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Modern Aspects of Polycystic Ovary Syndrome (Review)

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ABSTRACT

Polycystic ovary syndrome (PCOS) is a fairly common disease, which is one of the most pressing problems in gynecological endocrinology. The review article provides current data on the etiology and pathogenesis of PCOS. The rationale for the frequent combination of hyperandrogenism and insulin resistance in PCOS is given. It also discusses the characteristic clinical manifestations of PCOS and modern approaches to diagnosis and treatment, including drugs with neurotransmitter action (sibutramine, orlistat), drugs from the group of insulin sensitizers - metformin, progestogens or low-dose single-phase COCs with 3rd generation progestogens, synthetic antiestrogen - clostilbegit, and other drugs. . The prospects and methods of surgical intervention and tactics for infertility against the background of PCOS are considered.

PCOS mainly occurs in women of reproductive age, among whom the incidence of the disease is 4-12%. Indicators of the frequency of detection of this disease are quite variable due to the heterogeneity of clinical and endocrinological manifestations and the ambiguity of their assessment. In various European studies, the prevalence of PCOS is 6.5–8%. The disease is especially common in patients with anovulatory infertility, hyperandrogenism and associated dermatopathies. It should be noted that in the last decade there has been an increase in the number of patients who do not have typical manifestations of PCOS[11].

Polycystic ovary syndrome (PCOS) is the most common endocrinopathy affecting women of early reproductive age, the pathophysiology of which is still puzzling to many researchers. This syndrome is classically classified as hyperandrogenism and/or hyperandrogenemia, menstrual and ovulatory dysfunction, voluminous multifollicular ovaries on ultrasound (ultrasound), and metabolic disorders such as hyperinsulinemia, dyslipidaemia, and obesity. The etiopathogenesis of PCOS has not been fully elucidated, but it appears that the hypothalamic-pituitary-ovarian axis, ovarian and/or adrenal androgen secretion may contribute to the development of the syndrome. Infertility and poor reproductive health in women's lives are closely related to elevated androgen levels [1,4].

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Polycystic ovary syndrome (PCOS) is characterized by ovulatory dysfunction and hyperandrogenism. Its etiopathology is not well understood, but genetic factors appear to play a role[10].

Polycystic ovary syndrome (PCOS) is the most common endocrinopathy, which was first reported in 1935 by I.F. Stein and M.L. Leventhal [1]. WHO estimates that the proportion of PCOS affecting women of reproductive age worldwide is 116 million (3.6%) [2]. Worldwide, the prevalence of PCOS ranges from 2.2% to 26%. Based on the 1990 US National Institutes of Health (NIH) diagnostic criteria, the prevalence in the US, Europe, Asia, and Australia is 5 to 9% and approximately 4 to 21% when the 2003 Rotterdam criteria are applied in clinical practice. severe PCOS in women of reproductive age [3]. In India, the prevalence estimate is 10%, but there are no clear statistics [4].

PCOS is mainly characterized by hyperandrogenism and/or hyperandrogenemia, menstrual and ovulatory dysfunction manifesting as oligomenorrhea, amenorrhea or chronic anovulation, and a polycystic ovary morphology (PCOM: excess preantral follicles in the ovaries) [5] . Clinical hyperandrogenemia results in excessive terminal hair growth on the face or body, indicative of masculine traits known as hirsutism and leading to cosmetic consequences such as acne and alopecia (male pattern baldness). Conversely, biochemical hyperandrogenism leads to excessive androgen production and insulin resistance [6]. It is also associated with metabolic risk factors including hyperinsulinemia, type II diabetes mellitus, hypertension, dyslipidemia, and cardiovascular disease [7].

PCOS is a multigenic trait described in Fig. 1: Impact of polycystic ovary syndrome on women's lives; many pathways may be involved in its etiology. Researchers have been studying PCOS for centuries and have put forward many hypotheses about the development of PCOS and its characteristic features, but the etiology of the syndrome is still unclear. The pathogenesis of PCOS is associated primarily with defects in theca cells, along with neuroendocrine dysfunction of the hypothalamic-pituitary-ovarian system, leading to hyperandrogenism[10].

Under normal conditions, the hypothalamus signals the pituitary to release gonadotropin-releasing hormone (GnRH), which further stimulates the normal signaling pathway to release luteinizing hormone (LH) and follicle-stimulating hormone (FSH). Studies have shown a significant increase in the frequency and amplitude of the LH surge, reflecting an increase in GnRH secretion with moderate/reduced FSH secretion, which indicates the presence of hypothalamic defects in PCOS [13]. An elevated LH/FSH ratio is commonly seen in ovulatory women with polycystic ovary morphology (PCOM) [20]. Excessive hypothalamic secretion of GnRH in PCOS patients demonstrates reduced sensitivity to estradiol and progesterone inhibition [5,7]. Research has also shown the role of the neuropeptide kisspeptin, encoded by the Kiss 1 gene, as a GnRH pulse generator.

