ABSTRACT

Polycystic ovary syndrome (PCOS) is one of the most common endocrine disorders in women. It is characterized by numerous hormonal and metabolic disturbances, among which hyperandrogenism, insulin resistance, as well as disruption in carbohydrate and lipid metabolism play an important role.

The study aimed to present the PCOS, taking into account the skin lesions often present in the disorder. The collected information concerns the mechanism and purposes for the development of clinical symptoms as a result of disturbances in a female body.

The diagnosis of PCOS is determined by the presence of two out of three criteria: excess of androgen hormones, anovulation or their rarity, and the image of polycystic ovaries on ultrasound, while excluding other disease entities.

Keywords: polycystic ovary syndrome, PCOS, hyperandrogenism, acne, hirsutism, alopecia

INTRODUCTION

Polycystic ovary syndrome (PCOS) is one of the most common endocrine diseases among women. It is estimated that it affects 3-12% of the population of females of reproductive age. It is the main cause of menstrual disorders and is often also related to infertility. PCOS is one of the most heterogeneous endocrinopathies, characterized by the presence of numerous hormonal and metabolic disorders: hyperandrogenism, insulin resistance and often accompanying hyperinsulinism, as well as disturbances in carbohydrate and lipid metabolism, which significantly contributes to obesity [1-3].

PCOS was first described by Stein and Leventhal in 1935 [2]. During a conference organized by the National Institutes of Health in 1990, the criteria for the diagnosis of PCOS were defined, including the rare occurrence of ovulation and symptoms of androgen excess. To date, according to the findings made at the conference in Rotterdam in 2004, the
diagnosis of this syndrome is determined by the presence of two out of three established criteria: 1) clinical and/or biochemical symptoms of hyperandrogenism, 2) lack of ovulation or their rare occurrence, and 3) polycystic ovaries by ultrasound, while excluding other disease entities [2, 3]. The development of PCOS is influenced by genetic, hormonal, and environmental factors. According to the available literature sources, the probability of the disease was reported in about 50% of sisters of sick women [1]. The studies conducted so far indicate that the course, frequency, and clinical picture also depend on ethnic factors and the race of women, and the diversified nature of the disease is important in the method of its diagnosis and treatment [2-4].

ETIOPATHOGENESIS OF PCOS

The full mechanism of development of PCOS has not yet been elucidated. The recognized theories suggest that pathogenesis is associated with metabolic and hormonal disorders [3, 5]. The etiopathogenesis of the disease consists, among others, of androgen excess, hyperinsulinism, insulin resistance, and disturbances in both carbohydrate and lipid metabolism [2, 3]. Three models of pathophysiological changes in the course of PCOS are known: gonadotrophic, ovarian, and insulin-dependent models. In the gonadotrophic model, pathology relates to the disturbance of the luteinizing hormone (LH) secretion and the biological activity of the follicle-stimulating hormone (FSH) produced by the pituitary gland. The ovarian model relates to abnormalities in the synthesis and metabolism of androgens in the ovary, while the insulin-dependent model, referred to as the primary etiological mechanism, is associated with disorders of insulin secretion and activity. A significant role in the development of PCOS is also attributed to immunological factors and the phenomenon of oxidative stress frequently occurring in the body [5].

Three important pathways involved in the pathogenesis of PCOS include insulin secretion and action, steroidogenesis coding, and other hormonal and metabolic pathways [6]. In women with PCOS, lipotoxicity is observed, as manifested by abnormal metabolism of adipose tissue as a result of increased levels of free fatty acids, tumor necrosis factor α (TNF-α), interleukin 6 (IL-6), and interleukin 18 (IL-18) in the blood serum [2]. Lipotoxicity is one of the factors responsible for the pathogenesis of insulin resistance. As a result of the weakening of lipase activity, responsible for the breakdown of fat cells, the lipolysis process of adipose tissue and its sensitivity to the lipolytic effects of catecholamines are disturbed [2, 3]. More than half of women suffering from PCOS are overweight, which is often the consequence of disturbances in the perception of satiety and an increased physiological feeling of hunger due to the increase in leptin concentration. Abdominal obesity, also known as android obesity, usually affects women with PCOS. Weight reduction significantly reduces the level of insulin, leptin, and testosterone in the serum [2]. Obesity has a significant effect on increasing insulin resistance and inducing hyperinsulinemia, as well as reduced fertility, as a result of an imbalance of steroid hormones, which leads to increased symptoms of hyperandrogenization. It happens as a result of a decrease in the concentration of sex steroid binding protein and an increase in the concentration of insulin-like growth factor-1 (IGF-1) [6].

