus (fasting glucose, glucose tolerance test or glycated hemoglobin A1c) for overweight adults and adolescents at any age. Women with PCOS who are planning pregnancy are recommended to perform a glucose tolerance test at the pre-pregnancy stage.

In women with anovulatory infertility, PCOS is detected in 55-91% of cases, which, taking into account the frequency of occurrence of PCOS in the population, is of great importance in a difficult demographic situation. Ethnic characteristics should be taken into account when making a diagnosis of sleep disorders, for example: increased body mass index (BMI) in women of the Caucasus, North America and Australia; more pronounced hirsutism in women of the Middle East, Latin America and the Mediterranean; a significant percentage of women with central obesity, IR, black acanthosis in residents of Southeast Asia and indigenous Australians; lower BMI in women of East Asia (excess body weight already at a BMI >23 kg/m²); high BMI and metabolic characteristics in African women [3].

It is necessary to remember about the negative psychosocial consequences and the impact on the quality of life of the components of the disease. With sleep, there is a high prevalence of anxiety (moderate to

severe) up to depression, especially among adolescents. Unwanted hair growth, alopecia, acne, overweight, non-onset of pregnancy - these features, regardless of the severity and complaints presented, should be considered important for patients [3].

The success of the therapy of PCOS depends on many factors, these are: the awareness of the patient herself about her disease, the awareness of medical professionals about new research and therapies, an interdisciplinary approach to treatment with the involvement of psychologists/psychotherapists, nutritionists, etc., if necessary [3]. To evaluate the management tactics of patients and the effectiveness of therapy for PCOS, taking into account modern international recommendations, we conducted a retrospective clinical study.

The purpose of the study. Assessment of patient management tactics and the effectiveness of polycystic ovary syndrome (PCOS) therapy, taking into account modern international recommendations.

Material and methods. A retrospective analysis of outpatient records of 1606 female students of higher and secondary educational institutions of Perm who applied to a gynecologist at the consultative and diagnostic polyclinic of the Academician E.A. Wagner State Medical University of the Ministry of Health of the Russian Federation for 2019 was carried out. A detailed survey and assessment of the menstrual calendar in girls with NMC (238 patients, 21.2%) revealed that 4 of them had postcoital bleeding, 8 had ovulatory bleeding. Twenty patients incorrectly assessed their cycle, they showed no signs of hyperandrogenism and ultrasound criteria for PCOS, and they were excluded from the study.

Thus, the study group included 206 girls with OCD and amenorrhea. The average age of the patients was 21.3 ± 0.19 years (from 18 to 26 years), the average age of menarche was 14.3 ± 0.24 years, the cycle duration was 63 ± 12.1 days (from 25 to 180 days), the duration of menstruation was 5.8 ± 0.2 days. Secondary amenorrhea was detected in 5 (2.4%) patients. All the girls lived a sexual life, did not plan pregnancy and did not use hormonal contraception.

The severity of hirsutism was studied on the Ferriman—Gallway scale, alopecia on the Ludwig scale. The level of anti-muller hormone (AMH) was determined by enzyme immunoassay in blood serum (reference values, according to laboratory data: 0-12.6 ng/ml). The blood glucose level was measured by the glucose oxidase method (reference values, according to the laboratory: 3.05–6.1 mmol/l). Ultrasound of the pelvic organs was performed using a transvaginal sensor (3.5–5 MHz). The level of anxiety was assessed using the PHQ-9 patient Health Questionnaire (Patient Health Questionnaire).

The results of the study. According to the data of 1606 outpatient charts, the reasons for contacting a gynecologist were: the need for consultation on contraception - in 228 (14.2%) patients, routine examination without complaints — in 201 (12.5%) patients, a positive test for the presence of human chorionic gonadotropin — in 56 (3.5%) patients, other complaints — in 1121 (69.8%) patients. The structure of complaints is presented as follows: discharge from the genital tract or discomfort in the genital area — in 674 (60.2%) patients, irregular menstruation — in 238 (21.2%), abdominal pain of various nature and duration — in 117 (10.4%), pain and a feeling of formation in the mammary glands — in 49 (4.4%), painful menstruation — in 43 (3.8%).

Clinical signs of hyperandrogenism were detected in all 206 patients of the study group: 35% noted the growth of dark facial hair, the periarticular area, the white line of the abdomen, the inner surface of the thigh (score on the Ferriman—Gallway scale at the initial admission to the clinic — 6-9 points); 21.4% complained of acne of varying severity (face, upper chest, upper back, shoulders); 1.4% noted alopecia (stage I on the Ludwig scale), 42.2% revealed a combination of several signs.

