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Modern Ideas about Polycystic Ovary Syndrome

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Annotation: Polycystic ovary syndrome (PCOS) is the most common form of endocrinopathy, occurs in 5–10% of women of reproductive age and accounts for 80%, and according to some data, even 90% of all forms of hyperandrogenism [1, 2].

The classic form of PCOS, or sclerocystic ovaries, was described by Stein and Leventhal in 1935 as a syndrome of amenorrhea and enlarged ovaries, combined in 2/3 of cases with hirsutism and in every second case with obesity. However, it was subsequently noted that there was a wide variety of forms of the syndrome, manifested by significant variations in the clinical picture of the disease, endocrine profile and morphological signs of the classical syndrome, and therefore the term “polycystic ovary syndrome” was proposed. In recent years, the concept has been put forward, which has received general approval, that the clinical manifestations associated with polycystic ovary syndrome (PCOS) should be interpreted as a syndrome, and not as a disease, this is a more accurate and specific term.

The modern definition of PCOS assumes the presence of clinical and biochemical manifestations of hyperandrogenism in combination with chronic anovulation, with the exclusion of other causes of hyperandrogenism (androgen-producing tumors, non-classical form of congenital adrenal hyperplasia, hyperprolactinemia). The etiology and pathogenesis of PCOS remains not fully understood until now, despite the huge number of studies devoted to this problem.

There are several important milestones in the history of PCOS research. These are the first publications on LH hypersecretion, appearing in 1958. After the introduction of radioimmune diagnostic methods, elevated LH levels are considered as diagnostic criteria for PCOS. Although in 1976 R. Rebar et al. [3] formulated the concept that PCOS can develop even with normal LH levels. The next important step is the discovery of the relationship between PCOS and insulin resistance made by C. Khan et al. in 1976 [4] and Burghen in 1980 [5]. In 1981, M. Swanson et al. [6] were the first to describe ultrasound signs of PCOS in women, but only after J. Adams et al. in 1985 [7], the diagnostic criteria for PCOS were clarified and characterized, and ultrasound diagnosis of the syndrome became possible. Subsequent studies have proven the heterogeneity of PCOS; to this day, discussions are ongoing regarding not only the pathogenesis of the syndrome, but also its diagnostic criteria.

Pathophysiology of PCOS

Among the numerous biochemical manifestations of PCOS, the most common is ovarian hyperandrogenism, elucidation of the causes of which is a central link in understanding the pathogenesis of the syndrome and its consequences. Impaired steroidogenesis in the ovaries is now an established fact in PCOS. This may be due to an internal defect in the ovary itself, as well as to the influence of extraovarian factors, in particular hypersecretion of LH and insulin.

Currently, there are many points of view on the pathogenesis of PCOS. Until the last decade, the leading theory of the pathogenesis of PCOS was the “central” theory, according to which PCOS are caused by a violation of the circhoral rhythm of luliberin secretion, the emissions of which are characterized by high amplitude and randomness, which leads to hypersecretion of LH, with relatively low FSH due to the blocking effect of inhibin [8]. Under the influence of LH, stimulation and hyperplasia of theca and ovarian stroma cells occur, in which ovarian androgens are synthesized, which is accompanied by an increase in their production and leads to skin manifestations of androgenization, anovulation and disruption of the rhythm of menstruation. High levels of androgens lead to increased extragonal estrogen synthesis in adipose tissue, which promotes adipocyte

proliferation and obesity. A high level of androgens reduces the synthesis of transport proteins in the liver, resulting in an increase in the level of free active fractions of androgens and estrogens, which aggravates the severity of hyperandrogenism and hyperestrogenism and can contribute, along with anovulation, to the development of hyperplastic processes in the endometrium.

Since the early 80s, a fundamentally new approach has been proposed to explain the pathogenesis of PCOS from the perspective of the leading role of insulin resistance and hyperinsulinemia [9]. It is assumed that in PCOS, type C insulin resistance, which is caused by post-receptor measurements of insulin receptors, is of primary importance; insulin hypersecretion is considered as a compensatory response to tissue resistance to the action of insulin. It is known that insulin is not only the main glucoregulatory hormone, it can have a number of other biological effects leading to an increase in the production of androgens in the ovaries and contributing to the development of PCOS. Recent studies have demonstrated that PCOS is an integral part of the metabolic syndrome, which is associated with a high risk of developing such severe consequences as type 2 diabetes mellitus and cardiovascular diseases [10, 11].