Literature data indicate a significant role of insulin resistance and elevated insulin levels in the etiopathogenesis of PCOS [4, 7]. For the proper biological activity of insulin is important to combine with an appropriate, specific receptor and create the correct so-called receptor complex. The results of research conducted so far indicate the correct number of insulin receptors and their affinity for insulin. Therefore, the occurrence of insulin resistance in the group of women affected by PCOS is influenced by intracellular disturbances in the signaling pathways of tyrosine kinase activity [4]. It is worth emphasizing that insulin resistance concerns especially (in about 70% of cases) in obese women. However, it can be diagnosed regardless of body weight and body mass index (BMI), and therefore also occur in slim women (about 30% of cases) [1, 4]. In about 10% of women diagnosed with PCOS, impaired glucose tolerance was observed with normal body weight [3].

Apart from insulin resistance and its abnormal secretion, the group of factors influencing the etiopathogenesis of PCOS includes ovarian steroidogenesis, abnormal ovarian stimulation, internal ovarian tissue defects, and adrenal and ovarian hyperandrogenism [6]. In women with PCOS, increased secretion of androgens is observed, which is often associated with their excessive production in adipose tissue or the ovaries and adrenal glands, especially in obese women. Additionally, the reduced concentration of sex hormone binding globulin (SHBG) contributes to the increase in the level of androgens in the body, leading to hyperandrogenism, which may be particularly influenced by the accompanying hyperinsulinemia [3, 8, 9]. Elevated insulin levels can lead to hyperandrogenemia by direct effects on the hypothalamus [9]. Steroidogenesis is stimulated by insulin through interaction with the insulin receptor and IGF-1 receptor located within ovarian cells and as a result of simultaneous stimulation of androgen production by the LH of the ovarian tissue cells [2, 3].

Clinically observed androgenization is a common syndrome of disorders in women with PCOS, manifested by various symptoms, including acne, hair loss, hirsutism, or dark keratosis. However, it should be remembered that androgens participate in the development of the reproductive system in the female fetus, and their appropriate amount in adult women affects the proper functioning of the reproductive system, libido, bone turnover, muscle mass, and the work of the brain [10]. The group of androgens includes testosterone and dihydrotestosterone (DHT), which are produced by the transformation of testosterone under the influence of the 5α-reductase enzyme [11, 12]. DHT shows
high biological activity due to its increased ability to bind to the androgen receptor [12]. Testosterone precursors are dehydroepiandrosterone (DHEA), dehydroepiandrosterone sulfate (DHEA-S), and androstenedione. Its synthesis is significantly related to the amount of SHBG and is subject to the laws of feedback [11, 12]. It is worth noting that the skin is an organ that actively participates in the synthesis of steroid hormones and their transformation into more active derivatives [12]. The process of steroidogenesis takes place mainly in keratinocytes, sebaceous glands, and hair follicles, therefore it significantly influences the development of skin lesions in the clinical picture of hyperandrogenization [11, 12].

Recently, the possible influence of oxidative stress on the pathogenesis of PCOS has been carefully analyzed [3, 5]. Research indicates a sustained elevated level of oxidative stress indicators and a simultaneous decrease in antioxidant levels in women with the syndrome, which may largely affect the increased risk of cardiovascular disease, as a result of e.g. the processes of lipid oxidation [13, 14].