Blood pressure values in 100% of the patients were within the normal range, ranging from 100/60 to 125/85 mmHg). The average BMI in the study group was 22.4 ± 0.97 (normal body weight — 63.1%, excess body weight — 20.9%, grade I obesity — 14.6%, grade II obesity — 1.4%). In 1 patient with grade II obesity and in 2 patients with grade I obesity, glucose levels above 6.1 mmol/l were detected, the girls were referred for consultation to an endocrinologist.

According to ultrasound data in the study group, 37.5% of patients revealed a multifollicular structure of the ovaries. Oligoanovulation was observed in 78.6% (162 patients). An increase in AMH levels (above 12.6 ng/ml) was registered in 28.6% of patients with NMC.

Based on the examination, the diagnosis of PCOS was established in 102 patients, which is 49.5% of the total number of patients with NMC. Based on the international protocol (2018) [3], patients can be divided by phenotypes: phenotype A — 55 (53.9%) of patients, phenotype B — 23 (22.5%), phenotype C — 24 (23.6%), phenotype D — not revealed, which differs from the data on the frequency of occurrence noted by other authors: phenotype A — 53%, phenotype B — 27%, phenotype C — 15%, phenotype D — 5% [4].

Among patients with diagnosed PCOS, AMH levels above 12.6 ng/ml were observed in 70.5%.

A survey of female students with PCOS in order to evaluate reproductive plans showed that 4.9% of patients do not have specific plans, 8.3% are not against pregnancy, 86.8% do not plan pregnancy within the next two years and, as a result, need effective hormonal contraception. It should also be noted that 2 girls have only homosexual sex. At the same time, they were diagnosed with PCOS, and they need the use of hormonal contraception for therapeutic purposes.

Assessment of the anxiety level of patients with sleep disorders using the PHQ-9 questionnaire showed: the general norm in 68.9% of patients, minimal depression in 22.8%, mild depression in 7.3%, moderate depression in 1.0%. Patients with signs of depression of varying degrees are recommended to consult a psychotherapist.

Hormonal contraception was prescribed to all patients with PCOS: 104 (98%) patients received a combined oral contraceptive (COC) containing 20 mcg of ethinyl estradiol and 3 mg of drospirenone (Dimia), taken daily for 24 +4 days, 2 (2%) patients received a monocomponent gestagenic drug (Lactinet-Richter) due to diagnosed migraines. During the first month, 9% of the girls who took Dimia had periodic scanty spotting, and 2% had nausea. These symptoms were treated independently, without additional pharmacological correction. After 6 months, from the beginning of observation and administration of COCs (Dimia), 93% of patients noted a decrease in clinical hyperandrogenism, normalization of the menstrual cycle. A repeated assessment of the anxiety level showed a general norm in 73.3%, and minimal depression in 26.7%.

Discussion. In accordance with foreign recommendations [3], the NMC has the following characteristics:

- 1-3 years after menarche, the cycle has a duration of less than 21 and more than 45 days;
- more than 1 year after menarche — at least 1 cycle per year for more than 90 days;
- more than 3 years after menarche — cycle of less than 21 and more than 35 days (less than 8 cycles per year);
- primary amenorrhea after 15 years (or after 3 years from the appearance of telarche).

In the classical version of PCOS, after a timely menarche, the menstrual cycle is not established, oligo- and/or opsomenorrhea is formed. Primary amenorrhea is extremely rare. Secondary amenorrhea can form after a few years in 20-30% of patients.

It should be noted that NMC is not a mandatory criterion for PCOS, anovulatory cycles are possible even with regular menstrual bleeding. In NMC, the diagnosis of PCOS should be clarified according to other criteria.

Oligoanovulation occurs in 75-85% of patients. The presence of chronic anovulation is indicated by the absence of ovulation in two cycles out of three [1].

It should also be remembered that NMC and oligoanovulation are a normal component of puberty. The physiological maturation of the hypothalamic-pituitary-ovarian system has been going on for many years, and today there is no clear understanding when a teenager's menstrual cycle should be assessed as irregular. It is noted that the earlier the menarche occurred, the faster the cycle normalizes. So, in girls with menarche at 12-13 years old, after 1 year, more than 50% of cycles become ovulatory, if the onset of menstruation occurred at 15 years old, oligoanovulation and NMC can persist until the age of 18 [3].

In our study, the fact of overdiagnosis of NMC — 31 (1.9%) was recorded. The girl from all those who went to the gynecologist noted a cycle of up to 45-60 days 1-3 times during the last year. The average age of such patients was 18.02 ± 0.14 years, the average age of menarche was 15.1 ± 0.24 years. Previously, they had already contacted a gynecologist with complaints of irregular menstruation and received unjustified

symptomatic treatment with progesterone drugs, vitamins A and E, neurotropic drugs (glycine), sedatives (valerian).