Familial cases of PCOS are well known, and advances in molecular biology have provided the basis for the search for gene defects responsible for this process. Currently, PCOS is considered as a multifactorial, heterogeneous disease, in the occurrence of which genetic disorders leading to activation of cytochrome P-450 and steroidogenesis in the ovaries, the so-called hereditary enzymopathies, play an important role. Disturbances in the mechanisms of action of a dozen growth factors have been identified, which can cause disturbances in the interaction between the cell and the follicular fluid.

Clinical signs of PCOS

Ovarian hyperandrogenism is the main symptom of PCOS. Even those researchers who do not consider elevated androgen levels when diagnosing PCOS recognize that hyperandrogenism is the most important feature of this syndrome. The numerous effects of androgens determine the diversity of the clinical picture of the disease. Since the hair follicles of the skin have receptors for androgens, androgens promote increased hair growth, an increase in their diameter and pigmentation, which is clinically manifested by excess male-pattern hair growth - hirsutism. Hirusutism is not synonymous with hyperandrogenism, since the severity of skin manifestations of androgenization is determined not only by the level of secreted androgens, but also by the activity of transport proteins that regulate the activity of androgens and the sensitivity of androgen receptors to the action of androgens associated with racial characteristics. Signs of hirsutism are characteristic of approximately 70% of patients with PCOS [12]. Moreover, in the European population, the incidence of hirsutism is approximately 10% lower than in the Eastern population. Skin manifestations of androgenization can include acne and seborrhea, since androgens can increase the activity of the sebaceous glands.

Patients with PCOS may experience other skin changes, in particular acantosis nigricans or “acanthosis nigricans,” which is a papillary pigmentary degeneration of the skin, manifested by hyperkeratosis and hyperpigmentation mainly in the inguinal and axillary areas. The presence of acanthosis nigricans is considered a dermatological manifestation of severe insulin resistance. The combination of hyperandrogenism and insulin resistance, called by R. Barbieri [9] “hairy syndrome” (HAIR syndrome), which occurs in more than half of women with PCOS, is combined with acanthosis nigricans in 5% of cases and is designated HAIR-AN syndrome, which reflects the presence hyperinsulinemia.

Androgens reduce the aromatase activity of granulosa cells, promoting follicular atresia, anovulation and menstrual irregularity, which is one of the classic clinical signs of PCOS. Menstrual irregularities often occur with menarche, manifesting as delayed menstruation of varying degrees of duration (oligomenorrhea) or absence of menstruation (amenorrhea). In approximately 20% of patients, delayed menstruation may alternate with bleeding (menometrorrhagia), clinically manifesting hyperplastic changes in the endometrium, characteristic of patients with PCOS. Diagnosis of abnormal uterine bleeding is important due to the high risk of developing endometrial carcinoma. PCOS is the cause of

infertility in 5–15% of women of reproductive age and occupies a leading place in the structure of causes of endocrine infertility. Although 10-15% of patients with PCOS may experience regular menstrual cycles with cases of chronic anovulation.

Androgens also have an anabolic effect, which contributes to the onset and progression of obesity, the presence of which is noted in 50–70% of patients with PCOS. Patients with PCOS are characterized by abdominal or visceral obesity, in which the WC/TB index exceeds 0.8. This is the most unfavorable type of obesity, aggravating endocrine disorders, increasing the risk of developing cardiovascular diseases, impaired glucose tolerance and diabetes.

Androgens, along with other factors, can increase insulin levels, leading to various metabolic disorders or aggravating existing disorders.

Diagnostics

The main feature of PCOS is the variety of clinical and biochemical manifestations of the disease, which, of course, complicates the diagnosis of the syndrome, which is based not only on the characteristic clinical picture of the disease, but also on ultrasound data, hormonal examinations and the results of a morphological study of resected ovarian tissue. Currently, there are fairly clear criteria for ultrasound diagnostics to identify PCOS. Most authors use Adams diagnostic criteria. Transvaginal ultrasound diagnosis is preferred, although the Adams diagnostic ultrasound criteria are based on transabdominal examination data. PCOS is characterized by an increase in ovarian volume of more than 9 cm, the presence of 10 follicles or more, with a diameter of up to 10 mm, which have stopped in their development as a result of the action of a number of factors located along the periphery of the ovary, under a thickened capsule [7]. The most specific diagnostic feature is the presence of a highly vascular, hyperechoic stroma, around which a large number of follicles are located. Although in 20–25% of patients with PCOS, stromal hyperplasia cannot be detected. This indicates that ultrasound diagnostics can help assess the condition of the ovaries and diagnose PCOS, but there is no “gold standard” on the basis of which a diagnosis of PCOS can be confidently made.

According to the concept outlined by HS.Jacobs [13], the presence of typical ultrasound signs of PCOS is the basis for the diagnosis and classification of the syndrome.