The ovary is the main site of steroidogenesis, where the differentiation of theca cells and granulosa cells plays a vital role in the development and maturation of follicles. In women with normal ovulation, the internal theca of the ovarian follicle and the zona fasciculata of the adrenal cortex contribute significantly to the secretion of androstenedione, and granulosa cells influence the conversion of androstenedione to estradiol by aromatase. In addition, the enzymes involved in the formation of androstenedione and estradiol are regulated by LH, FSH, and adrenocorticotropic hormone (ACTH) in the ovaries and adrenal glands [2]. The conversion of cholesterol precursor into biologically active steroid hormones is known as steroidogenesis.

In women with PCOS, overactive ovarian thecasteroidogenesis causes an overproduction

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of androgenic steroids, mainly 7-hydroxyprogesterone and androstenedione, resulting in hyperandrogenism [8]. In addition, in women with PCOS, aromatase activity is reduced, and follicle development is impaired and stopped due to a relative decrease in FSH secretion, which leads to excessive accumulation of androgens and hyperandrogenemia [12]. Thus, hyperandrogenism appears to play a critical role in the pathogenesis of PCOS, contributing to the reproductive and metabolic aspects of the syndrome.

In the literature, you can find the following classification of PCOS - the "typical" form - includes classic symptoms - menstrual dysfunction according to the type of oligomenorrhea with menarche (and secondary amenorrhea), bilateral ovarian enlargement, anovulation and primary infertility, moderate hirsutism. All other patients who do not have a complex of classic symptoms of PCOS are classified as "atypical" forms. The “atypical” form of PCOS includes patients with impaired fat metabolism, there may be secondary infertility, secondary oligoamenorrhea or menstrual irregularities by the type of bleeding, unilateral enlargement of the ovaries, etc. The effect of surgical treatment of these women, according to some authors, is insignificant [14]

The pathogenesis of PCOS seems to be extremely complex and, despite the large number of proposed theories of the development of the disease, none of them has fully revealed the causes and mechanisms of development of endocrinological and metabolic disorders in this disease. There are many supporters of the hypothesis of the formation of PCOS against the background of a primary (from the pubertal period) violation of the circoral rhythm of gonadoliberin. During puberty, which is critical in a girl's life, many environmental factors, heredity, etc. can contribute to the development of a number of endocrinopathies. Undoubtedly, an important role belongs to stress, which increases the synthesis of opioids (β-endorphin) and disrupts the neuroendocrine control of the regulation of GnRH and gonadotropins secretion. At the same time, the basal level of LH secretion increases against the background of a relative decrease in FSH production. Increased stimulation of LH disrupts the process of folliculogenesis: cystic atresia of follicles is formed in the ovaries with hyperplasia of theca cells, stroma and an increase in androgen synthesis. Against the background of a lack of FSH, there is an accumulation of androgens and a deficiency of estradiol. The latter stimulates the synthesis of LH, increasing its basal level[3,9].

There is a hypothesis about the important role of obesity and GI in the pathogenesis of PCOS in IR patients. However, GI is also observed in women without obesity, so excess body weight can only be a factor contributing to the development of IR in PCOS. The mechanisms of IR have not been finally established, but there is evidence that they are caused by disturbances at the receptor and post-receptor levels of insulin signal transmission into the cell. An important mechanism of IR may be a violation of insulin metabolism in the liver, controlled by C-peptide and β-endorphins. The latter play an important role in the neuroendocrine control of GnRH secretion, therefore, in PCOS, they may be involved in the pathogenesis of IR in some patients with PCOS. GA plays a certain role in peripheral IR, since androgens change the structure of muscle tissue towards the prevalence of type II muscle fibers, which are less sensitive to insulin. Concomitant obesity, more often visceral, in about 50% of patients exacerbates the existing violations of insulin sensitivity, providing a synergistic effect[13].

To date, it is known that the symptoms of PCOS appear in the late prepubertal and pubertal periods. Obesity and hirsutism occur before menarche; menstrual irregularities begin with the first menstruation. At the same time, retrospective determination of the time of onset of weight

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gain and increased hair growth is often difficult due to the gradual progression of processes [14]. It is known that in the development of cerebral forms of precocious puberty, the leading role is played by asphyxia, birth trauma, which already in the postnatal period can form a premorbid background for the development of neuroendocrine syndrome. Today, the role of chronic tonsillitis in the etiology of HSPPS has been absolutely proven, which indicates a special sensitivity of the hypothalamic region to tonsillar and adenovirus infections. The interaction of the neuroendocrine and immune systems is close and provides the adaptive capabilities of the body, the regulation of the most important function of living things - reproduction. This happens through specific receptors of immune system mediators (cytokines) that affect the neuroendocrine system, and the mediators of the latter regulate the activity and differentiation of cells of the immune system [4,11].

It is known that prolactin has a stimulating effect on the activation and differentiation of T cells, it plays an important role in IL-2 induced T-cell proliferation, and has the ability to induce in vitro expression of IL-2 receptors on rat spleen lymphocytes [12]. With polycystic ovary syndrome in lipocytes, the activity of aromatase, aromatization of androstenedione to estrone and 17P hydroxysteroid dehydrogenase increases. This, as well as increased weight, contribute to increased estrogen formation in peripheral tissues. The presence and severity of hirsutism determines the activity of skin 5a-reductase/enzyme converting testosterone to 5a-DHT. As a result, the ratio of estrone / estradiol increases, which is the reason for the effect on T-suppressors. Experimental data suggest that estrogens reduce the suppressive activity of T cells, and thus should increase the production of antibodies by B cells [12].