Hyperandrogenism (clinical — hirsutism, alopecia, acne, or biochemical) is a key diagnostic criterion for PCOS [3]. The prevalence of hirsutism in classical sleep reaches 75%, traditionally estimated on the Ferriman—Gallway scale (>4-6 points depending on ethnicity). The prevalence of alopecia is estimated according to the Ludwig visual scale, there is no generally accepted visual scale for acne assessment [1, 3]. The assessment of biochemical androgeny is difficult due to the lack of a unified view on which indicators should be determined. Such an assessment is necessary in cases where there are no signs of clinical hyperandrogenism (hirsutism, acne, alopecia). In our study, the level of androgens in the blood was not determined due to the obvious presence of clinical hyperandrogenism of varying severity in all patients of the study group.

In patients with NMC and hyperandrogenism, ultrasound is not mandatory for the diagnosis of PCOS, but it allows you to determine the full phenotype. An increase in ovarian volume (>10 ml) detected by ultrasound is a more reliable diagnostic criterion than determining the number of follicles. It is preferable to use transvaginal access in the early follicular phase [1, 3]. According to the International Protocol (2018) [3] Ultrasound search for symptoms of PCOS is not recommended earlier than 8 years after menarche due to the high incidence of multifollicular ovarian structure at this age. The term "cystic" is not correct, since the essence of the process is not the formation of ovarian cysts, but the concentration of a large number of immature follicles. At the same time, risk groups for developing PCOS among young girls can be identified with subsequent reassessment.

In newborn girls, the level of AMH is minimal and practically undetectable. Increasing during puberty (3.5 ± 1.8 ng/ml), it reaches a maximum at reproductive age ($2.1-7.3$ ng/ml), decreases after 35 years and by menopause is zero [5]. In our study, the average AMH level in patients with PCOS was 11.2 ± 1.8 ng/ml. Traditionally, it is believed that the level of AMH in sleep is higher than in healthy women [3], however, in 1 patient we recorded an indicator equal to 1.1 ng/ml, which corresponds to a "decrease in the functional reserve of the ovaries", according to the literature [5]. In 35.3% of patients with CSF, the AMH level exceeded 20 ng/ml. Determination of serum AMH levels cannot be the only diagnostic test for PCOS. In the future, after the standardization of the study and the determination of thresholds based on large-scale studies, AMH may play a major role in the diagnosis of sleep disorders.

The International Protocol (2018) [3] recommends regular assessment of anxiety levels in patients with sleep disorders. The assessment can be carried out using questionnaires PHQ, GTR-7 (generalized anxiety disorder), etc. If the test results are positive, the patient should be recommended to consult a specialist. Among patients with PCOS, the prevalence of eating disorders and a tendency to disorderly eating is high.

The choice of treatment tactics. The choice of therapy depends on the individual characteristics and reproductive plans of the patient. Treatment of PCOS should include not only drug therapy, but also lifestyle adjustments (healthy diet, adequate physical activity). A 5-10% weight loss over 6 months provides significant clinical improvement [3].

The guidelines prepared by Australian researchers recommend the following amount of physical activity for women over the age of 18 [3]. To maintain health and prevent weight gain, moderate physical activity lasting > 150 minutes / week, or intense (> 75 minutes / week), or a combination of both types of exercise, divided into 2 non—consecutive days during the week.

To reduce weight, moderate physical activity lasting > 250 min /week, or intensive (>150 min /week), or a combination of both approaches, divided into 2 non—consecutive days during the week.

In addition, daily physical activity should include 10 thousand steps, 30 minutes of structured physical activity (household chores, cycling, sports, family or social activities) or an additional 3 thousand steps.

First-line drugs for the treatment of PCOS in adult women with hyperandrogenism and/or irregular menstruation are COCs. In adolescents who have not yet been diagnosed with PCOS, COCs can be used to correct the menstrual cycle and relieve clinical signs of hyperandrogenism. If there is no proper effect when taking COCs, then combination therapy using metformin drugs is possible. Surgical treatment is used only in patients planning pregnancy in case of ineffective drug stimulation of ovulation [3].

The use of estrogen-progestogenic hormonal contraceptives is most appropriate if long-term contraception is necessary in patients with PCOS. Microdosed drugs containing 20 micrograms of ethinyl

estradiol have fewer side effects, lower cost, but are comparable to other COCs in terms of bioavailability and metabolism. A large number of studies have not shown a significant effect of COC on changes in BMI, waist circumference, total testosterone and total cholesterol levels [3, 6].

It is recommended to use COCs containing drospirenone, a progestogen of the latest generation, which is a derivative of spironolactone. It blocks androgen receptors and has no metabolic activity unlike other progestogens. Taking into account the antiminerlocorticoid and antiandrogenic effects, the administration of the drug is justified in patients with clinical manifestations of sodium retention (weight gain, edema, mastalgia), as well as with androgen-dependent dermatopathy [6].