Most clinicians agree with this, however, there is an opposite opinion that for a more accurate diagnosis of the syndrome, a combination of ultrasound signs with menstrual irregularities and/or signs of hyperandrogenism is necessary. There is no complete mutual understanding on this issue. In European countries, PCOS is usually diagnosed based on characteristic sonographic changes in ovarian morphology. In contrast, in the United States, greater importance is attached to endocrine disorders, among which the most important is the increase in the level of ovarian androgens. Differences in diagnosis are likely due to different interpretations of concepts such as PCOS and PCOS, PCOS and multicystic ovaries. It is important to distinguish polycystic ovaries, characteristic of women with Stein-Leventhal syndrome, from the so-called multicystic ovaries, sometimes detected in women of reproductive age, patients with hypogonadotropic amenorrhea, girls in puberty, which are characterized by the presence of many follicles of various sizes located throughout the ovary , which does not have stromal hyperplasia.

An important method for diagnosing PCOS at present is Doppler ultrasound, which makes it possible to detect a significant increase in blood flow in the ovarian stroma, indicating pronounced neovascularization of the stroma in PCOS [14]. An increase in the intraovarian concentration of vascular endothelial factor in PCOS has been established, which can disrupt the regulation of intraovarian blood flow, leading to the persistence of many follicles, resulting in characteristic signs of PCOS.

Despite the similarity of morphological changes in the ovaries, different manifestations of the syndrome are often noted: variability of hormonal disorders, very diverse symptoms of the syndrome, including GA, obesity, menstrual irregularities; these manifestations can be either independent or combined. In this regard, ultrasound signs of PCOS cannot be used to predict the nature of the clinical

manifestations of PCOS, as well as for the classification of PCOS, which should be based on clinical symptoms and some endocrine parameters. If there are ultrasound signs of PCOS without other symptoms of the disease, the diagnosis of PCOS should not be made automatically.

Since PCOS is a hyperandrogenic condition, in most cases the diagnosis is made when elevated androgen levels are detected. In this regard, the determination of a number of androgens in blood plasma is indicated, which includes the determination of total and free testosterone, androstenedione and DEAS [15]. Patients with PCOS are characterized by an increase in the level of the main ovarian androgens - testosterone and androstenediol. Adrenal hyperandrogenism, manifested by an increase in DEAS levels, may be observed in 50–60% of patients. Important importance is attached to the study of the level of sex steroid binding globulin (SSBG), a protein that binds 80% of testosterone, limiting the biological activity of androgens, since in a bound state they are not able to exert biological effects. With a decrease in PSSG, the level of free testosterone and the clinical manifestations of hyperandrogenism increase.

An increase in LH levels and the LH/FSH index, although not a universal sign, is considered as one of the biochemical markers of PCOS. According to some settings, the LH/FSH index in PCOS should be more than 1.5 or 2, according to others - more than 3, and the LH level should exceed 8 μU/ml. An increase in LH/FSH is typical for approximately 70% of patients with PCOS. High LH levels are an important factor that impairs fertility. There is evidence that when LH levels are more than 10 μU/ml in the early follicular phase, there is a negative effect on oocytes, the embryo and the endometrium, which causes an increase in the frequency of miscarriages [16].

When examining women with hyperandrogenism, 2 goals are pursued. The first is to exclude disorders that can mimic PCOS and require specific therapy, such as virilizing tumors, non-classical form of congenital adrenal hyperplasia, Cushing's syndrome [17]. The second goal is to establish the presence of insulin resistance and hyperinsulinemia, which is a characteristic sign of PCOS and is diagnosed in 60–70% of patients. Hyperinsulinemia is characteristic of 30–40% of patients without obesity and 70–75% of patients with obesity, which indicates the adverse effect of excess body weight on metabolic and hormonal parameters [18]. Obesity can increase androgen levels by increasing peripheral androgen synthesis and decreasing PSSH levels. Hyperprolactinemia is characteristic of 15–20% of patients; an increase in estrone due to the peripheral conversion of excess androgens and a decrease in progesterone levels to anovulatory values are also characteristic.

If the patient undergoes laparoscopy with biopsy or resection of the ovaries (which should not be performed at the initial stage of treatment), then the characteristic signs of PCOS are: thickening or uneven thickness of the tunica albuginea, the presence in the cortical layer of primordial and many cystic-resisting follicles, stromal hyperplasia, hyperplasia and /or luteinization of theca intern.

Most researchers believe that early initiation of therapy in patients with PCOS can help preserve fertile potential, prevent hyper- and neoplastic processes of the endometrium, as well as late complications of the syndrome, such as cardiovascular diseases and diabetes mellitus.

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