**SKIN CHANGES IN PCOS**

The skin is the organ of the target action of androgens, derived both from the blood and the local processes of their synthesis. Keratinocytes and fibroblasts, as well as skin appendages such as sebaceous glands, sweat glands, and hair follicles, are involved in the process of steroidogenesis, where the enzymatic process with the participation of 5-α-reductase leads to the reduction of testosterone to DHT and the conversion of DHEA and androstenedione to more active metabolites. The conducted studies indicate an increased expression of enzymes involved in the steroidogenesis process in dermis cells, hair pigment cells, as well as hair papilla cells, and sebocytes [11, 15-17]. This fact confirms the importance of hyperandrogenism in the development of clinical symptoms of androgen activity in the course of PCOS [11]. Among the skin lesions in PCOS caused by hyperandrogenemia, the following are observed: hirsutism, androgenic alopecia, acne, and seborrhea. Dark keratosis is also characteristic of many women with PCOS and is associated with insulin resistance [5, 8, 10-15].

**Hirsutism**

Hirsutism is defined as the occurrence of male hair in women and is the result of the interaction of circulating androgens and the sensitivity of the androgen receptors. The occurrence of both excessive hair and hair loss due to the action of androgens in one person is associated with a different response of the hair follicle to circulating androgens. In the area of the upper lip, chin, chest, nape, nipple, lumbosacral region, upper abdomen, white line, arms, and medial thighs, androgens stimulate the change of vellus hair into terminal hair - thick, saturated with pigment, extending the phase anagen. On the other hand, in the frontotemporal area and on the top of the head, miniaturization of the hair follicles occurs under the influence of androgens, with the shortening of the anagen phase [18].

Hirsutism affects 5-10% of women of childbearing age. In 80-90% of cases, is associated with endocrine disorders as a result of excessive secretion of androgens (including diseases of the ovaries and adrenal glands), and its the most common cause is PCOS which may affects up to 60-70% of women in this group. Excessive hair is observed in one, some, or all of the previously mentioned places [19-24]. However, hirsutism is detected in some women despite normal androgen levels. The so-called ‘idiopathic hirsutism’ is associated with excessive sensitivity of the hair follicles to the circulating level of androgens that are typical for women [23].

To assess the severity of hirsutism, the so-called Ferriman and Gallwey scale, in which the intensity of hair in the area of the upper lip, chin, breast, upper back, buttocks, the middle part of the abdomen, lower abdomen, arms, and thighs should be determined. The table is from 0 to 4 points for a given area. Obtaining more than 8 points is the basis for determining the presence of hirsutism of varying severity. 8-15 points are for mild hirsutism, 16-25 points for moderate form, and over 25 points determine a severe degree of hirsutism [5, 19, 20, 23]. Hirsutism may coexist with other symptoms of hyperandrogenization, which include: androgenic alopecia, acne, seborrhea, keratosis, and android obesity [19, 23].

The problem of hirsutism often leads to lower self-esteem and psychosocial disorders, especially among young women, and often results in difficulties in establishing interpersonal relationships [20, 21]. When hirsutism is diagnosed, it seems extremely important to take multidirectional actions aimed at reducing the appearance of bothersome symptoms, as well as eliminating the causes of excessive hair growth. An important issue is a properly selected and conducted method of pharmacological treatment, as well as cosmetological procedures, which can significantly reduce aesthetic problems. The combination of both directions of action may contribute to obtaining satisfactory therapeutic effects [20, 22, 23].

Pharmacological treatment is based mainly on the use of preparations containing estrogen and progestogen, which decrease the concentration of free testosterone by inhibiting LH and FSH, reducing the production of androgens in the ovaries, and increasing the synthesis of SHBG in the liver [19, 22, 23]. Another effective drug is spironolactone which competitively inhibits the activity of the androgen receptor and 5-α-reductase [19, 23]. Flutamide and finasteride are also used to treat hirsutism [19, 22, 23].