According to the instructions, nausea is one of the most frequent (1:10-1:100) adverse events, and acyclic discharge is less frequent (1:100-1:1000). The results of our studies correspond to the frequency of adverse events indicated in the instructions and confirm the high safety of this drug [6].

When prescribing combined hormonal contraceptives, contraindications should be taken into account — thrombosis (arterial and venous) currently or in history, risk factors for thrombosis (including hereditary), migraine, severe liver diseases, etc. [6-8].

In our study, there were no contraindications to the appointment of hormonal contraception in patients with PCOS. An additional criterion for the appointment/non-appointment of COC is headache [7, 8]. Headaches were detected in 2 (1.96%) patients with sleep disorders during the survey, and a neurologist diagnosed migraine without aura. They were prescribed hormonal contraception based on gestagen-containing drugs (Lactinet-Richter).

It should be remembered that women with PCOS have a higher risk of endometrial cancer. In case of prolonged endometrial hyperplasia, abnormal uterine bleeding, prolonged amenorrhea, the patient should be offered an endometrial biopsy. However, screening evaluation of endometrial thickness is not recommended [3]. In accordance with international criteria for the acceptability of contraceptive methods, long-term use of combined hormonal contraception reduces the risk of endometrial cancer [7-9].

According to the literature, the majority of patients noted a pronounced positive trend during 9 months of taking COCs. It is necessary to inform patients that after discontinuation of the drug, the symptoms of hyperandrogenism may resume in most women. In this regard, a long-term intake of COCs is necessary until the decision on pregnancy planning is made.

Conclusions. Every 10th patient of young fertile age who goes to a gynecologist has an NMC (12.8% of all those who applied initially). Inadequate assessment of the menstrual cycle without taking into account modern characteristics of the normal menstrual cycle leads to overdiagnosis and, as a result, the appointment of unnecessary therapy. The incidence of PCOS among women of young fertile age with NMC was 42.9%. Clinical hyperandrogenism of varying severity was detected in all patients with PCOS.

Phenotype A is most common in 53% of cases, which does not contradict the research of other authors. Reproductive behavior is characterized by the lack of effective contraception and pregnancy plans over the next two years (more than 80% of patients). It should be remembered that the lack of adequate treatment for PCOS leads to a significant decrease in fertility and, as a result, the formation of infertility and an increased risk of oncopathology.

The use of microdosed COCs containing drospirenone (for example, Dimia) in the treatment of SLEEP in 93% of cases provides a decrease in the severity of clinical hyperandrogenism, normalization of the menstrual cycle and improves anxiety indicators by 16.5%.

List of literature

1. Adamyan L.V., Andreeva E.N., Gasparyan S.A. and others. Polycystic ovary syndrome in reproductive age (modern approaches to diagnosis and treatment). Clinical recommendations (treatment protocol). M.; 2015.
2. Panarina O.V., Rashidova M.A., Belenkaya L.V. and others. Modern ideas about the pathogenesis of polycystic ovary syndrome (literature review). The scientific act of biomedicine. 2017;2(4):9-14.
3. Tiede H., Misso M., Costello M., et al. International evidence-based guidelines for the Assessment and Management of Polycystic Ovary Syndrome 2018. Monash University: Melbourne, Australia; 2018.

4. Beglova A.Yu., Elgina S.I. Phenotypic features of the level of anti-muller hormone and ultrasound parameters of the ovaries in women of reproductive age with polycystic ovary syndrome. *Mother and child in Kuzbass*. 2019;1(76):10-14.
5. Bulavenko O.V. Antimuller hormone as a marker of a woman's reproductive system. *Reproductive endocrinology*. 2011;1:27-29. DOI: 10.18370/2309-4117.2011.1.27-29.
6. GRLS. Instructions for the use of the drug for medical use of Dimia. (Electronic resource). URL: [https://grls.rosminzdrav.ru/Grls_View_v2.aspx?routingGuid=5921317a-35ac-4ff5-9067-cb8e97fb3b9eandt =](https://grls.rosminzdrav.ru/Grls_View_v2.aspx?routingGuid=5921317a-35ac-4ff5-9067-cb8e97fb3b9eandt=). Date of application: 06.12.2019.
7. Medical criteria for the acceptability of the use of contraceptive methods. WHO 2012, 4th ed. M.; 2012.
8. Medical criteria for the acceptability of the use of contraceptive methods. WHO 2015, 5th ed. Geneva; 2015.
9. Muek A.O., Seeger H., Rabe T. Hormonal contraception and the risk of endometrial cancer: a systematic review. *Endocrine cancer*. 2010;17: R263–R271. DOI: 10.1677/ERC-10-0076.
- 10.