Diagnostics. Currently, three definitions of PCOS are used, according to which the presence of hyperandrogenism, chronic anovulation and PCOS in various variations is necessary for the diagnosis. All three sets of diagnostic criteria include clinical or biochemical hyperandrogenism and anovulation. Clear Rotterdam criteria should be used for morphological features of PCOS (presence of at least one ovary with 12 follicles 2-9 mm in diameter or ovarian volume > 10 ml and no dominant follicle > 10 mm), criteria adjusted for the woman's age does not exist [11].

Disorders that resemble PCOS are relatively easy to rule out; therefore, all women should be screened for TSH and 17-hydroxyprogesterone levels. In the presence of amenorrhea or hirsutism, hyperprolactinemia may be present. Thyroid dysfunction can be observed in women with menstrual irregularities. In women with hyperandrogenism, a nonclassical form of congenital adrenal dysfunction should be excluded, which, according to various sources, occurs in 1.5–6.8% of patients with manifestations of hyperandrogenism. In selected women with amenorrhea, virilization, or physical findings unrelated to PCOS, such as proximal muscle weakness (Cushing's syndrome) or prominent frontal tubercles (acromegaly), possible other diagnoses should be considered and ruled out [14,13].

Diagnosis of PCOS is most problematic in women who are close to menarche or perimenopause because amenorrhea and oligomenorrhea are natural stages in the development and aging of reproductive function, as are changes in androgen levels in the bloodstream and ovarian morphology. Due to the fact that evidence has been obtained of the important role of the genetic component in the development of PCOS and reproductive and metabolic disorders in male and female relatives, it is necessary to carefully collect a family history [9].

Treatment. Weight loss in patients with obesity and polycystic ovary syndrome can be used as the first stage of treatment followed by pathogenetic therapy. It should be noted that in

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modern methods of treating obesity, priority is given to diets and hypocaloric nutrition, which a person must adhere to throughout his life, otherwise the lost kilograms will return, and even in excess.

The effectiveness of infertility treatment in PCOS depends on the clinical and hormonal characteristics of the course of the disease, the age of the patient, the adequacy of preparatory therapy, and the correct selection of the ovulation induction scheme.

Hormonal treatment of endometrial hyperplasia in insulin resistant PCOS patients on the background of metabolic therapy. It should be noted, that the indication for ovarian resection is not only infertility, but also recurrent hyperplastic processes.

Identification of the relationship between hyperinsulinemia and ovarian hyperandrogenism led to the use of drugs that increase the sensitivity of peripheral tissues to insulin, the so-called insulin sensitizers, in PCOS treatment regimens [8]. In clinical trials, it was found that a decrease in the level of circulating insulin leads to a decrease in testosterone production and in some cases contributes to the onset of ovulation even without the use of specific stimulation therapy with clomiphene or gonadotropins [2].

The goal of any surgical intervention in PCOS is to destroy or remove the part of the androgen-producing ovary, thereby restoring the normal relationship between the central structures and the ovaries [8]. Previously, it was believed that the ovary has a great regenerative capacity and can take the same shape and size without the formation of scar tissue and with the preservation of its function even when 5/6 of its volume is removed. These views have now changed. It has been proven that surgical trauma is not so safe and can reduce the functional activity of the ovary up to its complete suppression [9]. Some authors note that it is inappropriate to carry out any therapeutic measures (conservative or surgical) without solving the problem of infertility. According to many authors, surgical interventions on the ovaries in PCOS have a short-term effect, and conservative ones are generally aimed only at the onset of pregnancy. In this regard, neither surgical nor conservative methods allow to cure a patient with PCOS completely [11]. Prevention. Despite the rather high overall effectiveness of various methods of ovulation stimulation (80–85%) in restoring reproductive function in PCOS patients, most practitioners report a recurrence of clinical symptoms. Mostly, recurrence is observed in patients who have realized a generative function using conservative methods of treatment, as well as after PCOS cauterization [2]. Therefore, after childbirth, it is necessary to prevent the recurrence of PCOS, which is important given the risk of endometrial hyperplastic processes and the long-term consequences of insulin resistance - cardiovascular diseases, insulin-dependent diabetes mellitus. For this purpose, it is most expedient to prescribe COCs, preferably monophasic ones. The progestogenic component of COCs reduces the synthesis of Gn-RH by the hypothalamus, as a result, the production of gonadotropins by the pituitary gland (LH and FSH), which leads to a decrease in the production of androgens in the ovaries. In turn, ethinyl estradiol, which is part of COCs, increases the synthesis of DSH in the liver, thus reducing the content of free biologically active testosterone in the blood [11]. In addition, the progestogenic component has a beneficial effect on the endometrium, preventing the development of hyperplastic processes. Preference should be given to third-generation drugs containing progestogens with pronounced antigonadotropic and antiandrogenic effects [12].

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