Among the treatments aimed at reducing excessive hair in the course of hirsutism, both temporary hair removal treatments are used: shaving with a razor, using tweezers, waxing, electric epilators, home devices emitting intense pulsed light (IPL), the use of cosmetic products in the form of depilatory creams, discoloration, as well as professional cosmetology treatments including electrolysis and
electro-epilation, laser hair removal and IPL. Eflornithine hydrochloride is also used (but not available in Poland) [19, 20]. Before starting hair removal treatments in a beauty salon, the cause of hirsutism should be diagnosed by a doctor, e.g. an endocrinologist or a gynecologist, to minimize the impact of abnormal hormone management on the hair growth cycle, and thus improving the effectiveness of in-office treatments [20].

Androgenetic alopecia
Androgenetic alopecia (in Latin: Alopecia androgenica) is a common problem, affecting up to 60% of women, among whom one of the most numerous groups is women suffering from PCOS [11, 21]. Hair loss is a physiological process that involves the loss of approximately 70-100 hairs per day. The daily loss of more than 100 hairs over a period of more than a few weeks is worrying. The basis of androgenetic alopecia and its therapy is also hormonal diagnosis [25].

The problem of androgenetic alopecia in women usually begins at the age of 20, but it may also appear in 15-year-old girls [11]. The first characteristic symptom of female androgenic hair loss is thinning of the hair in the central part of the scalp, with a 2-3 cm strand of hair in the frontal area and no complete hair loss (fig. 1) [11, 13].

In a clinical trial, the Ludwig scale pattern of the severity of androgenetic alopecia is used, which covers three stages of androgenetic alopecia. Stage I concerns the appearance of a lumen at the top of the head. In stage II, a gradual expansion of the lumen is observed, and in stage III, the scalp becomes visible [25, 26].

The basis for the development of androgen-dependent alopecia is the shortened phase of the hair anagen, with the simultaneously extended telogen phase (resting), which is caused by the high concentration of androgens, increased activity of 5-α-reductase (type 2) in the skin, responsible for the conversion of testosterone into more active DHT and increased androgen receptor expression [13, 25]. Androgens also cause miniaturization of the hair follicles, caused by impaired microcirculation within the scalp, due to the constriction of local blood vessels, making the hair thin, weak, and short, with reduced dye saturation. Paroxysmal loss of telogen hair, i.e. hair in the resting phase, is not observed. Additionally, the cellular metabolism of the hair matrix is disturbed, and sometimes inflammation develops, as a consequence of which the hair follicles are degraded and atrophied [13, 21, 25, 26]. When the correct level of androgens in a woman’s system is confirmed, hormonal alopecia may be caused by an increased sensitivity of the hair follicles to androgens [21, 25]. Research indicates a significant role of insulin, especially hyperinsulinemia, in the weakening of the hair follicles, as a result of a direct increase in the local synthesis of androgen hormones and inhibition of the IGF-1 binding protein, directly affecting the cycle of hair growth and androgen metabolism [27]. The effect of cell insulin resistance is also investigated [28]. Excessive hair loss can be caused not only by changes in the metabolism of the hair follicle cells but also by the loss of the synchronous development rhythm of adjacent hairs.

The treatment of androgenetic alopecia often involves pharmacological therapy based on the use of, inter alia, cyproterone acetate, spironolactone, flutamide, finasteride, and oral estrogen-gestagen preparations [25]. In local treatment, minoxidil is used, which significantly improves the blood supply to the hair follicles as a result of the expansion of local blood vessels [21, 25].

Acne and seborrhea
Increased androgen synthesis in the female body significantly influences the increased production of sebum by the cells of the sebaceous glands. Due to impaired stimulation of sebocytes, seborrheic skin diseases may develop, including seborrheic dermatitis, seborrhea, and acne [11].

In terms of the problem of androgenization in women, especially those struggling with PCOS, one of the main skin problem is acne vulgaris (fig. 2), in which pathology, apart from genetic predisposition, seborrheic problems, and disorders of the keratinization process of the ducts leading to the gland’s sebaceous bacteria, Cutibacterium acnes, colonizing the hair follicles, play a significant role [10, 11, 21, 29].

These bacteria, as a result of the secreted products that decompose sebum, contribute to the development of inflammatory skin lesions [29]. The secretion of sebum by sebocytes is regulated by the concentration of male sex
hormones and depends on the reactivity of the sebaceous glands to androgens circulating in the blood [10, 13]. Acne is mainly located in the sebhorheic areas, where DHEA-S and DHT stimulate the activity of androgen receptors located in the hair-sebaceous unit, influencing the increased secretion of sebum and the accumulation of keratin in the ducts leading to sebaceous glands [30].

Treatment of hormone-dependent acne includes the use of oral antibiotics, retinoids, sulfones, and combined contraceptives. Androgen receptors located in the sebaceous glands are blocked, which reduces the production of sebum and the development of inflammatory eruptions. Estrogens significantly increase the production of SHBG, which, by binding androgens, leads to a reduction in the concentration of free androgens in the serum; in the serum, tail [21]. Topical treatment includes the use of retinoids, antibiotics, benzoyl peroxide, azelaic acid with antibacterial, anti-inflammatory, anti-seborrhoeic, and keratolytic properties, salicylic acid with comedolytic and anti-inflammatory properties, zinc compounds, and spot-applied ichthyol [21, 29].

Dark keratosis
Hyperandrogenism and insulin resistance in PCOS is strongly associated with the dark color of the skin, called acanthosis nigricans. It should be noted that these changes are characteristic of very severe insulin resistance [4, 31, 32]. The lesions can occur in various parts of the body, including the neck, armpits, groin, ankles, and elbows, under the breasts, and around the navel. Due to the increasing incidence of obesity and diabetes, an increased incidence of dark keratosis has also been observed recently, ranging from 7% to 74%, depending on age, race, or obesity degree [31]. The pathophysiology of dark keratosis is related to the multifactorial stimulation of the proliferation of epidermal keratinocytes and skin fibroblasts, in which the basic role is attributed to insulin and IGF-1 [32]. Fibroblast growth factor (FGF) and melanocyte-stimulating hormone-α may play a role in the pathogenesis of hyperpigmentation. The activity of the receptors for these factors is increased by the IGF-1 [31]. All of these receptors are present on keratinocytes and fibroblasts and stimulate cell growth. Obesity-related dark keratosis is the most common type of these changes. It can appear at any age but is more common in adulthood. It is usually associated with insulin resistance, and weight loss may lead to the reduction or resolution of skin lesions [32].

SKIN THICKNESS IN PCOS
The research carried out among women with PCOS by Böttcher B. et al. assessed the thickness of the skin, which is influenced by many factors, including location, age, gender, or hormonal balance (e.g. menopause) [33]. The skin thickness was measured using ultrasound diagnostics. At the same time, blood tests were carried out to determine, inter alia, the concentration of androgens, estrogens, cholesterol, prolactin, LH, and FSH. The results of the study showed a greater thickness of the skin in patients with endocrinologically and clinically diagnosed polycystic ovary syndrome, compared to the control group. The influence of increased levels of androgens and estrogens as well as metabolic abnormalities, including abnormal insulin levels, has been confirmed. However, the existence of a significant relationship between the thickness of the skin and the level of testosterone, the effect of which on skin cells may be affected by disturbed lipid metabolism, has not been proven [33].

SUMMARY
PCOS is a metabolic disease associated with disturbances in the body's homeostasis, mainly insulin resistance, lipid metabolism disorders, and obesity-related to it, as well as hormonal disorders. It is manifested by many endocrine skin lesions, which include: hirsutism, seborrhea, acne, and androgenetic alopecia, a brief description of which is presented in this article. PCOS affects an increasing group of women of reproductive age, and the accompanying skin symptoms may cause discomfort to women and make them seek solutions also in cosmetology offices, hence the knowledge of the clinical picture of PCOS seems important for practising cosmetologists.

REFERENCES / LITERATURA


